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A critical assessment of factors effecting blister pack formation in the pharmaceutical industry

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**A Critical Assessment of Factors Effecting
Blister Pack Formation in the Pharmaceutical
Industry**

By

Keith W Allen

A Doctoral Thesis.

Submitted in partial fulfilment of the requirements for the award of the degree of
Doctor of Philosophy of Loughborough University

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Department of Materials

Supervisor: Dr G.W.Critchlow

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Abbreviations

AES – Auger Electron Spectroscopy
APS – Alcan Packaging Singen
AFM – Atomic Force Microscopy
bpm – Blisters Per Minute
BSI – British Standards Institute
CEN – European Committee for Standardisation
CLF – Current Lidding Foil
COCs – Cyclic Olefin Co-polymers
cpm – Cycles Per Minute
DMF – Drug Master File
DSC – Differential Scanning Calorimetry
EMA – European Medicines Evaluation Agency
EU – European Union
EP – European Pharmacopeia
FDA – Food and Drugs Administration
FTIR – Fourier Transform Infrared
GC – Gas Chromatography
GSK – GlaxoSmithKline
GPTD – Global Packaging and Technical Development
GRAS – Generally Recognised As Safe
HDPE – High Density Polyethylene
HSL – Heat Seal Lacquer
ICH – International Conference Harmonisation
IR – Infrared
IPCs – In Process Controls
JP – Japanese Pharmacopeia
LDPE – Low Density Polyethylene
MDPI – Multi-dose Powder Inhaler
MHRA – Medicines Health Regulatory Association
MSG – Mont-Saint Guibert
MVTR – Moisture Vapour Transmission Rate
NLF – New Robust Lidding Foil
NCEs – New Chemical Entities
NDA – New Drug Application
OPA – Orientated Polyamide
OPP – Orientated Polypropylene
OTC – Over The Counter
PA – Polyamide
PCTFE – Polychlorotrifluoroethylene
PE – Polyethylene
PEL – Packaging Evaluation Laboratory
PET – Polyester
PLA – Poly Lactic Acid
PMA – Polymethylacrylate

Abbreviations - Continued

PP – Polypropylene
PS – Polystyrene
PVA – Polyvinyl acrylate
PVdC – Polyvinylidene Chloride
PVC – Polyvinylchloride
R&D – Research and Development
RFID – Radio Frequency Identifications
RH – Relative Humidity
SIMS – Secondary Ion Mass Spectroscopy
SEM – Scanning Electron Microscopy
SOP – Standard Operating Procedure
SPM – Strips Per Minute
UPVC – Un-plasticized Polyvinylchloride
USA – United States of America
USP – United States Pharmacopoeia
µm – Micrometres
VAPT – Variable Angle Peel Tester
WVTR – Water Vapour Transmission Rate
WHO – World Health Organisation
XPS – X-Ray Photoelectron Spectroscopy

Abstract

Blister packing is a very complex process, incorporating many areas of science and technology. To date there have been many studies carried out evaluating various types of blister materials, sealing and forming processes and heat sealable adhesives. However, there has never been a reported study pulling together all of the critical factors involved in achieving optimised blister packing. There is also very little on this topic in terms of published literature.

The aim of this study is to evaluate all critical aspects of blister packing to resolve ongoing machine and material issues by enabling the introduction of alternative materials and processes. Further to a critical evaluation of the available literature and studies on the various types of blister sealing equipment and tool design, the alternative types of materials used to produce the blister packs were also evaluated to identify the critical features and parameters required to achieve a totally sealed hermetic pack.

More recent studies have evaluated the seal quality of new and existing Multi-Dose Powder Inhalation (MDPI) lidding and base foils. These novel studies have utilised techniques such as Scanning Electron Microscopy (SEM) and calculated peel strength data using developed test protocols. Moisture ingress determination based upon both theoretical and actual calculations have also been deduced. A further study has also been carried out to determine the heat transfer from the heated sealing tools to the product for platen type blister sealing.

This study set out to give an overview of the packaging requirements of the pharmaceutical industry, the purpose being to highlight the critical aspects of a heavily regulated industry and to explain the various stages of the packaging process to identify any areas of development and improvements that could be made as part of any subsequent studies.

Once an overview had been undertaken, it was necessary to identify the current and new materials under development that are and will be used for blister packaging in future applications. It has also been necessary to determine the required protection in terms of moisture vapour, light transmission, seal strength and seal integrity that the products require. Prior to any decisions on the areas to research as part of my studies it was essential to understand the types of blister designs and material construction with the necessary additives such as stabilising agents, stability agents and antiblock agents. The rationale being to avoid repetition of any previous developments and to use those developments and previous studies to further enhance the performance of the current materials, developing totally new concepts and blister structures.

Once the materials were identified a study was carried out into two types of blister sealing equipment, namely rotary and platen sealers. This was essential in developing a good understanding of the process and technology available when introducing new materials and alternative blister designs. Furthermore, it was key in understanding the problems associated with blister packs and in resolving ongoing material and equipment issues.

Further research was then directed towards other critical aspects of blister sealing, such as dwell time, temperature, pressure and the importance of the adhesive function. After which the types of testing that is carried out on the finished blister to ensure that a good hermetic seal is achieved was identified. This guarantees that the product will be preserved during its shelf-life and the required dose will be administered throughout.

The study then focused on a number of operational improvements and introduction of new materials, such as alternative types of lidding and base laminates, new heat seal lacquers and new rotary blister sealing tools.

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Chapter 1

Introduction into the Main Factors Effecting Blister Pack Formation in the Pharmaceutical Industry

1.1 Overview of Packaging for the Pharmaceutical Industry

1.1.1 Introduction

Pharmaceutical packaging requires high attention to detail due to the critical nature of the materials required to protect the active product throughout its shelf-life, sometimes for up to five years^{1,2}. The types of packaging material / design can also be influenced by the respective markets and heavily regulated by the authorities³.

A simple general definition of packaging indicates that it is the economical means of providing protection, presentation, identification, information and convenience for a product until it is used or administered^{4,5,6}.

The pharmaceutical pack must protect the product against light, humidity and oxygen, also mechanical, climatic, microbiological and human hazards, it may require child resistance and / or pilfer-resistance, it must also be compatible with the product and of its contents³.

Today blister and strip packaging compete for a wide range of solid dose tablet forms. Figures show that blisters are more popular in Japan and Europe, with 80% usage compared to 20% bottles. In the UK blisters are less popular, with 60% blisters compared to 40% bottles. In the US bottles are preferred, with 10% blisters and 90% bottles¹.

Blister packages are recognised as an improvement over the early foil-strip package¹. In most forms the tablet or capsule is visible through the blister side of the unit-dose package¹. This provides one more safety measure in the hospital dispensing process¹.

Recognition of the product prior to opening the package reduces medication errors, as well as waste of products opened by mistake that must later be destroyed². The transparent blister can be made of one of several thermoformable polymers or combinations of polymers that provide improved barrier properties, or the heat seal capabilities needed to seal the blister side to the lidding stock^{4,7,8}. The selection depends on the chemical and physical barrier demands of the pharmaceutical product^{7,8}. The more moisture sensitive the product, the better the moisture vapour transmission barrier properties must be⁸.

Available materials range from relatively inexpensive Polyvinylchloride (PVC) to the expensive Polychlorotrifluoroethylene (PCTFE), and laminated structures⁹. Studies have shown that the choice of film thickness affects both material costs and barrier properties, such as the thicker the material the greater the protection to moisture, permeability and oxygen^{7,10}. This theory has also been discussed further in **Chapter 4**.

Other considerations are machinability, production rates, depth of the blister, wall thickness, uniformity of the blister and sealing properties to the lidding stock^{1,7,8}. Highly specialised testing must therefore take place to verify the integrity of the blister pack. The reverse side of the hospital unit-dose package is the lidding stock. This usually takes one of two forms; either a lamination of aluminium foil / paper or a single film of aluminium. Both structures have a heat-seal lacquer on the product side to seal against the base material^{1,7,8}.

Pharmaceutical packaging may also be required to be child resistant, this is dependant on the nature and toxicity of the active product to meet market and legislative requirements¹.

1.1.2 Child Resistant Packaging Legislation

Recent discussions within the pharmaceutical industry regarding child resistant packaging has resulted in a European standard being drafted¹¹. The guidelines indicate that all Paracetamol, Aspirin and Iron containing products will be affected¹². Historically, blister packs were not part of the legislation that required a child resistant design / closure for Paracetamol and Aspirin products. However, due to the number of incidents with child poisoning and the fact that there has been an increase in the use of blister packs and the majority of these blister packs fail the US type testing, it was agreed to adopt the European standard¹¹. The European Committee for Standardisation (CEN) is based on the German DIN standard 55559¹³, which reduces the amount of child testing and details an approved list of materials¹¹. This draft standard also mirrors very closely the British Standards Institute (BSI) standard where an entry criterion of 8 blister pockets accessed from 10 constitutes a failure during child panel testing¹¹. Studies have shown that child safety figures show that there has been a 58% increase in incidents of child poisoning¹¹. However, this is contradicted by a research study that only shows an increase of 1% from 1984 to 1997¹¹.

The standard will apply to Aspirin, Paracetamol and Iron containing products, both Over The Counter (OTC) and prescription only. This will impact on between 550 to 600 licenses in the UK¹¹.

Medicines Health Regulatory Agency (MHRA) would require comparative data on stability if the same contact materials were used, and full shelf life testing, with a matrix of stability testing if materials change¹².

There is also a consumer lobby growing within the European Union (EU) to oppose the 8-unit entry criterion of the draft CEN standard and instead seek to introduce an entry limit based on toxicity of the individual product / compound⁷. Furthermore, a report written the World Health Organisation (WHO) to assess the predicted toxic dose of various products and compounds on children

supports this proposal¹⁴. If toxicity is brought into the equation then this may impact a vast majority of products within the pharmaceutical industry¹².

A working party has been set up by the pharmaceutical companies, with sponsored research on mechanical testing, (project BLISTA)¹⁵. It is a EU sanctioned project and time-scales for the project are unknown. This is due to the uncertainty of the requirements of the CEN and BSI standards¹⁶.

1.1.3 Packaging Development

At one time packaging development was considered as a separate topic tagged on to the end of the development programme almost as an afterthought. Now the situation is different and the development approach is a totally integrated one^{17,18}. This situation has, however, changed in recent years. Research and Development (R&D) expenditure has tripled since 1990¹⁷. However, the number of new innovative drugs in the pharmaceutical sector approved by the Food & Drugs Administration (FDA) each year has not shown a comparative upturn¹⁷.

At the same time other factors have conspired to complicate the registration situation, increasing the amount of data that has to be supplied which again, slows down the development process¹⁸. The manufacturer could reclaim this additional development cost by increasing the cost of the product, but today in the current economic climate, this is not possible and many pharmaceuticals are finding that their prices are being reduced rather than increased¹⁸. What options, therefore, does the manufacturer have?.

He can:

- Reduce the testing carried out, but in fact the requirements to develop and introduce a new pack are forever increasing.
- Do the development programme quicker by better planning and optimising the development approach, thus the pressure is on to make

the development process more effective and this means integrating all aspects overlapping the development wherever possible.

Glass, being so inert, does not present a very interesting problem to the Packaging Technologist. However, once plastics are involved the situation changes and the regulatory authorities for example, are much more interested in the composition and performance of the package¹⁸.

New Chemical Entities (NCEs) are so few and far between these days that companies regularly look at their ageing products with a view to revamping them by means of new presentations^{17,18}. One way to do this is to repackage the product in a more sophisticated way.

Occasionally the pack and product administration system cannot be separated, an example is a pump container for aerosols or a powder dispenser such as the spin-haler. Thus one cannot separate the pack and the product just as one cannot physically separate the product and the pack, therefore, they cannot be separated in regulatory terms¹⁸. A drug is affected by the packaging, both in practice and in the eyes of the regulatory authority. For example, in the United States of America (USA) a parental drug produced in a plastic container, even an old drug such as sodium chloride (saline) does not fall within the category of Generally Recognised As Safe (GRAS), but is regarded as a new drug. (Federal Food and Drug Cosmetic Act S201(P))¹⁸.

If you cannot separate the product and the pack whilst the products are becoming more sophisticated, it is not surprising that there is increased regulatory attention on the pack¹⁸.

In packaging development the aim must be to try and develop a pack for worldwide use. At the same time the pharmaceutical development department will also be trying to develop one product worldwide¹⁸.

This trend, however, will be countered by marketing developments trying to obtain precisely the right product for each market¹⁸. Just as market needs differ, local regulatory agencies may also have different requirements. Marketing departments are also reducing the number of variants required and standardising the packaging components to reduce the number of presentations in the market place¹⁸. But what about all the different regulatory agencies, of which there are over 150?¹⁸.

In regulatory terms the situation is not quite as bad as it might appear. If we look at the world market, we will see that Europe represents at least 27% of the market, the USA 27% and Japan not far behind at 18%¹⁸. In total, this represents nearly 72% of the total market. The situation may be further improved if the International Conference on Harmonisation (ICH) between these three areas eventually comes to an agreement¹⁸. If this happens, the multiplicity of requirements will be significantly reduced. Although, some harmonisation between the three is taking place it would seem that at present, in regulatory terms, the world has split into three different types of system: Europe, USA and Japanese. Other countries tend to follow one of these 3 approaches¹⁸.

1.1.4 Advances in Technology

There have been many new developments in recent years, such as covert and overt anti-counterfeiting features; more child resistant materials and advanced forming technology to reduce the amount of material used and to achieve more complex pocket designs. There has also been developments in blister sealing tool designs to achieve a tighter stronger blister pack¹. There is also ongoing research into pure aluminium only base laminates to reduce cost, and Cyclo Olefin Co-polymers (COC) and PVC / PCTFE films to give improved moisture barriers^{19,20}. There has also been developments in desiccated base films, by introducing a desiccant scavenger as a coated film under the product contact layer (heat seal lacquer) within the base laminate^{20,21}.

These new advances in technology have led to more complex designs and a need for tighter control over specifications and test requirements¹⁸. Any failure of the packaging system may result in ultimate failure of the active product to administer its required dose^{1,2,8}. For these reasons careful consideration of materials, equipment and design is essential. One of the most significant advances in pharmaceutical packaging is the unit-dose blister pack^{1,2,5,8}.

1.1.5 Innovation in Pharmaceutical Packaging

With the accelerated pace of globalisation pharmaceutical companies are faced with notable increases in the complexity of their organisations and processes. Therefore, the need to create packaging strategies and implement them swiftly and efficiently has become ever more demanding. Coupled with the increasing regulatory requirements, technical and marketing challenges, packaging innovation has become paramount to the future growth and success of the pharmaceutical industry^{22,23}.

The basic requirement for maintaining product integrity and patient safety still remains top priority within the industry. However, this is becoming increasingly difficult with the worldwide distribution of pharmaceutical products in extreme climate and environmental conditions, whilst being forced to reduce the cost of goods. Furthermore, balanced against increasing costs in the fight against counterfeiters, as well as enhancing patient compliance, child resistant packaging, tamper evidence and the need for higher barrier films the old blister pack, bottles and cartons may no longer be suitable for the new market requirements^{22,23}.

This section has focused on presenting an overview of the pharmaceutical industry; the following section gives an introduction to the role of blister sealing within this sector.

Chapter 1 Section 2

1.2 General Introduction into Blister Sealing

The materials of interest in the present study are used to form blister packs for semi and solid dose products supplied within the pharmaceutical industry. A blister pack is produced by forming pockets in either an aluminium type base foil or polymer based laminate using a pressure driven forming die²⁴. The pockets are filled, typically with a tablet or capsule, a foil lidding material (top foil) is then heat sealed to the base material (bottom foil)²⁵. Tablets and capsules are usually dispensed by pushing through the lidding foil, although some variants employ a peelable lidding foil, generally used for child resistant blisters²⁴. The importance of the adhesive function within the blister pack is critical to the dispensing process, it also guarantees the protection of the product throughout its shelf-life²⁴, and protects the material under stressed conditions, both when forming the blister and at extreme climatic conditions²⁵.

1.2.1 Problems Associated with Blister Packing

The attainment of successful blister packaging is not without its problems. If any containment of the blister pack is breached, resulting in moisture and any extraneous contaminants migrating into the product it may cause instability of the drug product and at worst case mean the prescribed dose will not be administered²⁵.

Examples of product failure are as follows:

1. Materials are prone to delamination between the plies, such as the Orientated Polyamide (OPA) layer within the PVC/aluminium/OPA base material.
2. Pinholes and splits can also be experienced during forming.

3. High temperatures are also required for rotary sealing, which can cause the print on the lidding material to lift.
4. Ingress of moisture through the seal mainly through the product contact (PVC) layer within the base laminate.
5. Retained solvents used as part of the printing process trapped inside the lidding material which can cause handling problems on line, also a distinct odour can be given off.
6. More recently problems have been experienced with the implementation of the revised ICH guidelines for the Asian market with the increase in temperature and humidity storage conditions for product on stability.

One of the most critical aspects of the process is material selection at the development stage of a product^{7,18}. Careful consideration of the requirements of the product is of the uppermost importance. For example the blister pack may require an additional barrier from moisture, oxygen or light to protect the drug product^{1,7,18}.

All these points must be considered when selecting the material. To give an example, the aluminium / aluminium blister is the ultimate moisture barrier²⁵, it also protects the product from light²⁴. There are also clear base films such as straight PVC and PCTFE that give very good clarity, PCTFE also giving a good moisture barrier¹⁹. However, both materials would not be suitable for light sensitive products, so to enhance this barrier a pigment in the form of titanium dioxide can be added to make the film opaque. If you need total product protection, or if the product will be exposed to extreme climatic conditions then the tropicalised blister could be considered, this consists of a second aluminium base film for additional protection²⁴.

1.2.2 Pack Design and Blister Layout

During development it is imperative that the blister layout has been appropriately designed with the maximum distance from the edge of the pocket to the edge of the blister card, ideally 5.0 mm, with a minimum of 3.0 mm²⁴, as described in **Chapter 2**.

One of the most important features of the blister design is the type of knurling pattern used, it can be positive or negative, pyramid or dimple design²⁴. It is a very complex and detailed subject that requires the knowledge and expertise of suppliers, both of the blister films and the sealing equipment, this is also discussed further in **Chapter 2**.

1.2.3 Blister Sealing Equipment

It is important to note that there are two main types of blister sealing machines; a rotary type that is in continuous motion and platen, which is an intermittent motion machine²⁶. There are advantages and disadvantages associated with both, in particular, rotary gives a more uniform seal because of the continuous seal roll design, whereas platen sealing gives a flatter more cosmetically acceptable blister, giving a stronger peel strength between the lid and the base laminates because of the even distribution of the seal pressure between the top and bottom sealing plates, and the additional dwell time to seal the blister²⁶.

The critical parameters of temperature, pressure and dwell time must be optimised to ensure the heat seal lacquer on the lidding material is transferred to the contact layer of the base material²⁵, usually PVC. If these parameters are not correctly set it will result in leaking blisters²⁶. Gross leaking blisters will be detected during the In Process Controls (IPCs) using the standard methylene blue dye test, but leaking blisters due to micro channels through the sealed area will not be detected by the dye test and may cause problems of stability over time⁸.

1.2.4 Protection and Use

In order to obtain a full blister evaluation it is necessary to consider a number of requirements. For instance, a pack may have to provide protection against:

1. Ingress from the atmosphere which may result in product deterioration, such as oxygen, moisture, carbon dioxide and micro-biological hazards^{1,8}.
2. Migration of product ingredients from within the product to the outside atmosphere¹.
3. Migration from the pack into the product, such as discolouration and softening of the heat seal lacquer^{1,8}.
4. Mechanical damage to pack or product^{1,8}.
5. The pack must also provide a convenient means for removing the product without exposing other units to the atmosphere or problems to the user²⁷. Furthermore, the pack must retain the product in good condition throughout its shelf life²⁷.

The aforementioned points need to be established by performing transportation and stacking tests over a range of temperatures and humidity's and as part of a formal stability programme¹. As with all pack selections, detailed knowledge of the product, the packaging materials and the process to be employed is an essential requirement⁴.

1.2.5 New Developments

As previously mentioned, there have been many new developments in recent years, such as covert and overt anti-counterfeiting features, more child resistant materials and advanced forming technology to reduce the amount of material used and to achieve more complex pocket and tool designs for a tighter

stronger blister pack²⁷. There is also ongoing research into pure aluminium only base laminates which can also significantly reduce material costs. A non destructive type leak test equipment is also being developed to replace the current destructive methylene blue dye test, this will allow the product to be re-worked²⁷.

Although there have been advancements in the blister sealing process there is still a need to develop new heat seal adhesives, new materials and more efficient seal tools, all with the prime objective of enhancing blister design to improve the overall effectiveness and the appearance of the end product. The present study focuses on evaluating the seal quality of new and existing blister lidding and base foils, calculating peel strength, heat transfer and moisture permeability data in blister foils. In particular this study will address the following aspects of blister seal packaging:

- New heat seal lacquers to give improved sealing characteristics.
- New primary contact materials with improved barrier to moisture.
- New base laminate that is more resistant to delamination.
- The heat transfer through primary contact blister foils.
- The peel characteristics of different blister packs.
- Development and qualification of new sealing tools.

This section has focused on the main considerations when developing the blister pack; the following section provides a Literature Review of the critical aspects of blister sealing within the pharmaceutical industry.

The Literature Review is divided into the following critical / key areas:

- The critical aspects of blister sealing.
- The principles of adhesion.
- The strength of adhesive joints.
- Surface analysis.
- Heat transfer into blister strips.

Chapter 2 Section 1

Literature Review

2.1 Critical Aspects of Blister Packing

The following sections discuss the critical aspects of the blister sealing operation, including the materials, additives and processes used to produce blister packs.

2.1.1 Materials and Laminates used to Produce Blister Packs

It is essential to understand the materials that are commercially available to the pharmaceutical industry to produce base laminate, the majority of which are detailed below.

1) PVC

The most widely used material is un-plasticised PVC (UPVC), typically ranging from 150 – 300 micrometre (μm) in thickness². Material thickness depends on the angle of draw, depth of draw and general protective (mechanical and climatic) functions required²⁵. Many companies offer grades of rigid, un-plasticised, non-toxic and odour free PVC to suit the pharmaceutical industry¹.

Coloured, tinted or opaque PVCs are also available. Some grades of PVC form better than others^{28,29}. It is therefore, necessary to perform machine trials and material testing in order to find the most suitable structure. PVC, being more moisture permeable than many of the plastics, is only satisfactory for products not susceptible to moisture, or with products requiring short shelf-life protection^{28,29}. Against oxygen, PVC provides better protection than most plastics^{28,29}.

It should be taken into consideration that certain organic materials will permeate through or soften PVC by means of a plasticising type effect^{1,28}. Therefore, items containing certain volatile constituents may not be suitable for PVC blisters²⁸. Due to the excellent clarity, and forming characteristics of PVC, and the fact that the structure of PVC can be easily modified it is used as the base carrier for other less permeable coatings or laminates, such as Polyvinylidene Chloride (PVdC), Polyethylene (PE), and PCTFE^{19,28,29}.

Impact modified PVC is another alternative, this material forms faster than the standard UPVC but gives lower protection to moisture permeation¹.

2) Polystyrene (PS)

Some early use was made of this material, which also shows good clarity and forming but has greater moisture vapour permeability than PVC^{1,28,29}.

3) PVC Coated with PVdC or Laminated with PVdC Film

PVdC coatings were very popular when laminated to cellulose films because of their low moisture vapour permeability. Coatings have been applied to PVC over a range of weights from 10 to 90g/m², 36g/m² provides a coating of approximately 25µm².

PVdC or Saran® film has also been laminated to a PVC base film. The main problem with the use of either film or coating of PVdC is the low bond-strength, and frequently it can be easily peeled away from the base PVC¹. Experience has shown, that once the material has been formed into a blister strip the bond strength appears adequate, but a poor bond at the edge of a blister strip could reduce moisture protection²⁶. However, to date the PVdC has invariably been on the outside of the blister. With PVdC in contact with the forming mould some sticking has been noted and this could increase if a build-up occurs with longer

runs^{28,29}. Careful attention to cooling or reverse air thrust can help reduce this effect²⁷. Ideally, the PVdC should be on the inside of the blister strip but difficulties have been experienced in achieving a good PVdC bond to the heat seal lacquer on the lidding material²⁷. However, this situation has now improved and PVdC coated foil can now be used as a contact layer to bond to the lidding material¹⁴.

4) PE / PVC

This material, again with the PE on the outside, was an early introduction in an attempt to improve the moisture-vapour protection of PVC^{1,5}. However, the improvement achieved was relatively small for the cost involved and some loss of clarity also occurred^{1,5}.

5) High Density Polythene (HDPE)

This was again used in earlier work but produced difficulties in forming and adhesion to the lidding material^{1,5}. This, coupled with poor clarity, has prevented any further progress although there appears to be no reason why it should not form satisfactorily on the more sophisticated machines used today^{1,5}.

6) Polypropylene (PP).

PP has been used with limited success, this is primarily due to the high forming temperature required and the fact that some machines have insufficient heat output to cope with the increase in temperature⁵. The material is also difficult to control, excessive thinning of the blister is likely to be a problem and thereby reduce the barrier properties⁵.

If thinning does occur, then the required moisture protection is not achieved⁸. Blisters are also translucent and tend to show imperfections, usually in the form of striations due to non uniform forming, the softening point is therefore, critical.

20µm PP coated with 40g/m² PVdC gives three to five times the moisture protection of UPVC^{5,30}.

7) PVC / PVdC / PE / PVdC / PVC

This material has been developed and used with success in Japan. The original construction was:- PVC 125µm/PVdC10µm/PE 30µm/PVdC10µm/PVC125µm

Experience with machine trials has suggested moisture vapour protection approaching PCTFE^{1,4}. Although it forms well, it has some restrictions due to the overall caliper indicating the need for thinner material. Such a material has now been developed^{1,5}.

- PVC 100µm/PVdC 12g/m²/PE 25µm/PVdC 12g/m²/PVC 100µm

Having the more moisture protective material, (i.e. PVdC) sandwiched between layers of PVC does appears to provide more control, in terms of stretch and gives up to five times the moisture protection of UPVC^{1,5}.

8) PCTFE

PCTFE is the most impermeable plastic film to the transmission of water vapour, and is widely used in the pharmaceutical industry³⁰.

PCTFE type combinations with PVC are also commercially available using Low Density Polyethylene (LDPE) as a laminate or resin in conjunction with adhesives^{1,4,5}. The base PVC is usually 150 – 250µm in virtually all combinations of PVC with other materials, it is the PVC which takes the shape of the mould, the other material being stretched with it under warm conditions^{1,5}. Some machines have incorporated top and bottom heaters through which the web runs in an endeavor to apply the correct amount of heat to two different materials⁹.

However, as the softening temperatures of PVC and PCTFE are so widely different, PVC being 90°C and PCTFE 120 - 215°C, the heat cannot soften both plies without causing an adverse effect on the other¹⁹. Although, one key advantage of laminating PCTFE to PVC is that the moisture vapour protection of PVC can be improved up to 12 times⁸.

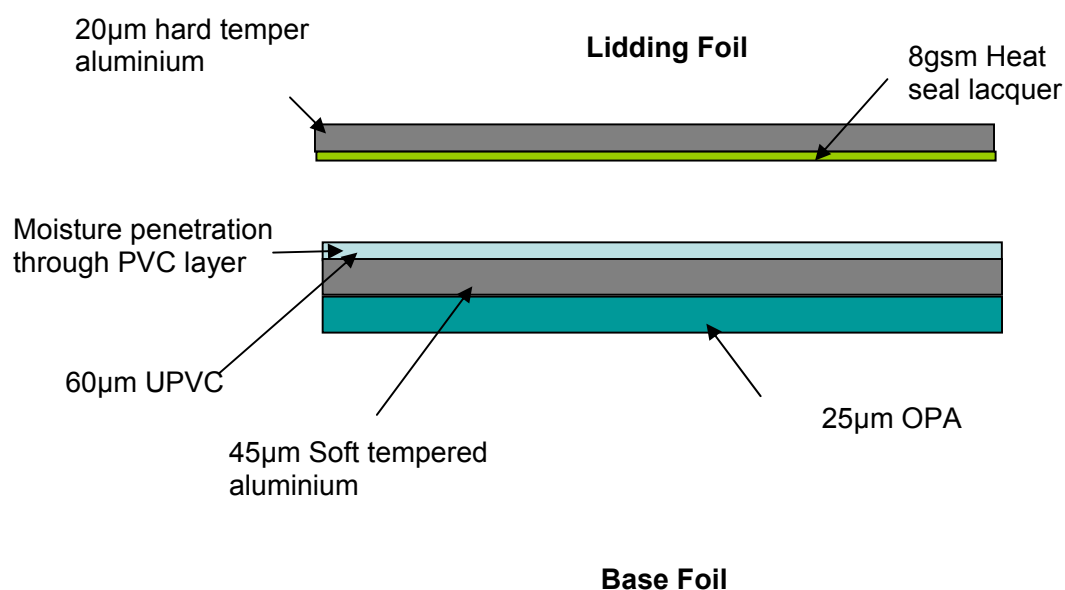
2.1.2 Types of Blister Pack

In order to study the new material types and blister designs it is essential to understand the blister designs that are currently being used in the pharmaceutical industry, some of which are detailed below.

Push-Through Blister

One of the most common structures for double foil blister materials used throughout the pharmaceutical industry is shown in Figure 1, this is of the push-through type.

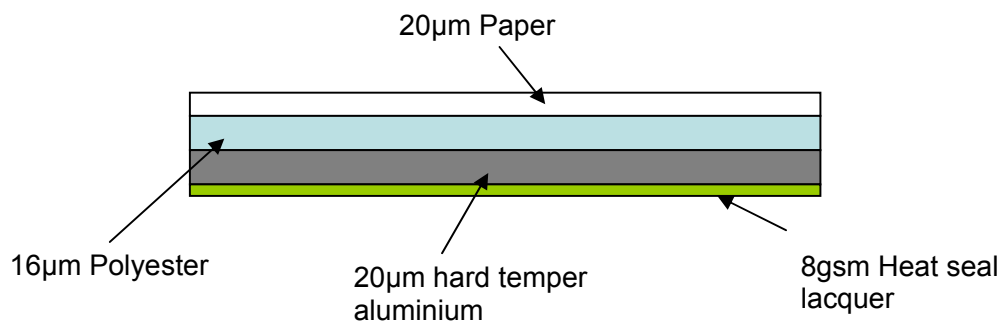
Figure 1 – Push through Blister⁸



Peelable Lidding Foil

Peelable lidding blisters have an outermost paper layer bonded to a polyester layer which, due to its strength prevents the product being pushed through the lidding foil^{12,31}. By sealing the lid foil within a tightly controlled temperature range, it is possible to achieve a seal that is permanent enough to prevent moisture ingress and is weak and semi permanent enough to allow the two layers to be peeled apart¹², see Figure 2.

Figure 2 – Peelable Lidding Foil^{8,12}



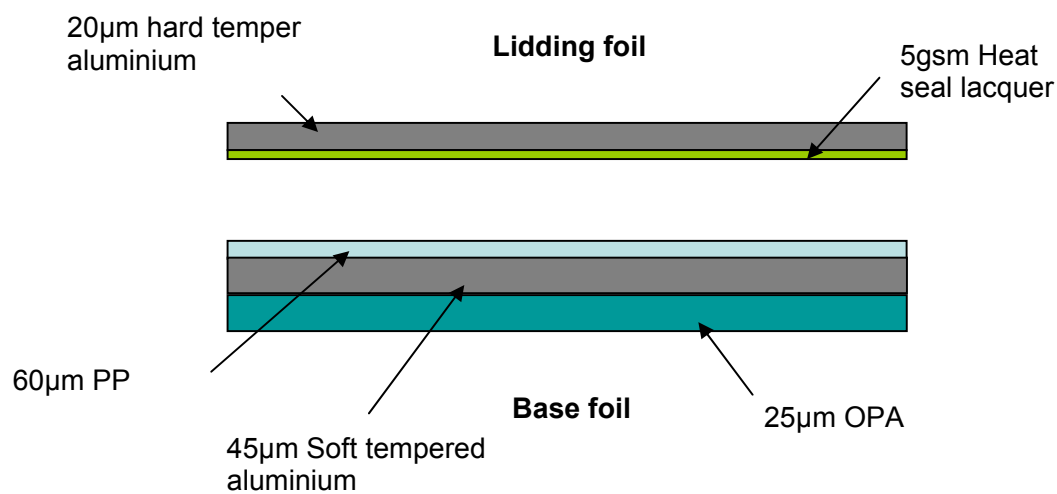
This structure can be used to produce blister packs, which meet child resistant requirements in some markets^{12,32}. Also, the paper surface is more amenable to on line printing and individual pocket identification²⁸.

Validation of peelable lidded blisters can be more critical than for conventional push through blisters for several reasons. Firstly, the paper layer is a barrier to heat, and requires significantly higher sealing temperatures and longer dwell times to achieve a satisfactory seal²⁷. This can mean that the blister thermoformer is operating at or beyond the limit of its capability²⁷. Secondly, it is essential to validate both the higher as well as lower operating temperatures to ensure that packs are adequately sealed whilst retaining their peelable properties²⁷. To overcome the problem with excessive sealing temperatures the heat seal lacquer can be pre-heated, either by a pre-heating station or contact with the sealing roller prior to sealing²⁷.

PP Based Materials

Alternative lid and base foil materials are available which use PP as the base sealing layer instead of PVC, for environmental reasons, as detailed in Figure 3. This also necessitates a different lacquer on the lid foil and a higher sealing temperature to achieve an effective seal^{25,26}.

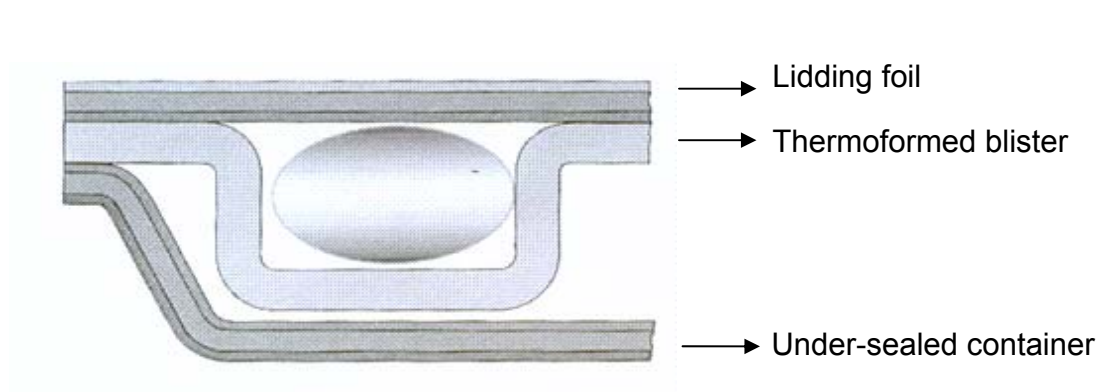
Figure 3 – PP Based Material⁴



Tropicalised Blisters

A tropicalised blister is a thermoformed blister pack with a single base foil pocket sealed to the underneath and covering the whole of the thermoformed film^{1,8,9}, as detailed in Figure 4. This has the advantages of compactness of the thermoformed blister combined with the moisture protection of a double foil blister. A specially modified machine is required to manufacture such a pack⁸.

Figure 4 – Tropicalised Blisters⁸



Lidding Foils for Pharmaceutical Blister Packs

The lidding foil used can depend on the type of opening required, either push through, peel or tear-off. The type of sealant and the child resistant properties can also determine the foil used³², reference Table 1.

Table 1 – Types of Lidding Foils and their Application²⁴

Method of opening	Application
Pushing through aluminium foil / laminate.	Pressure resistant products – Tablets / Capsules.
Peeling of aluminium foil / laminate.	Products not suitable for push through – Powders, friable (brittle) tablets and capsules.
Tear-off of sealed pack using tear off aid.	Fragile and pressure sensitive products.
Peel / push versions – Paper / Polyester (PET) / Al / heat seal lacquer.	Child resistant packs.

The following heat seal lacquered, coated or laminated aluminium foils, optionally printed and over lacquered can be used²⁴:

- Aluminium foils, thickness 20 or 25µm.
- Aluminium foil, embossed, thickness 30µm.
- Aluminium / paper laminates (25µm Al/35 or 40 or 50g/m² paper).

- Aluminium / plastic laminates (25µm Al/12µm PET).
- Aluminium / plastic / paper laminates (25µm Al/12µm PET/50g/m² paper).
- As well as any other possible combinations.

The heat seal lacquer must be compatible with:

- The inside layer of the base laminate, such as PVC, PP and PE.
- The method of opening.
- The product packed.

The compatibility of the product to be packed and the heat seal lacquer is of uppermost importance, as the substances contained in the drugs or components of the capsules / tablets may cause softening of the sealant²⁴.

Therefore:

- The seal strength may be reduced (leaking packs).
- A migration of drug may occur.
- An interaction between product and sealant may happen (tablets sticking to the bottom material).

Another factor having effect on the seal strength is the ageing of the material. The sealants used are organic substances which over the time degrade by exposure to oxygen and atmospheric moisture^{5,6}. Providing the suppliers agreed storage and transport conditions are not compromised, the materials have a storage time of at least 18 months before use⁸.

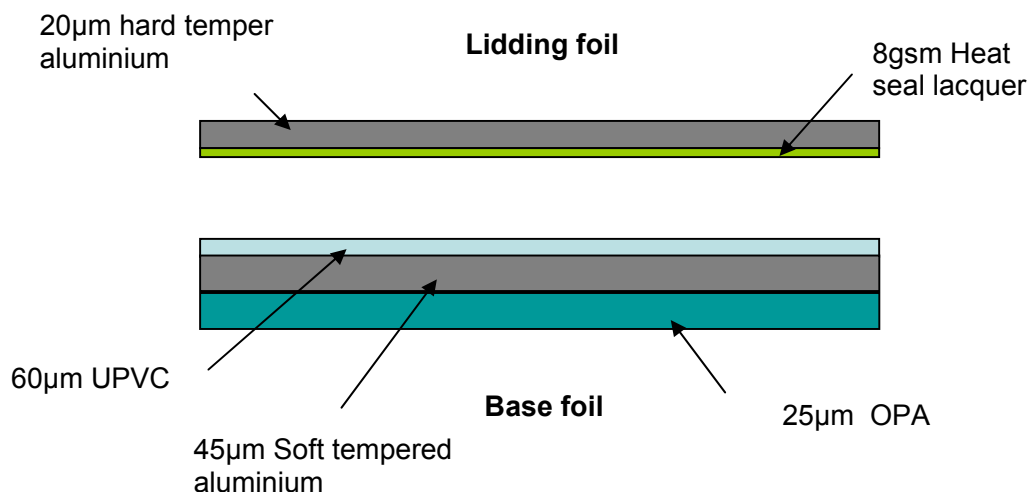
An additional parameter to be observed is the adjustment of the packaging materials to the production condition. Temperature differences may generate the creation of condensation water resulting in a bad sealing and causing damage to the product²⁷.

Double Foil Blister (Formpack) Sealing

Formpack can be used as a base laminate for single unit dose blister packs for a wide range of sensitive pharmaceutical products, which need the utmost protection for long shelf-life, even under tropical conditions. Formpack is a three layer base laminate²⁴:

OPA / aluminium / sealing layer, mainly PVC, as detailed in Figure 5.

Figure 5 – Double Foil (Formpack) Blister



More and more of the pharmaceutical industry is concerned about the growing volume of counterfeited pharmaceutical products^{24,33,34}. Formpack blisters give a higher degree of protection over other types of packing²⁴. In addition Formpack can be printed between the aluminium and OPA laminates. This can only be done during the production of the laminate²⁴. Studies have been successfully carried out to evaluate a new heat seal lacquer and coldform (Formpack) base laminate. The results of these studies are detailed in **Chapter 4**.

An ever increasing demand for protective functions, mainly with regard to moisture and UV light, is being made of pharmaceutical packaging⁸.

This is caused by:

- A high sensitivity of the product to light, moisture and oxygen.
- The demand for a barrier against the diffusion of components and active product.
- Substances such as essential oils and alcohol.
- The use of the products in tropical regions.
- The need for the products to have an extended shelf life.

The conventional blister pack having a base laminate made from plastic film cannot in all cases adequately guarantee that the product retains its quality during the required shelf life^{24,33,34}. It is known that thickness of the plastic film after deformation is only approximately 34% of the original thickness in the thinnest area²⁴. With Formpack water vapour can only migrate through the sealed seam²⁴. The migration of moisture into the cavity of the thermoformed PCTFE laminate is twelve and thirtyone times higher respectively²⁴, as shown in Table 2.

Table 2 – Comparison of Permeability of Formpack and PCTFE Laminates

Material	Moisture Vapour Transmission Rate (MVTR) (Mg/d: 40°C/90% RH)			
	Sealed seam 3mm wide	Cavity	Blister total	Ratio
Formpack - 25µm OPA / 45µm Al / 60µm PVC	0.0016	0.0000	0.0016	1
51µm Aclar UltRX 2000 / 200µm PVC	0.0058	0.0130	0.0188	12
15µm Aclar RX 160 / 200µm PVC	0.0058	0.0434	0.0493	31

The Formpack laminate is formed by cold forming without any heat, as happens with PVC and / or PCTFE thermoforming²⁷.

To determine the blister form and the plug geometry from the Formpack blister, Alcan, who are a major supplier of Formpack to the pharmaceutical industry has developed a suitable computer programme called – STREC^{24,35}. This allows computing the blister form in conformity with the dimensions of the product to be packed, without the danger of partially over stretching the material^{24,35}.

Although, during the forming process of Formpack pinholes or cracks in the aluminium of the cavity can still occur even if the calculation for the design of the forming tool was carried out^{24,35}.

These can be caused by:

- Defective plugs.
- Excessive deep drawing.
- Faulty manufactured forming tools.

Problems as a result of these faults could be:

- Persistent pinholes in the aluminium.
- Cracks in PVC film / aluminium.
- Cracks in aluminium / OPA film.
- Cracks in PVC film / aluminium / OPA film.

All of which could influence the shelf life of the product.

Pinholes of >100µm in diameter are detectable by automatic light transmission inspection though the base laminate immediately after forming²⁷. These pinholes are not always detectable during the standard vacuum leak test as the plastic films within the structure, such as the OPA and / or inner sealing coat; PVC, PE, PP, or Surlyn are usually not damaged²⁷. Nevertheless, it is possible that moisture penetrates into the cavity after a certain period and thus affects the shelf life of the product^{24,27}.

2.1.3 Additives used in the Manufacturing Process of Blister Films

To gain a better understanding of the blister manufacturing process it was essential to understand the additional process constituents and additives that can be incorporated at the manufacturing stage to enhance the mechanical and physical properties of the blister films.

Plastic flexible blister films make extensive use of different additives to meet different plastic performance requirements and processing capabilities³⁶. Additives are dispersed in a plastic matrix without significantly affecting its molecular structure³⁷. The types of additive used in the production of blister films are summarised in Table 3.

Table 3 – Additives used in Blister Production^{37,38,39,40}

Additive	Definition	Function
Antiblocking Agents	These agents are substances that prevent or reduce blocking, such as with film or sheet, when added to plastic compound or applied to their surface.	<p>The blocking action is an adhesion between touching layers of plastic, such as one that may develop under pressure during storage or use.</p> <p>The extent of blocking depends on temperature, pressure, humidity, physical properties of the plastic itself, and processing conditions. If the plastic has a low softening point or if it picks up moisture readily, it will have a greater tendency to block than with a plastic which has a high softening point and does not pick up moisture.</p>
Antioxidant Agents	An antioxidant is defined as a substance that opposes oxidation or inhibits reactions promoted by oxygen or peroxide.	These agents are of major importance because they extend the plastic's useful temperature range and service life. In the specific case of plastics, they retard atmospheric oxidation or the degradative effects of oxidation. For this reason, they are also known as ageing retardants.
Stabilising Agents	Stabilising Agents are additives that reduce the degradation effects caused by the result of irreversible chemical reactions or physical changes that can ultimately lead to product failure.	All plastics (polymers), natural or synthetic, degrade under normal use conditions with progressive loss in aesthetic appearance and mechanical strength. Time periods for the different plastics can range from less than an hour to many decades. These agents vary considerably in the rate at which they degrade. For many applications, degradation must be inhibited by stabilisers to assure the required product shelf life.

2.1.4 Types of Blister Sealing and Forming Equipment

Relevant to the present study on the subject of blister sealing it is essential to get a full understanding of the different types of blister sealing and forming equipment, and a comparison of the advantages and disadvantages of rotary and platen type blister sealing. **Appendix 1** shows the main components of both rotary and platen sealing equipment and gives a schematic diagram of the layout of the production lines.

There are four basic types of automatic type equipment, as used in the pharmaceutical industry.

- 1) Intermittent motion machines. Each stage is carried out on a flat platen station, the web being moved from station to station by an intermittent motion; to soften the web, form the blisters, fill between stations, seal the lid foil and finally cutting out the finished blister. Platen machines offer greater flexibility in blister design^{2,5}.
- 2) Continuous motion machines. On this type of machine all operations, except punching out are performed as a part of a continuous process on drums, or cylinders. This type of equipment can achieve higher speeds and therefore, higher output. Depth of draw and angle of draw are more critical on this type of machine for both distribution of wall thickness and ease of release from the mould to avoid jerking of the web^{2,5}.
- 3) Combination of intermittent motion and continuous motion machines. This is a more recent innovation and carries out the forming operation, pressure or pressure plus plug assist on platens, then transfers by a free or tensioned loop to a continuous motion for filling and sealing. Punching out remains intermittent. The sealing can also revert to intermittent motion^{2,5}.
- 4) Reciprocating motion on a platen operation, thereby, changing it into virtually a continuous motion operation^{2,5}.

Rotary vs Platen Blister Sealing

The rotary process offers more control on dwell time and satisfactory control of heat, but uniform pressure may be more difficult to achieve due to imperfections or lack of uniformity in the web^{24,26,27}. A good impression may therefore, be created by adjustment of pressure in order to compensate for such unevenness to circa 10^5 Pa. The continuous motion machine relies on an impression, or nip being obtained between two rollers, one of which is heated to circa 225°C , while the other is cooled and contoured to take the blister shape to circa 18°C ^{24,26,27}. The seal is only made at the tangential contact of the two rollers, and therefore, the dwell time always has to be extremely short, circa 0.7 seconds^{24,27}. This type of seal probably has better control, by tension on the uniformity of seal achieved across the web^{24,26,27}. In addition a good temperature control can be maintained by using smaller diameter seal rollers²⁷. The effectiveness of the seal is normally checked both visually (uniformity of impression) and by vacuum tests^{24,26,27}. The pattern of the sealing tool is normally a lattice or sunken pyramid type design, as depicted in **Appendix 2**. Figures 6 / 7 & 8 detail both the platen and rotary sealing processes²⁷.

Figure 6 – Platen Sealing Thermoformer²⁷

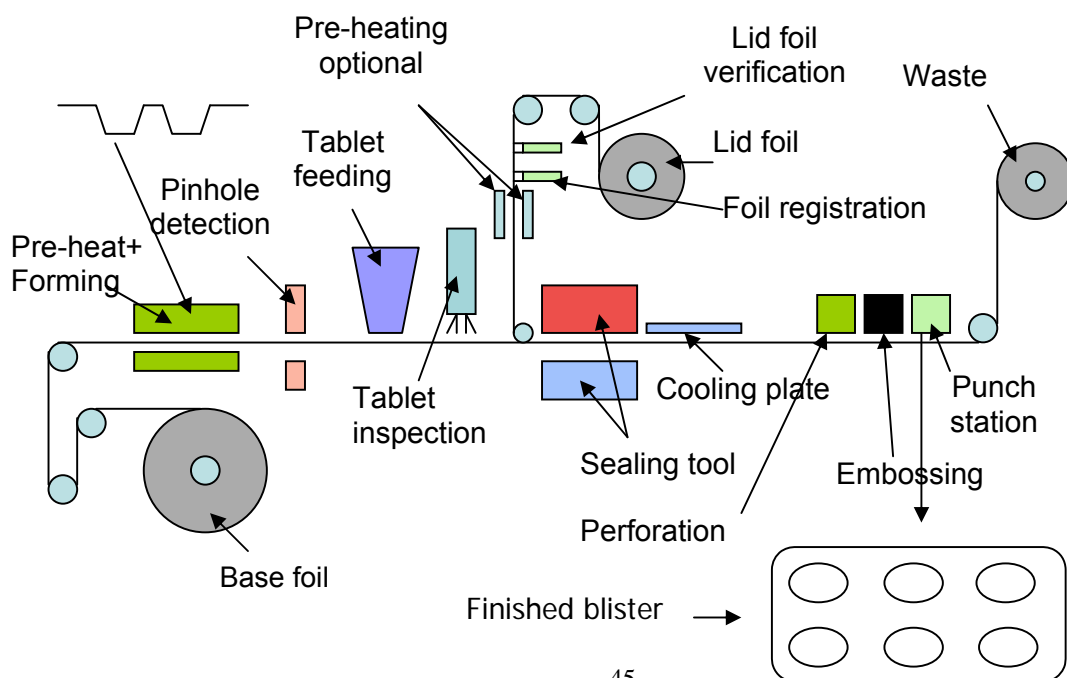


Figure 7 – Rotary Sealing Thermoformer²⁷

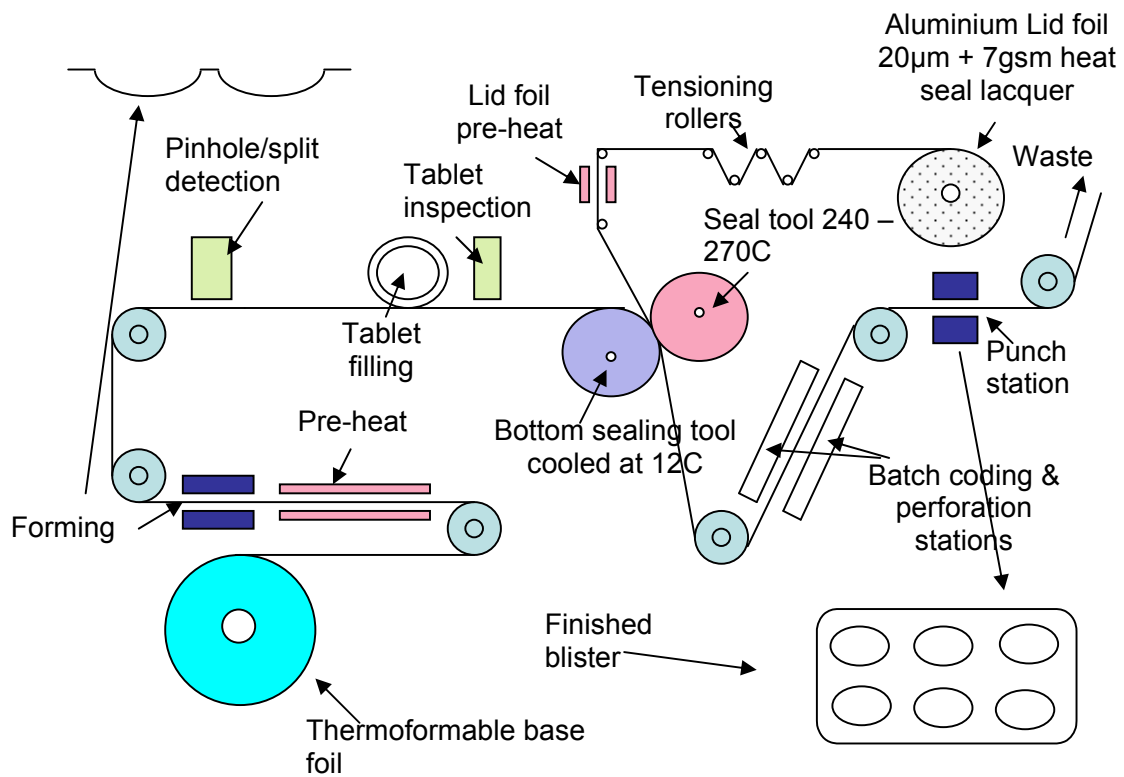
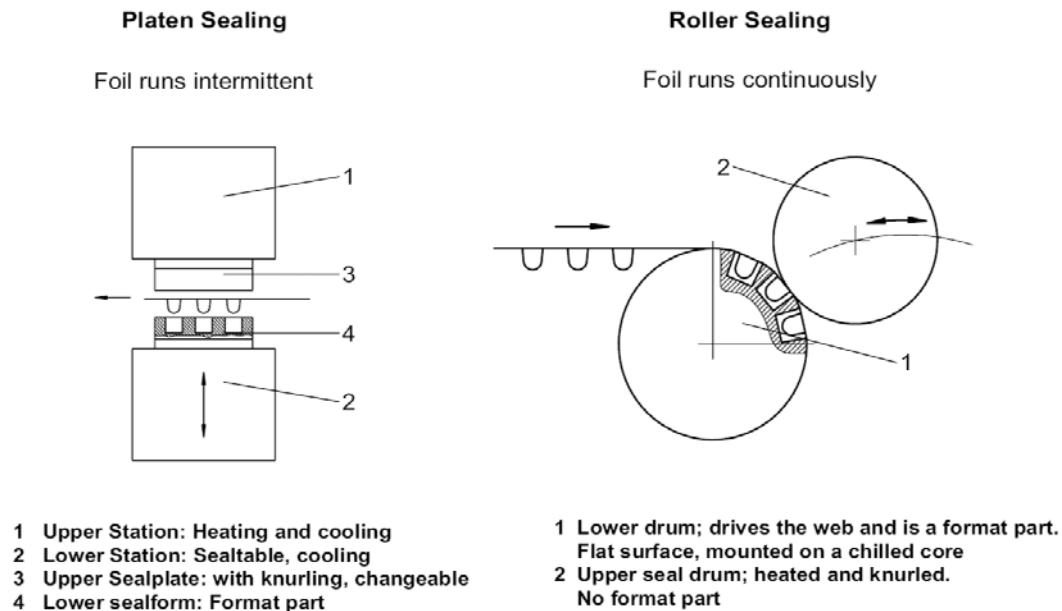


Figure 8 – Schematic of the Rotary and Platen Sealing Stations⁴¹



The roller sealing can reach a linear speed up to 17 m/min.
While platen sealing up to 10-11 m/min.

The rotary sealing allows higher machine speeds, but has the following disadvantages compared to the plate sealing method⁴¹:

- Since rotary sealing is a line sealing method, it requires high sealing wheel temperatures.
 - Stronger variations in the tightness of the pack.
 - Difference in the specific sealing pressure due to line sealing.
 - Vaulted (curled) blisters may cause possible problems during cartonning.
- For transport reasons the geometry of pocket has to include a steep edge angle (approx. 75°).

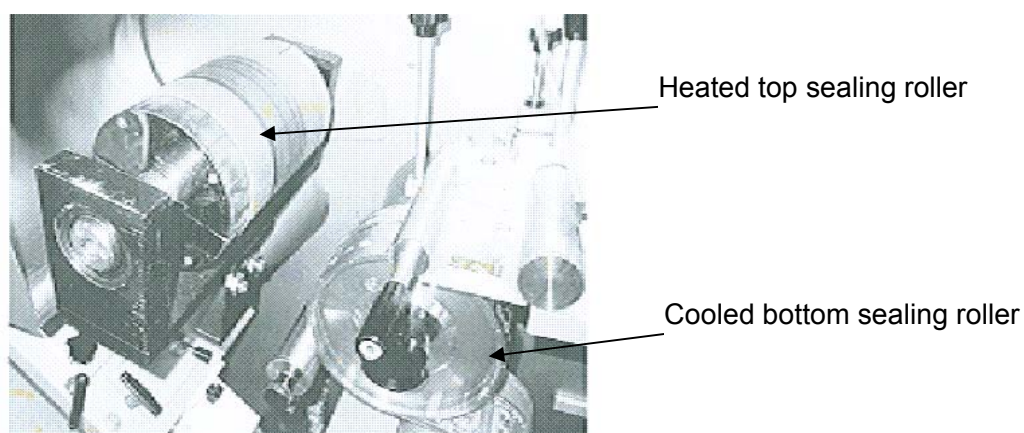
Plate sealing is an intermittent process which is only possible at low machine speeds^{26,27}. The sealing pressure required is higher than that for rotary sealing^{26,27}. The advantages offered by this process are mentioned below^{26,27}:

- Lower sealing temperature.
- Uniform sealing pressure.

- Flat packs.
- No special format design adjusted to the sealing die necessary.

Heat sealing is generally expressed as a combination of three factors; temperature, dwell time and pressure⁴². However, careful consideration to cooling, the width of seal and seal pattern are also essential in achieving a good seal⁴². The rotary sealed blister foil strips are sealed between two rotating wheels. Generally, the top wheel is heated and the bottom wheel is constantly cooled either by air or water²⁷. The temperature is applied and controlled by direct heating involving elements housed inside a cylindrical wheel, see Figure 9. The temperature is controlled electronically to $\pm 15^{\circ}\text{C}$. A thermostat is used to control the temperature around a pre-determined optimum setting²⁷. This allows a constant heat source when the large mass of the sealing wheel either retains the heat or conducts the heat away²⁷. The large mass of the heated sealing wheel contains hotter and cooler zones depending on the area mass, the centre of the wheel retaining more heat²⁴. The differing degrees of contraction and expansion caused by the variation in mass gives rise to pressure differences along the blister, causing heavy or light seal impressions²⁷.

Figure 9 – Rotary Sealing Arrangement²⁴



The heating method can also involve the pre-heating of the lidding material which raises the temperature of the seal lacquer prior to final sealing. The

temperature of the top sealing wheel has been optimised according to the dwell time period employed. This represents the contact time between the source of the heat and the surface being heated⁴².

The actual dwell time is very small due to the small area of contact between the two sealing wheels. Therefore, to compensate for the extremely small contact area a much higher temperature than other conventional sealing methods is used⁴².

Types of Blister Forming Equipment

Research has shown that the Moisture Vapour Transmission Rate (MVTR) of a blister is influenced by the types of forming equipment and forming conditions⁸, the following section briefly describes the different types of forming processes and the importance of good film thickness distribution.

Blister machines are based on the fact that a film softened by heat⁴³ can be formed in a mould by means of:

- Mechanical forming – between male and female moulds.
- Vacuum – whereby the softened film is drawn into or over a mould by negative air pressure.
- Pressure – in which the softened film is forced into or over a mould by positive air pressure. This may also be used as a final stage of a mechanical forming operation.
- Pressure plus plug-assist – mechanical and pressure.
- Vacuum plus plug-assist – mechanical and vacuum.
- Vacuum and pressure.

The distribution of wall thickness for a given blister depends upon many factors⁴²:

- The type of material.
- Thickness (caliper) of the material.
- Blister design, such as the depth of draw/shape of pocket / angle of draw.
- Uniformity of temperature.
- Heating cycle, type of heating and how applied.
- Speed for forming the web.
- Type of forming, vacuum, pressure and / or mechanical.
- Layout of design related to web.

For an identical blister using female moulds, it would be expected that a vacuum formed blister is thinner at the top of the blister but thicker near the base web²⁴. A pressure formed blister gives generally a better thickness distribution, although slightly thicker at the top compared to the supporting walls⁴².

Pressure + plug assist offers the more uniform distribution²⁶. Distribution of wall thickness can be checked by measurements on a graph like lattice marked on a surface of the base web⁸. The degree of thinning is then indicated by the dimensions and distortion of the squares. In-built strain within the blister can be observed under polarised light. In all instances the blister should be adequately radiused both at the base where it meets the flange and at the top²⁴.

Heating and Forming

The heat necessary to soften the web is provided by either infrared heaters (continuous) or by thermostatically controlled heating elements on the pre-heat station of platen or intermittent machines²⁷. The temperature applied varies according to the type of machine and depends on a time / speed relationship⁴².

2.1.5 Critical Aspects of the Blister Sealing Process

So far, this review has discussed the type of materials employed and equipment used to produce a blister pack, but to gain a full in-depth knowledge of the complete process it is imperative to understand the critical aspects of the blister sealing process:

Heat Seal Strength

Seals are typically made by applying pressure with heated surfaces to opposing faces of the composite materials, melting the thermoplastic materials of the contacting surfaces⁴². In the case of blister sealing, the two contacting surfaces are generally the heat seal lacquer on lidding foil and the PVC layer on the base material⁴².

The process of making heat seals relies on the basic thermoplastic properties of the polymers on the inside seal layer of the blister film⁴². In theory, this welding process involves a dynamic fluid material moving under pressure⁴². A matching pair of sealing jaws is maintained at a constant temperature and brought together with the blister material between them²⁷. The thickness of the material and the minimum distance between the jaws and closing force dictate the pressure at the sealing interface²⁷. The dwell time during which maximum pressure is maintained is dictated by the line speed of the machinery, this is the time when the sealing tools are in contact with the material⁴². For rotary sealing the dwell time is between 0.1 to 0.7 seconds and for platen sealing around 1 to 2 seconds²⁷. The process assumes that the outer layer of the blister film is sufficiently heat resistant themselves to avoid melting and / or delaminating between the laminated plies⁴². Oriented plastic films of nylon, polyester or PP are the usual thermoplastic options^{43,44}. Pressure effects at the interface of seal layers can be enhanced by using serrated or ridge surfaces on the sealing tools that mate with complementary patterns in the closed position. Although recent developments have resulted in different types of tool designs such as,

negatively etched top sealing roller and plain top seal rollers for rotary sealing, but with an etched bottom drive roller, as developed as part of my research studies²⁷.

Sealing Process

After filling the formed bottom material, it is thermally bonded to the lidding foil in the sealing station. Sealing can be made in cycles (plate sealing) or continuously (rotary sealing), as previously described.

In order to obtain a tight seal, the following parameters have to be considered:

- Sealing temperature.
- Dwell time (machine speed).
- Sealing pressure.
- Surface geometry of sealing die.
- Flatness of sealing dies.
- Uniform distribution of temperature in the sealing die.
- Feeding of lidding foil free of creases into sealing station.
- Thickness variations of bottom and lid material within the range of tolerances.
- Tempering of lid material.

Sealing Temperature / Dwell Time

The required dwell time and sealing temperature depends on the thermal conductivity of the composite material. Since polymers do not have free electrons to promote thermal conduction, they are, compared to metals bad thermal conductors²⁴.

Thermal conductivity shows which quantity of heat passes through a body of defined volume at a certain temperature drop per unit of time²⁴. To confirm the

correct sealing parameters are being used, such as temperature, speed and dwell time, it is advised to calculate the thermal conductivity of the blister laminates. This is to determine the heat transportation through the lidding material into the drug product²⁴.

In theory, depending on the lidding foil used, higher sealing temperatures and / or dwell times maybe required. However, an increase in dwell time results in lower productivity.

To compensate an increase in temperature may be considered, but this may result in:

- Possible warping of the sealing dies (flatness).
- Longer heating periods.
- Longer cooling period.
- Thermal damage of outer side of material.
- Off-setting of printing inks.
- Reduced binding strength of adhesive to foil / paper.

The sealing temperature could be reduced by pre-heating either the heat seal lacquer on the lidding material or the PVC layer on the base material, (the softening point of the PVC being between 90 to 100°C)¹. Such pre-heating can be done by installing a heating table with direct heat contact²⁷. However, due to the low softening point of the heat seal lacquer, the inner side can be heated with radiant heat at a minimum distance²⁷. For child safety reasons, the laminate should require at least two layers preventing the child access to the drug product. However, from a technical sealing point of view, no paper should be used, because apart from the high thermal resistance, its moisture content will have negative effects when attempting to achieve a well bonded seal²⁷.

The high temperature required for sealing causes an evaporation of the moisture which at the same time reduces the sealing heat so that consequently the setting of the temperature has to be increased²⁴.

An increase of sealing temperature for the purpose of an increased machine performance does not only have the aforementioned effects, but also influences the product packed⁸. The bottom material also absorbs heat, and there is an exchange of heat between the inside layer and the product⁸. The product is additionally heated by radiation between the heated sealing surface and the air in the blister pocket²⁷. For this reason a study was carried out to determine the heat transfer between the sealing wheels at point of contact to the product using the laws of heat transfer. The results of this study are documented in **Chapter 4**.

Sealing Temperature Optimisation

Blistering machines vary widely in the configuration of heating elements and thermocouple controls to the sealing plates²⁷. However, there are a number of key points which should be followed in order to establish the optimum process window for any given combination of machine, material and pack configuration. The starting point for this investigation is the sealing temperature recommended by the material supplier, say for example 170°C. It is normal to commence trials well below this value at around 150°C, at a point where adequate sealing would not normally be expected to occur.

Before commencing the run, the actual temperature on the plate surface is measured using a hand held probe and is recorded at various positions over the platen. The machine would then be run for 10 minutes and the temperature on the machine readout noted at 0, 5 and 10 minutes, with a repeat of the hand probe readings immediately after stoppage. Blisters from all positions are tested for leaks, seal strength, burst strength, seal integrity, delamination of plies,

MVTR and are physically examined for cosmetic appearance. The whole process is repeated at 10°C increments until the upper limit is reached where material damage is evident, such as ripping, puncturing, discolouring or print removal. This will then indicate the upper and lower operating temperatures for the predetermined pressure and dwell settings. If the machine has the capability of variable tablet feed rate, sealing pressure and sealing station dwell time, then a much more complex matrix of sealing trials is required to establish a processing window covering all variables²⁷. A simpler alternative is to fix one or both variables by physically removing the means of adjustment²⁷. However, care must be taken to ensure that settings cannot be disturbed during maintenance²⁷. This approach and methodology will be used to determine the heat seal window for the development of the new robust lidding foils and heat seal lacquer in the present study, as detailed in **Chapter 4**.

Sealing Pressure

The closing of the sealing die is of critical importance in achieving a tight seal⁸. For a satisfactory seal the pressure over the whole sealing area has to be uniform⁸. During each cycle the sealing station has to operate at a constant closing pressure (platen sealing) and on a constant sealing surface for rotary sealing⁸. This requires absolutely flat sealing areas⁸. If these requirements are met, the seal obtained is so tight that no air channels are visible between the individual blister pockets (cavities) when removing the product by pushing it through the lid foil⁸.

Cooling

As a general rule 'HEAT IN' must be balanced by 'HEAT OUT'. The removal of excess heat may be necessary for several reasons:

- The heat, if retained by the pack, may be transferred to the product and give rise to physical or physico-chemical changes.

- The seal will not be effective until a certain lower temperature is reached.

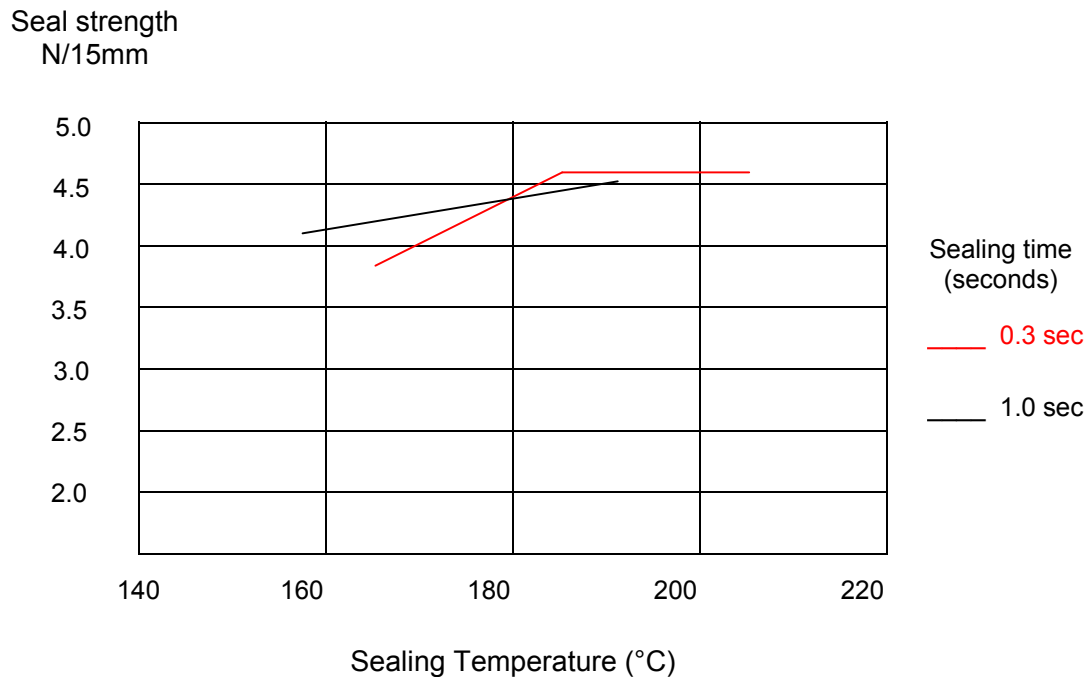
Cooling may be achieved by the reverse of the mechanisms by which heat is applied²⁴. If poor sealing occurs when the environmental temperature around the machine rises, the cooling mechanism should be one of the first factors to be checked⁸. The normal procedure to overcome this problem is to raise the temperature, increase the pressure and the dwell time, all of which could worsen the situation if the problem is related to the cooling system⁸. Having introduced the subject of heat sealing along conventional lines, one should be aware that many more factors must be considered in evaluating the effectiveness of a seal, all of which will be discussed more in-depth as part of this study.

Influence of Heat Seal Lacquer on Seal Strength

The selection of heat seal lacquer to be applied to the lidding foil has a direct impact on the seal strength²⁴. Besides the difference in strength, the different films also have different reaction temperatures²⁴. The softening point should be as low as possible, so that the machine can be adjusted to lower sealing temperatures or to higher speeds²⁴.

Decisive for the tightness of seal directly after the sealing process, i.e. in hot conditions, is the hot-tack of the heat seal lacquer^{8,24}. The strength of the seal in hot condition must be higher than the tension of the base and lidding webs²⁴. Figure 10 shows a firm seal when sealed to PP, where the hot-tack has to give a minimum 4.5 N/15mm seal strength.

Figure 10 – Hot Tack of Lacquer RP424 when Sealed to PP⁵



In Figure 10 the seal area under test was 5mm x 45mm, with a separation speed of 25m/min and a sealing pressure of 0.8 N/mm². The material construction of the test specimen was a 16µm aluminium lidding foil with a heat seal lacquer coating weight of 3.5g/m² and a 191µm base material²⁴.

Faulty cavities due to insufficient coverage of heat seal lacquer can be detected by unsealed channels from the edge of the blister to the cavity by transmitted light microscopy²⁴. By means of electron microscopy one can easily detect the channel after removal of the push through foil. Micro channels will cause problems with stability over time⁸. This defect is normally not detected by the vacuum test.

The composition of the heat seal lacquers is dependent on the type of plastic material which is to be sealed:

- PVC and PVdC coated PVC: copolymers of vinyl chloride and vinyl acrylate.

- PP: copolymers of PP.
- PET: polyester resins or PVC / acrylate.

A very good seal between the surfaces of the sealing layers is achieved by chemical coordination⁸.

Importance of Heat Seal Lacquer Weight

Heat seal bonding between the lid and base materials increases slightly with increased coating thickness; however, a normal heat seal coating does not add significantly to a foil's bursting strength¹⁰.

The sealing lacquer / coating weight is dependent on the type of sealing layer. The coating weight of lacquers for sealing to PVC has been reduced from 12g/m² to 6 to 9g/m², whereby $7.0 \pm 1.5\text{g/m}^2$ are mainly used¹⁰.

Assuming the appropriate heat seal lacquer is used, and the lacquer is faultless, the impermeability of a blister, related to the sealing, is influenced mainly mechanically through non parallel sealing tools and temperature fluctuations within the sealing plates or sealing rollers and soiled surfaces of the sealing tool¹⁰.

Protective Outside Lacquer

The outside, preferably the dull side of the aluminium foil, is protective lacquered and / or printed and over lacquered¹⁰.

The term 'printing primer', is also used instead of protective lacquer. These terms explain at the same time the need for lacquering the outside. If the hard or soft-tempered aluminium lidding foil is not lacquered, the surface of the aluminium can be rubbed off during the packing process and even more so during transport¹⁰. This results in a black appearance visible on the bottom of the

cavity in the areas which are in contact with the blisters stacked below, a phenomenon known as 'aluminium corrosion'¹⁰.

Further disadvantages are deteriorated adherence of the printing inks and insufficient gliding movement of the bottom foil against the aluminium foil resulting in sticking when stacked in the packaging machine⁴⁵.

The printing over lacquers are applied because of their higher temperature stability and to avoid ink smearing and off-setting during slitting and re-winding. The heat stability is especially necessary for rotary sealing due to the higher sealing temperatures and sealing pressures of this process⁴⁵.

It can happen, that during the sealing process steam comes out of the sealing tool²⁷. This steam will condense on cooler parts of the machine and over the time yellow to brown drops form²⁷. These may drop on the lidding foil of the sealed blister strip and the print will be partly removed²⁷.

The reason for this is that the printing inks and / or protective lacquer contain a plasticiser⁴⁶. If it contains a monomer plasticizer, such as dibutyl-phthalate or dioctyle-phthalate, they will partly evaporate during sealing process⁴⁶. However, printing inks that contain polymeric plasticiser's do not exhibit the same phenomenon⁴⁶.

Print on the Inner Side

Calendar packs and specific market designs may require print on the inner side of the lidding foil¹. We now have to cope with the requirement of the FDA that all substances which come into contact with pharmaceuticals have to be approved according to the FDA list²⁷. Currently, only natural pigments (white and brown / gold) comply with these requirements²⁷. All synthetic colours may not have direct contact with the product and have to be protected by means of a plastic film or sealant²⁷.

The printing ink may be nitrocellulose based. Heat sealable printing inks have to be used for colour with an opacity of $\leq 5\%$ and printing is carried out in critical areas of the sealing, such as the land area between the cavities²⁴.

The resulting print quality is not as good as if it was printed on pre-lacquer, due to the unevenness of heat seal coated surface. To guarantee the print quality, printing should be carried out on a pre-lacquer of approximately 1.0g/m^2 .

Foil Coatings

In most applications, aluminium foil is combined with other materials such as coatings, inks, papers, paperboards and plastic films⁴³.

The principle reasons for coating the foil include:

- To render the foil surface heat sealable.
- To increase the foil's scratch or scuff resistance.
- To increase tensile or burst strength.
- To produce a specific surface, such as, slip, non-slip, release or decorative.
- To improve adhesion of other coatings or printing inks.
- To enhance the water vapour / gas barrier properties of low gauge foil.
- To increase the foil's resistance to corrosive agents or products.
- To impart high gloss and three dimensional depth to foil decoration or printing.
- To improve the UV resistance of a printed surface.

Coatings are employed to protect the pack, the product or both¹. Coatings generally can be classified as decorative, protective or heat sealing¹. In most instances a coating is selected for one characteristic, but one coating may incorporate all three, as in tinted heat sealable protective coatings with food / product compatibility¹.

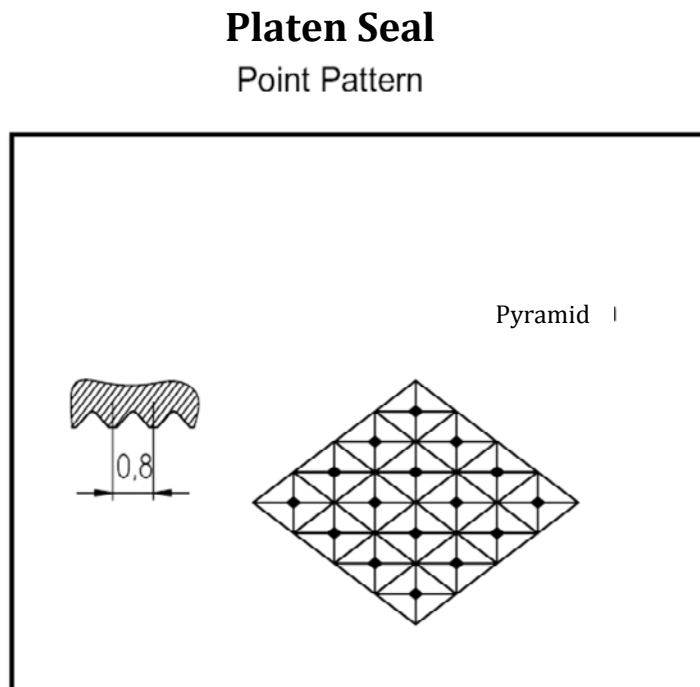
Machine & Tool Considerations

Among the features which are critical to achieving consistently sealed blisters are the design / construction and alignment of the sealing plates and their surface finishes²⁷. Appendix 3 shows an image of both a rotary and platen sealing tool.

Knurling Pattern

In order to seal the two blister foils together, one or both of the sealing plates, upper or lower has a knurled surface²⁷. The most common arrangement for rotary sealing is for the lower plate to be plain, and the upper plate to be knurled with a pattern of square topped pyramids²⁷, see Figure 11.

Figure 11 – Pyramid Pattern – Generally used for Platen Sealing⁸

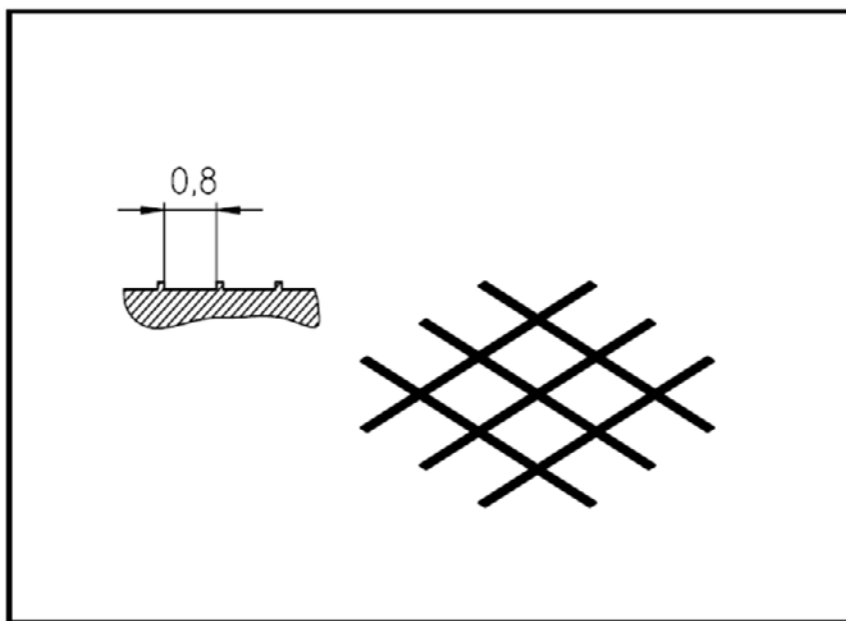


An alternative knurl pattern which has been used successfully is a matrix of

sunken pyramids²⁴, whereby the seal is formed by the interlocking grids between the pyramids²⁴. This greatly reduces the potential for micro-channelling, see Figure 12.

Figure 12 – Lattice Pattern – Generally used for Rotary Sealing⁸

Roller Seal Lattice Pattern



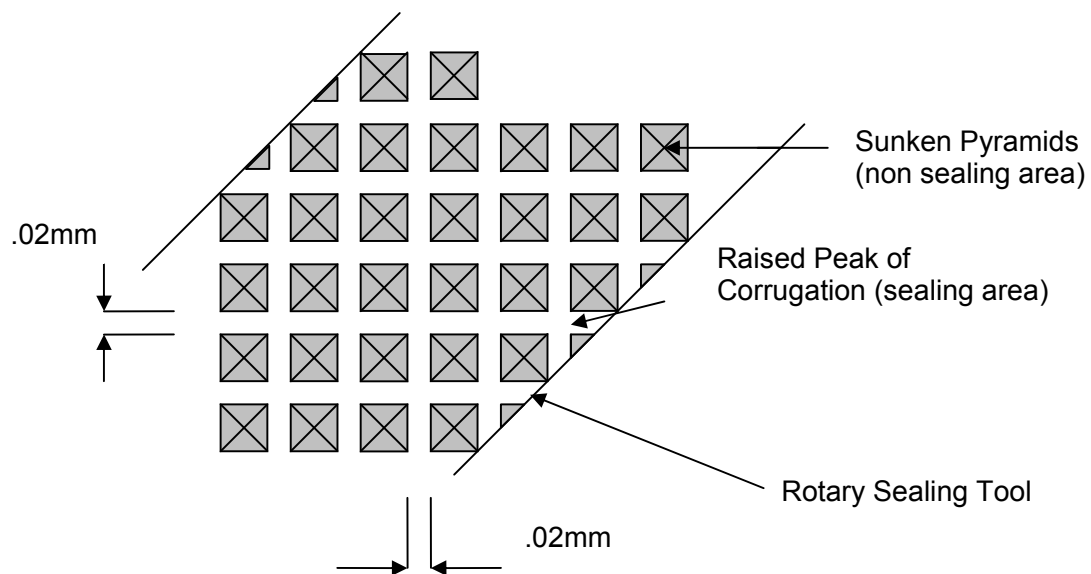
In the case of platen sealing, top and bottom knurled plates, dimpled or cross hatched are preferably used, whereas in the case of rotary sealing, generally only the wheel contacting the lidding foil is knurled²⁷. The most common sealing patterns in use for rotary sealing are either sunken pyramid, as previously mentioned, or corrugated type knurling³⁶. Generally, the peaks of the corrugated wheels / plates are ground off by 0.02mm, as detailed in Figure 13, depending on the material combination to be run, peaks may be ground off by up to 0.05mm¹⁰. The more acute the corrugation is, the larger the pressure exerted. However, this may result in physical damage to the lidding material¹⁰. Furthermore, it may well happen that the heat seal lacquer does not optimally

flow during the sealing process, thus resulting in leaking packs¹⁰.

Standard spacing between the corrugation lines used in rotary sealing is 0.8mm. In order to be on the safe side and to avoid the creation of capillaries, this spacing can be reduced to 0.4mm¹⁰.

When reducing the spacing between the lines, the sealing pressure has to be increased, since more peaks per surface unit have to be pressed into the blister¹⁰. However, it is not possible to increase the pressure endlessly, because if it is too high, then either the bottom web can start to delaminate or the heat seal lacquer can be squeezed from the sealing area by excess pressure exerted by the sealing tools¹⁰.

Figure 13 – Corrugated Seal Tool – Alternative Design used for Rotary Sealing²⁷



Sealing Plate Alignment

Most blister machines use flat top and bottom sealing plates, as opposed to rotary sealing. It is important, therefore, that the two plates are flat, well

supported and correctly aligned in order to ensure consistent sealing across all packs²⁷. It is possible to verify this by means of pressure sensitive film.

Other Factors Important in Achieving a Good Seal

In addition to the factors previously discussed, consideration must also be given to:

- The sealing jaw pattern (line, cross hatch, pyramid).
- The area or width of seal zone, if area is too narrow, the seal may not be totally effective.
- The condition of the machine, evenness of seal pattern and correct alignment of jaws.
- The type of temperature control and operational range, because simmerstats give poor control, but thermostats give tighter control, $\pm 7^{\circ}\text{C}$ possibly drifting to $\pm 15^{\circ}\text{C}$ with time. Electronic controls are more accurate, generally $\pm 2^{\circ}\text{C}$.
- Product contamination, as it can interfere with sealing.
- The material, as it must conform to specification, such as excessive calliper variation.
- How the seal is achieved, such as platen or tangential contact?, as in rotary sealing where only a point of contact is made between the top and bottom rollers, compared to the platen process where an area is sealed by flat contact between upper and lower seal plates.
- How the blister is removed from web by guillotining or punching. Hence accuracy and tolerance of cut are important so that an adequate heat seal margin is maintained.
- Adequate removal of heat involved in the sealing operation.

Some Additional Pack Factors

Hermetic Packs and Hermetic Seals:

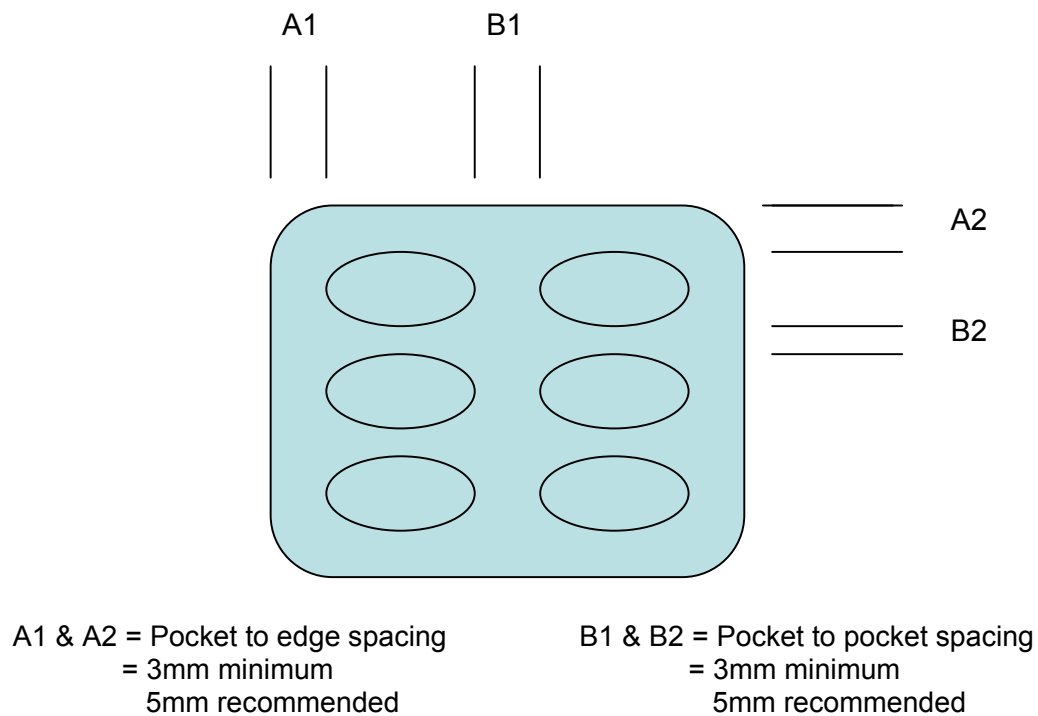
A few words are essential on hermetic packs and seals. The definition of hermetic means airtight, which translated into packing terminology, means that there should be virtually 'no exchange' between the product and the external atmosphere, such as no egress or ingress. In actual fact few blister packs will actually meet this latter definition¹.

The design of the blister layout and the pocket profile is critical to the performance of the pack and the degree of protection it gives to the product^{10,24,45}. It has been quite normal in the past to allow machine manufacturers to decide these parameters whilst designing new forming and sealing tools. However, it is important that the critical dimensions and essential testing necessary to validate new tooling are specified by the pharmaceutical company.

Pocket Spacing

The layout of the pocket blisters must be such as to guarantee a minimum seal area around each blister of at least 3.0mm²⁴. This includes pocket-to-edge and pocket-to-pocket dimensions, as well as pocket-to-perforations where relevant. Where possible, it is recommended that the pocket-to-edge dimension is set to a higher figure of 5.0mm to allow for variations in cutting and sealing²⁴, see Figure 14.

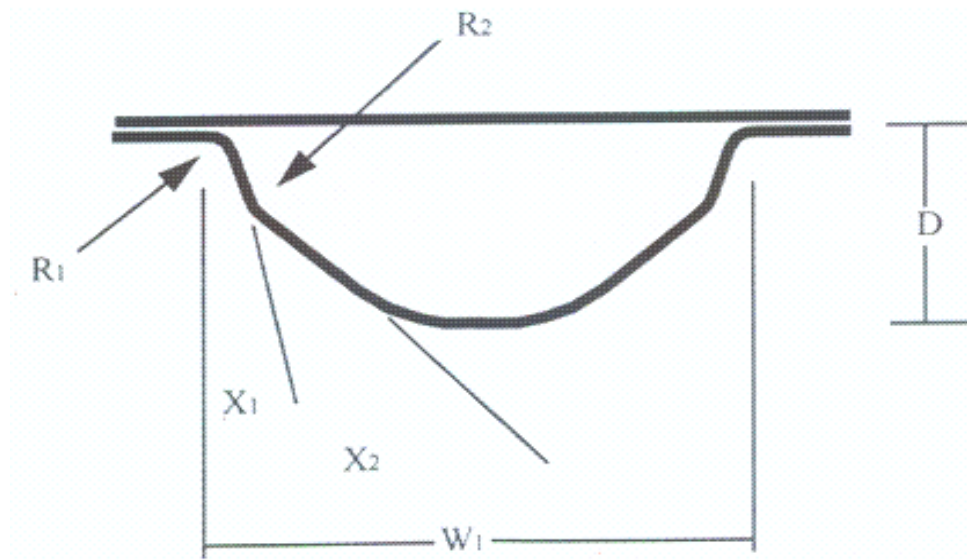
Figure 14 – Ideal Pocket Layout²⁴



Pocket Profile

A good pocket design and blister layout is essential to both the forming process and the performance of the blister in the protection of the product throughout its shelf life²⁷. Section 2.1.6 describes some of the problems associated with poor blister design. Figure 15 details the critical dimensions of a coldform blister pocket profile.

Figure 15 - Critical Dimensions of the Pocket Profile⁸



Where:

W_1 = Pocket diameter

D = Pocket depth

X_1 / X_2 = Blister step angles, ideally $>56^\circ$

R_1 = External pocket radius

R_2 = Internal pocket radius

The pocket depth is dictated by the thickness of the finished tablet, also the width and length are dependent on the tablet dimensions. The steepness of the pocket sides is critical to the mechanical performance of the base foil laminate, which can delaminate or split if overstressed, ideally $>56^\circ$ for platen, and $>75^\circ$ for rotary forming, because of the greater stress exerted in forming on the rotary blister line^{26,35}. It has been demonstrated that each new set of blister tooling should be subjected to a Hoogoven Screen Test to verify that the foil is not being stressed beyond its mechanical capability^{8,10,35}. The test involves a set of

blisters with a specially printed film, from which the degree of stretching can be measured.

2.1.6 Problems Associated with Blister Sealing

Leakage

Both permeation and leakage do the same thing, that is shorten product shelf life^{47,48}. Permeation can be determined, however, leaks are more evasive and unpredictable and at times very difficult to detect⁸. Where the permeation rate might be consistent throughout a production run of plastic film, leaks can still occur from one blister to the next⁸. The ideal is to have 100% leak testing on a production run. This is ideal but not practical in most applications.

Possible Causes of Leaking Blisters:

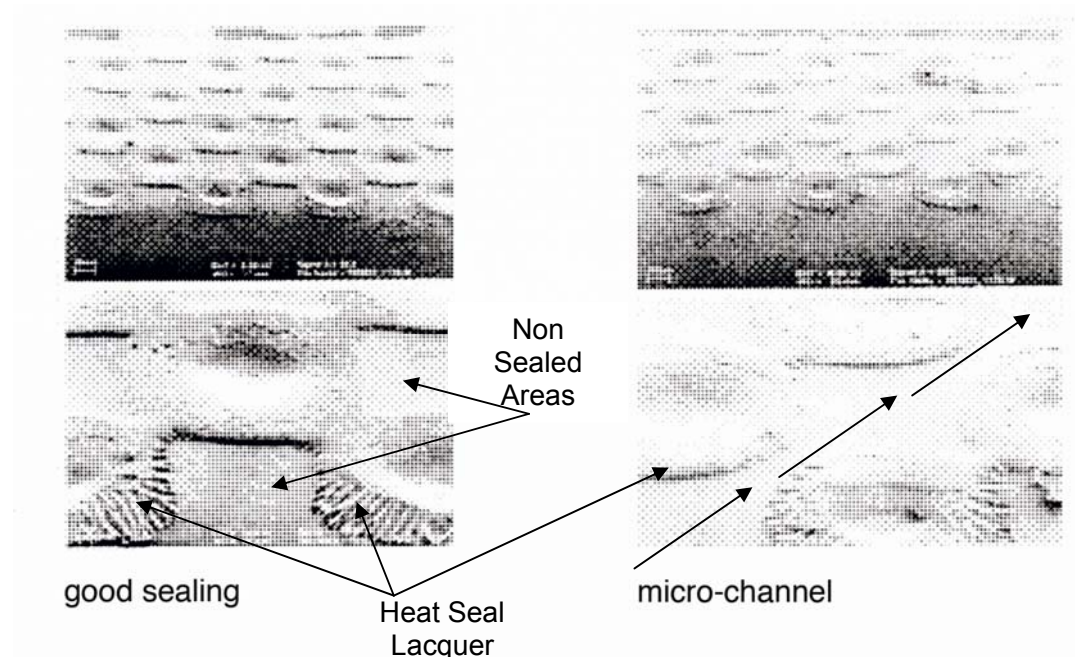
- Actual temperature of the sealing tool does not correspond to the validated temperature.
- Non-uniform temperature distribution in the sealing tool (variations <5 °C).
- Non-uniform sealing pressure due to uneven sealing plates.
- Varying distance between sealing rolls.
- Flatness of bottom web (thickness tolerance).

Defects of the sealing tool, faulty lidding foil and bottom material foil might also lead to leaky blisters⁸. Gross leaks are detected by means of a methylene blue dye vacuum test⁸. However, micro-channels through the seal cannot always be detected by this method⁸. One other method is to detect the channels is by observation using a Scanning Electron Microscope (SEM).

Parts of the seal with micro-channels will cause problems with stability over time⁸.

This defect is normally not detected by the vacuum test. Figure 16 shows SEM pictures of a tight sealing and one with micro-channels (same blister).

Figure 16 – SEM Pictures of Good Sealing and Micro-Channels⁵



Curling of Blister Strips

The heat sealing operation can impart a degree of 'curl' into the tray, thereby creating problems for automatic cartonning²⁷. The amount of curl depends partially on the type of machine employed, the type of web and design of the blister strip and what happens to the web when it leaves the sealing station²⁷. Theory suggests the different coefficients of expansion for foil and film are partly the cause, plus film shrinkage due to excess temperatures under the sealing platen causing molecular reorientation²⁷. Curl can be reduced or overcome by incorporating thermoformed ribs in the blister design or by reversing the web curvature by passing over a tension roller or through radiused guides²⁷.

Curl is less of a problem with soft foil as it stretches more readily and has less internal stress build up after forming and sealing¹⁶. Perforations between pockets reduce the internal stresses within the blister which will also reduce curl¹⁶. Paper, however, does have a grain (machine) direction and will curl parallel to the machine direction^{26,42}.

Poor Blister Strip and Blister Pocket Design

Blister pocket profiles should avoid square or near right angled corners or bases as this may make both release from the forming tool difficult and lead to thinning in those areas⁸. Generally blister pockets should have an adequate clearance with the product and have an adequate radius at both the top (dome) and where the pocket emerges into the blister flange⁸.

Satisfactory seals can be achieved with a separation of 2 – 3mm between pockets but there may be some danger of exposing the adjacent pocket when a product is pushed out, thus 3 – 4mm is preferable for both between pockets and margin seals⁸. With pocket perforations or scores between each pocket this distance becomes 5 – 7mm to allow for perforation or score⁸. In the case of peelable blisters it is necessary to extend the peelable edge by at least 5mm⁸.

Alternately, a cut away part at the edge of the blister strip internal to the design or on an edge seal may be employed, to enable a good grip for the peel feature⁸. Whether the edge seal remains uniform depends on such features as accuracy of registration, method by which web is held and drawn through the machine and the method of blister strip removal from the web⁸. If the tolerance of these is excessive then wider blister and edge seals will be necessary⁸. A blister of the push through type without perforations provides less wastage and can maximize machine output⁸. However, larger blisters with perforations, or perforations plus peel will lead to fewer blisters per stroke, more wastage and lower output⁸.

Additional Factors that can cause Problems with Blister Sealing

If there is excess moisture in the paper or an overly high sealing temperature, moisture may boil off during heat sealing and cause blistering or de-lamination. Using heat to heat up moisture, as well as paper may also reduce the overall temperature and prevent the correct temperature from sealing effectively. Therefore, effective sealing maybe dependant on the moisture content of the paper²⁴.

It should also be mentioned that cellulose based materials, paper and regenerated cellulose are prone to significant dimensional and property changes according to the Relative Humidity (RH) / temperature of the surrounding environment^{8,18,42}. Reels will therefore expand at the edges (dumbell) or contract (barrel) hence change in tension as moisture is gained or lost²⁴.

Stress can also be inherent when large tablets and / or capsules are sealed in an undersized pocket, stress such as folds or creases may occur within the margin seal from the edge of blister to pocket²⁷. Extra compression and / or heat may be necessary to ensure a good seal and avoid the presence of capillary type leakage channels. Increasing the pocket size may be necessary to avoid such situations²⁷.

There is also an impact on speed due to the critical parameters of the heat sealing process, such as temperature, dwell time and pressure. Therefore, it will be essential to optimise the machine speeds to achieve maximum throughput²⁷. Output could also be increased by the use of wider webs and a multiplicity of heat sealing operations, with larger or wider cylinders, but this would require major machine modifications and re-design^{1,45}.

Delamination caused by Poor Blister Forming Tool Design

The three most important functions in achieving a good seal are temperature, pressure and speed²⁷. However, consideration of the forming characteristics is also essential, because it is paramount to the overall sealing operation. If the critical parameters of the forming and sealing operations have not been fully optimised then delamination of the layers can occur under stressed conditions⁴⁹. Delamination can also occur if the humidity during the lamination process is low, thus reducing the bonding strength between the OPA and aluminium layers⁵⁰.

Furthermore, if either the temperature of the lower sealing plate has been heated up during production by continuous contact with the upper sealing plate or misregistration occurs between forming and sealing (sealing on the edge of the cavities) it can cause delamination earlier in the cycle⁴⁹. This phenomenon has been observed on Multi-Dose Powder Inhaler (MDPI) blisters after 12 months storage at 40°C/75%RH. The research undertaken as part of this study has given the background and technical knowledge to develop a material that is more resistant to delamination⁵⁰. This study is documented in **Chapter 4**.

This section has outlined the critical aspects of blister sealing such as, the importance of choosing the most appropriate materials and equipment, the necessity of good tool design and the need to optimise the critical operating parameters to mention but a few. However, probably the single most important factor in achieving a totally hermetic seal to protect the product throughout its required shelf life is the function of the adhesives within the blister pack. A detailed consideration of the factors influencing the adhesion of lidding materials was therefore, essential and is discussed in **Chapter 2**.

2.1.7 Overall Conclusions on the Critical Aspects of Blister Sealing

Blister sealing is a very complex and highly specialised process where there have, in recent years, been advances both in equipment and material, which have resulted in higher production output and increased equipment efficiencies. This study has identified the critical areas of the blister sealing process that must be considered when developing or implementing new materials and processes. Optimum tool design and blister layout, appropriate choice of materials and equipment all of which are essential components in achieving protection, containment and identification of the product throughout its shelf life.

However, probably the most important aspect is the function of the adhesive. The adhesive function within the blister pack is critical to the dispensing process, it also guarantees the protection of the product throughout its shelf life, protects the material under stressed conditions, both when forming the blister and at extreme climatic conditions, especially in tropical climates. It is therefore essential to understand the theories of adhesion, the types of adhesives that are commercially available and the important characteristics and properties of adhesives. The role of the adhesives are discussed in the following section. However, as we have discussed, the attainment of successful blister packaging is not without its problems, materials are prone to delamination between the plies, pinholes and splits can be experienced during forming, high temperatures are required for rotary sealing, ingress of moisture through the seal mainly through the PVC layer within the base film, to name but a few.

Another important aspect that must be considered is material / product compatibility at the development stage of a product to ensure there is no reaction with the product over time. Also, does the product require moisture, oxygen or light protection?. All these points must be considered when selecting the blister material.

During development it is also imperative that the blister layout has been appropriately designed with the maximum seal area around the pocket. Consideration to the type of knurling pattern and tooling design is also essential at an earlier stage of the development and the type of sealing equipment, such as rotary or platen sealing?. Furthermore, the critical parameters of temperature, pressure and dwell time must be optimised to ensure the heat seal lacquer on the lidding material is transferred to the contact layer. If these parameters are not correctly set it will result in leaking blisters.

The blister pack must also protect the product against mechanical, climatic, microbiological and human hazards, it may require child resistance and / or pilfer-resistance, such as Shell Pack or Dose Guard as offered by GP Solutions⁵¹.

In recent years there has been extensive research into developing new materials and new processes. All of which have been influenced by the properties of the product, cost, changeover time and output. There have also been contentious issues, such as the concerns over the potential replacement of PVC due to environmental pressures and the adoption of standards for child resistant packaging. There are also ongoing discussions relating to the type of protection the pharmaceutical companies should provide for moisture sensitive products, such as desiccated base films^{52,53}. The current study will aim to address some of these issues.

There are also focus groups within the industry addressing the environmental issues concerned with PVC replacements. As a result, various grades of PP have been evaluated, as substitutes for PVC either uncoated or coated, usually with PVdC. It should be noted that if PVC is condemned there is no logical reason why PVdC might not also be replaced as both contain chlorine. PP remains the preferred substitute although it requires higher energy to heat the polymer compared to other thermoformable materials, it has a fairly narrow forming temperature window, and needs more controlled forming and effective

cooling. PP either tinted or pigmented white with titanium dioxide, although offering better moisture barriers, still requires an additional coating for higher barrier properties. The elimination of PVC can also influence cold forming materials which usually have a layer of PVC on the inside. An Orientated Polypropylene (OPP) / foil / OPP material has been offered as a substitute.

Although cold formed materials started with 40µm foil and utilised a relatively shallow well radiused draw, perforation problems with the foil have arisen. As a result, many pharmaceutical companies have evaluated and introduced a 45µm foil. Gauges of up to 60µm are now readily available. PCTFE based materials using Alcar (trade name) 22A, 33C, 88A and more recently RX 160, Ultrix 2000, and Ultrix 3000, are also commercially available. These are being used for new moisture sensitive products. However, there are many alternative over wrapping systems which may be used to improve moisture barrier.

In this context the Japanese market require additional protection of their blister packs by means of a PE / AL / PET pouch. The question of whether to use for thermoforming, a multilayer material, a coated material, or the lowest cost material with some form of overwrap remains a contentious issue as to which is most environmental friendly. Multilayer materials are likely to be the most difficult to recycle but recovery of energy may be possible by effective incineration²⁸. One newer material for cold forming, uses an aluminium only base material, with an application of a heat seal lacquer on the inside.

However, as we have seen, blister sealing is still not without its problems, and there are many challenges still facing the pharmaceutical industry. Therefore, there is a need to further enhance the performance and the barrier properties of the materials, develop new improved processes and resolve ongoing machine / material problems, all of which will be researched as part of the current study.

The following section details the theories and techniques which will be of relevance to this study.

Chapter 2 Section 2

Literature Review

2.2 Principles of Adhesion

2.2.1 Introduction

This study addresses the following issues:

- Delamination of laminated materials within blister films.
- Different types of heat seal lacquers.
- Different types of blister materials.

In order to study these aspects it was essential to understand the principles of adhesion, the types of adhesives available for use and the theories of adhesion.

There are many important aspects of blister sealing, all of which are required to achieve protection / containment and identification of the product^{4,54,55}.

However, probably the most critical part of the pharmaceutical blister pack is the function of the heat seal adhesive on the lidding foil²⁷. The standard heat seal lacquer used on both the rotary and platen thermoformers is a hot melt type of adhesive typically 7 – 10g/m² PVC / Polyvinylacrylate (PVA) co-polymer. The adhesive is sealed to a PVC layer on the base laminate¹.

The bond is made by a combination of pressure / time and temperature²⁷. This type of adhesion is known as chemical adhesion, because we are bonding two non absorbent surfaces together and it relies on the specific attraction of the adhesive to the two surfaces to achieve the required bond⁵⁶.

As part of this thesis, studies have been performed looking at different heat seal

lacquers, with a view of developing a tighter pack with a higher degree of protection to moisture. However, prior to any development it was essential to get an understanding of the main principles adhesion and the different types of adhesives that are commercially available.

What is Adhesion?

Adhesion may be considered as a sum of energetic processes where the fracture energy (G) will involve a term associated with the energy required for breaking primary or secondary bonds at the interface when the joint fails⁵⁸. This surface energy term will be the thermodynamic work of adhesion (W_A) or of cohesion (W_C), depending if the joint fails at the interface or adhesively within one phase⁵⁸. To this surface energy term must be added a term ψ representing other energy absorbing processes such as plastic deformation or viscoelastic loss due to stretching of the material⁵⁸. Consequently, on this basis for a particular structure joint strength is influenced by:

- The strength of the interface, W_A
- The strength of the adhesive, W_C
- The distribution of stresses within the joint, Ψ

The factors that affect adhesion are intimately linked with adhesion mechanisms²⁹. There are a number of longstanding and newer theories of adhesion and these will be discussed in terms of their relevance to joint formation, particularly in the case of polymer-to-metal bonding. Also of particular bearing to the present study is the theory of abhesion, or poor adhesion, which lends itself to the explanation for lower than expected levels of adherence that sometimes occurs in joints⁵⁷. The focus of the present study is the modification of the adhesion between the MDPI aluminium lid and base structures, as discussed in **Chapter 4**, using a PVC / PVA based heat seal lacquer.

Also detailed in this section are experimental procedures employed throughout this research study. It is recognised that the complexity of adhesion problems requires analytical procedures that will identify the different types of adhesive failure on a microscopic level⁵⁷. For instance, reduced levels of adhesion between the lid and base foil substrates occurring on a microscopic scale causing weak interlayer formation at the adhesive / adherend interface can be identified⁵⁷. Consequently the techniques, analysis and experiments conducted throughout this study need to encompass this scale of activity. Thus, there will be a comprehensive account of adhesion tests, such as the T-peel test, surface analysis techniques like SEM and bulk adhesive investigative methods, for instance Fourier Transform Infrared (FTIR) Spectroscopy and Differential Scanning Calorimetry (DSC).

What is an Adhesive?

Adhesion is a fundamentally molecular attraction exerted between two bodies in contact^{58,59}. This may be with or without the introduction of a third body, such as the adhesive. In the present study we are only concerned with adhesion occurring through heat and pressure and by the thermal adhesive bonding of the MDPI sealed strip. Early definitions of an adhesive were fairly basic and only made reference to the fact that it bonds two surfaces together^{58,59}. An example of this is the definition put forward by Comyn⁵⁶, who describes an adhesive as “a material which when applied to the surface of materials can join them together and resist separation”. A further expansion of the definition has been made to encompass the polymeric nature of most adhesives⁵⁶. So in essence, an adhesive is a polymeric material that when applied to two or more surfaces can join them together to resist separation⁵⁶. By virtue of this definition it may be interpreted that an adhesive must do two things:

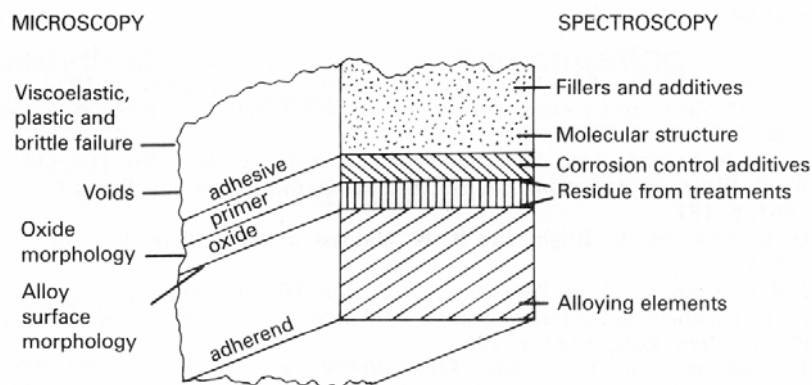
- 1) It must wet the surfaces.
- 2) The adhesive must harden and form a cohesively strong material.

These criteria form the basis of strong bond formation with adhesives. The factors that affect adhesion fall into one of the two categories. Thus it may be assumed that upon compliance of these two requirements a strong adhesive joint will be formed^{58,59}. The numerous influences on adhesion are discussed in the following section.

2.2.2 Factors required for Optimised Adhesion

The criteria that must be fulfilled to achieve good adhesion includes the condition of the substrate surface which is determined by pretreatment and the presence of a primer or coupling agent⁵⁸; the bulk mechanical properties of the adherends and the stresses present which relates to joint configuration. The properties of the bulk adhesive which determines cohesive strength of the adhesive itself must also be optimised⁵⁸. A bonded system consists of layers of different materials. Figure 17 illustrates the typical constituents of an adhesively bonded system. Since it is paramount that intimate contact must be made between the molecules of the adhesive and those of the atoms or molecules of the adherend it also follows that the adhesive must be in close contact with the primer, which in turn must be in close contact with the adherend via its oxide⁵⁸.

Figure 17 - Schematic Diagram of Interfaces in an Adhesively Bonded System⁵⁷.



The Importance of Wettability

As it is required that an adhesive must wet the surfaces to which it is being applied, it means that they are most often applied in the liquid state⁵⁷. This enables them to spread and make a contact angle θ approaching zero, thereby providing the conditions for intimate contact between the molecules of the adhesive and those of atoms or molecules in the adherend to take place⁵⁸. Upon application, the adhesive will generally be a liquid of relatively low viscosity⁵⁹. Once wetting has taken place there is then the possibility of interfacial interactions occurring⁵⁹. The contact angle is a measure of the extent of wetting as indicated by the angle a single liquid droplet makes with the surface⁵⁹. When a liquid wets a solid to the extent that the contact angle becomes zero the liquid is said to spread⁵⁹. Hence wetting, or the spreading of a liquid on a solid surface, is favourable for any adhesive which makes a contact angle $<90^\circ$ ⁵⁹.

For adhesion to occur the surface free energy of the solid must be greater than the critical surface tension of the adhesive⁵⁷. The rate and degree of wetting is determined by the surface energies of the adherend and adhesive and surface energies are determined by surface chemistries⁵⁷. All metals in common use have oxide coats which are of high surface energy⁵⁷. For example alumina (Al_2O_3), which is the natural oxide of aluminium, has a surface energy of 638 mJ m^{-2} , compared with $20\text{--}46 \text{ mJ m}^{-2}$ for most polymers / adhesives⁵⁷. This means that metals are easy to bond whereas there are greater difficulties associated with bonding some polymers⁵⁷. Table 4 gives surface energies of a range of materials, arranged in order of increasing energy, and therefore ease of bonding.

It is still possible to bond polymers with low surface energies such as PP, and PVC but only after such materials have undergone adequate surface pretreatment, for example corona discharge⁵⁷. Such methods chemically modify polyolefin surfaces by introducing new chemical groups that are polar which raise the surface energy of the material⁵⁸. This promotes adhesion by increasing the propensity of the treated surface to form bonds with the adhesive⁵⁸. The same principle is applied when pretreating metal surfaces prior to bonding. This is discussed further in the following section.

Table 4 - Surface Energy as an Indication of Bonding Capability⁵⁸.

Solid	γ_s^d (mJ m ⁻²)	γ_s^p (mJ m ⁻²)	γ_s (mJ m ⁻²)
Difficult to bond / low energy surface			
Polytetrafluoroethylene	18.6	0.5	19.1
Polypropylene	30.2	-	30.2
Polyethylene	33.2	-	33.2
Polymethylmethacrylate	35.9	4.3	40.3
Polyvinylchloride	40.0	1.5	41.5
Polystyrene	41.4	0.6	42.0
Rubber modified epoxide	37.2	8.3	45.5
Amine cured epoxide	41.8	3.3	45.1
Easy to bond / high energy surface			
Oxides			
Silica (SiO ₂)	78	209	287
Alumina (Al ₂ O ₃)	100	538	638
Ferric oxide (Fe ₂ O ₃)	107	1250	1357

2.2.3 The Influence of Surface Pretreatment on Adhesion

As mentioned above, part of this study is purely focused on the modification of the adhesive between the MDPI aluminium lid and base structures using a PVC / PVA based heat seal lacquer. However, it is paramount to understand the surface preparation methods applied to the adherend during lamination. The nature and character of the surface of an adherend is also very important in establishing the strength and durability of the adhesion to that surface, as summarised by Critchlow and Brewis⁶⁰.

Among the many factors that affect the durability of adhesive bond, the choice of surface pretreatment is crucial in achieving the required bond strength and

durability⁶⁰. The objective of surface pretreatment of an adherend is the following:

- Removal of contaminants or weak boundary layers.
- Modification of surface chemistry.
- Alteration of surface geometry.

By providing a clean surface, wettability is enhanced since contaminants that may impede the ability of the adhesive to spread across the surface of the adherend are removed⁵⁸. This also promotes intimate contact between the adhesive molecules and the atoms or molecules of the adherend⁵⁸.

Surface chemistry is important as it dictates the degree of contact achieved and also the magnitude of the interaction where contact has occurred and whether chemical bonding, hydrogen bonding or some van der Waals' force are involved⁵⁶. Whether surface contaminants can be displaced will also depend on the chemistry of the adhesive⁵⁶.

Increased roughness and intrinsic hydrolytic stability of the surface have also been identified as being important for good bondability⁵⁷. A common attribute to good adhesive performance is the concept of mechanical interlocking, whereby the adhesive interlocks around the irregularities of the substrate⁵⁸. The potential bonding area of a rough surface is greater than for a smooth surface⁵⁸. This is especially true if the irregularities are deep and narrow.

To stabilise and promote adhesion during the lamination process, there is a number of chemical and / or electrochemical treatments available. However, Alcan Packaging who supply the coldform base laminate to GlaxoSmithKline (GSK) use corona discharge to chemically modify the polyolefin surfaces by introducing new chemical groups that are polar which raise the surface energy of the material³¹.

2.2.4 Surface Morphology and Joint Strength

It is generally believed that to produce a durable adhesive bond a nano or micro-rough surface topography is beneficial. This may be achieved through mechanical roughening or electrochemical treatment⁵⁷, such as the case for the pretreatment of polymeric surfaces in the lamination of blister films. In the case of micro-roughened surfaces the exact nature of the effect of surface topography is a matter of some debate. One school of thought places importance on the mechanical interlocking theory, for example D.E Packham⁶¹. Others suggest the enhancement of energy dissipative mechanisms causing plastic deformation of the adhesive make a contribution⁵⁹. Thus, chemical pretreatments improve joint strength by a combination of enhancing W_A through the formation of primary bonds at the interface which facilitate transmission of stresses, ψ , from the interface to the bulk⁵⁷. The micro-roughness characteristic of chemical pretreatments also alters the way that the stress is distributed when the joint is loaded. This can increase the energy dissipation which occurs during fracture⁵⁷.

2.2.5 Bulk Adhesive Properties

It has been established that interfacial forces play an important role in developing initial joint strength rather than during subsequent mechanical loading of the joint⁵⁹. In this respect, bulk properties of the adhesive are among the many factors that influence the ultimate strength of the adhesive joint⁵⁷. If it is assumed that interfacial strength has been maximised and that the adherends are rigid and strong, it may be concluded that the strength of the joint is completely determined by the bulk properties of the adhesive⁵⁷. The polymeric nature of adhesives means their mechanical properties are also dependent on glass transition temperature (T_g) of the polymer⁵⁸. The mechanical properties of un-crosslinked and unfilled polymers change dramatically around this temperature³⁸. The most often illustrated property is the effect on modulus, it can decrease 10^4 fold as the polymer is heated from below

to above the T_g .⁵⁸ At temperatures far below the T_g the glassy polymer cannot elongate to a large extent when stressed and generally breaks at very low extensions⁵⁸.

As most adhesives are polymers the strength of their intermolecular bonds is significant in controlling the cohesive strength of the adhesive⁵⁹. Adhesives comprise a mixture of compounds which interact with the surface and each other during the bonding procedure⁵⁹. This process, referred to as adhesive curing, involves the provision of energy to the adhesive system which causes a reaction of the adhesive mixture⁵⁹. As curing proceeds, the viscous mixture becomes a rigid solid as the compounds react and cohesively link the adhesive, a process often referred to as cross-linking⁵⁹. This process enables strength to be established between the joined adherends.

From the polymeric nature of adhesives it is possible to assign the same mechanical properties as polymers. For example, modulus and strength in all its forms, such as tensile, fatigue, adhesive, creep resistance and toughness⁵⁹. However, difficulty arises when attempting to specify optimum values for these properties. As with any polymer, these properties depend on factors such as service conditions, application and type of adhesive, amongst others⁵⁹.

Mechanical properties of the bulk adhesive may also be manipulated by incorporating additive into the matrix of the material⁵⁷. For most commercially produced adhesives a range of fillers, antioxidants and other additives are present that may provide additional toughening or crack resistance⁵⁹. Adhesives formed by polymerisation or cross-linking reactions are often brittle, glassy solids with poor resistance to impact and peeling forces⁵⁹. Impact, and peel resistance can be improved by addition of a rubber toughener to the adhesive formulation⁵⁷. Improved impact resistance is achieved by introducing rubbery domains into the polymer morphology⁵⁷. Improved fracture toughness is attributed to the ability of the rubbery domains to absorb and dissipate energy associated with propagating cracks⁵⁷.

2.2.6 Hot Melt Adhesive

The heat seal adhesives discussed in this thesis are hot melt type adhesives and for this reason they require a greater understanding of the type of polymers that can be used, the manufacturing process and the advantages and disadvantages of hot melt adhesives. Hot melts are 100% solids thermoplastic adhesives^{59,62}. They are based on 'plastic' polymers such as polythene (and its copolymers), PP, PVA, polyamide (PA) and PETs^{57,63}. Adhesive formulators compound hot melts with suitable resins, waxes and stabilisers, to give the desired properties of adhesion, viscosity, flow characteristics, wettability and stability^{59,62}. Hot melts differ from conventional liquid adhesives because they set by cooling rather than by absorption or evaporation of a liquid vehicle, which may be water or a solvent⁵⁹. This gives hot melt adhesives the rapid bonding characteristic which is the chief reason for their popularity.

Hot melts can be divided into two different types, those that set to become hard and those that remain soft and permanently tacky, the latter are termed 'pressure sensitive'⁶³. The first types are the most widely used and are employed throughout the packaging and converting industry⁵⁹. Pressure sensitive hot melts are much less common and tend to be used for more specialist applications⁶².

The hot melt only has to lose heat to set^{59,62}. This can be very rapid when compared to the loss of carrier solvent required with emulsions or solutions^{59,62}. Table 5 compares the properties of hot melts with other adhesive systems, such as emulsion and solution and details the advantages and disadvantages.

Table 5 – Advantages and Disadvantages of Hot Melt Adhesives^{59,62,63}

Advantages	Disadvantages
High production speed, short compression time, small space requirements, immediate shipping of sealed materials. All due to the speed of set or rapid transition from a liquid to a solid state.	They have limited toughness and heat resistance when compared with the best water or solvent based adhesives.
Improved glue line control. The rapid set or solidifying of hot melts minimises spreading, wicking and dripping. In short, the adhesive stays where you apply it.	Hot melts are organic materials and if overheated, no matter how well stabilised, they are liable to degradation and charring. High quality hot melts should be used to maximise production output.
They can bond impervious surfaces.	Due to their fast set, penetration into many surfaces is minimal. Bonds tend to be surface bonds rather than deeply penetrating.
Hot melts are 100% solids and no volatile vehicle needs to be removed to set the bond.	
Hot melts do not contain residual emulsifiers or water soluble components which are present in water based systems.	

2.2.7 Properties of an Adhesive that effect Adhesion

As previously discussed, the most significant property which effects adhesion is the ability of the adhesive to wet out the surfaces to be bonded. Other properties that also must be considered are detailed in Table 6.

Table 6 – A Summary of Adhesive Properties that effect Adhesion^{59,64}

Property	Function
Viscosity	The viscosity of an adhesive is a measure of its flow properties. For optimum adhesion, the adhesive must completely wet the substrates over the area to be bonded. Thus, it has to flow out into a continuous film that is as thin as possible yet consistent with complete coverage. Thus, viscosity is an important property of a liquid adhesive which had to be considered to achieve an effective bond. If the viscosity is very high, the adhesive may not flow sufficiently to form a thin film in complete contact with the substrates. If it is very low, the problems may arise with too rapid penetration into porous materials which would then leave insufficient adhesive between the substrates to form an effective bond.
Tack	Once the adhesive has been applied, the joint must be made by pressing the adhesive substrates together. When the pressure is released, the adhesive must be capable of holding them together against the pull of any forces tending to separate them. The ability of an adhesive to withstand these forces is a result of its stickiness or tack.
Adhesive and Cohesive Forces	Cohesive forces are acting between the molecules within a substance whereas adhesive forces are similar forces acting between the molecules of dissimilar substances, such as between paint and metal.
Thermoplastic, Thermosetting	A thermoplastic material is one which will often soften on heating and return to its original state on cooling, the process being indefinitely repeated. A thermosetting material is one which undergoes a chemical change on heating, giving a solid material which does not revert to its original state on cooling. The change is irreversible.
Coating Weight	This is the amount of adhesive expressed as weight per unit area required to give the most satisfactory bond, expressed in g/m ² . Sometimes expressed as film thickness.

Table 6 Continued – A Summary of Adhesive Properties that effect Adhesion^{59,64}

Property	Function
<i>Rheology</i>	This term covers a multitude of physical properties, is difficult to define exactly, but includes forces such as those opposing deformation and flow. Adhesives with the same viscosity but different rheological properties will behave differently on the same machine.
<i>Heat Set</i>	A heat set adhesive is one which forms its bond on the application of heat and in which the water present is absorbed internally to form a gel.
<i>Heat Seal</i>	A heat seal adhesive, (as used in blister sealing) is one in which the dry film is activated by heating immediately prior to bond formation.
<i>Blocking</i>	An undesirable adhesion between toughing layers of a material when stored under pressure for long periods of time.
<i>Solid Content</i>	The solid content of an adhesive is that figure, expressed as a percentage of the total after all solvent has been driven off by heating.
<i>Setting Speed</i>	The time to form a bond under heat, pressure etc. by means of a chemical or physical change, gives a handling bond (initial bond).
<i>Open Time</i>	The time delay between application of the adhesive to one or both of the substrates and the bringing together of these two surfaces.
<i>Drying Speed</i>	The time to form the final bond. This may, or may not, be the same as the setting speed.
<i>Plasticiser</i>	A plasticiser is a material added to an adhesive in order to render the dry film of adhesive more flexible. An external plasticiser is incorporated in the adhesive as an addition after polymerisation is complete, whereas an internal plasticiser is added during the polymerisation process and forms an intergral part of the polymer used as the adhesive base.
<i>Cure</i>	Curing is a chemical reaction (cross-linking) which results in a physical change (hardening or setting) by means of increasing the temperature, the change being irreversible.

2.2.8 Heat Seal Strength

The container made of a multilayer flexible material can be no stronger than the seals that hold it together. Seals are typically made by applying pressure with heated surfaces to opposing faces of the composite materials, melting the thermoplastic materials of the contacting surfaces^{59,65}. The two surfaces are then welded together as the thermoplastics cool.

Cohesive coatings are the major exception to heat sealing. Such coatings are similar to pressure sensitive ones in that they will adhere when they are applied with pressure to another surface⁵⁹. Unlike pressure sensitives, cohesives adhere only to surfaces coated with similar coatings⁵⁶. In practice, cohesive coatings are applied as a perimeter pattern on the inside surface of a packaging film⁵⁹. The cohesive property allows this pattern coated film to be unwound from roll form on a packaging machine⁵⁹. The package is formed around a product using only pressure to adhere the opposing cohesive surfaces. Heat sensitive products, such as chocolate bars, can be wrapped in this manner without melting⁵⁹. Packaging line speeds can also be increased as the sealing pressure can be transmitted to the interface instantly⁵⁹. In contrast, heat sealing requires time to raise the interface temperature to the melting point, because the heated surfaces can contact only the opposite side of the surface to be sealed^{27,65}.

The process of making heat seals relies on the basic thermoplastic properties of the polymers on the inside of a multilayer flexible package (the seal layer)^{59,65}. In theory, this welding process involves a dynamic fluid material moving under pressure^{59,65}. However, heat sealing (as discussed in section 2.1.5) generally ignores the rheological properties of the molten polymer and uses a static set of temperature, pressure and time variables to control the heat sealing process on packaging machinery^{27,65}.

2.2.9 Theories of Adhesion Relating to this Study

Interactions occurring across an interface range from weak physical dispersion forces to hydrogen, covalent and ionic bonding⁵⁸. Moreover, surface roughness can allow for a mechanical contribution to the overall joint strength⁵⁶. The type of interaction(s) occurring in a system depends upon the chemical constitution of the adhesive and the substrate, and the topography of the adherend surface⁵⁹. In the previous section the mechanical and chemical contributions to adhesion have been alluded to, however, there are several more traditional theories for adhesion such as mechanical interlocking, physical absorption, diffusion and electrostatic theory, and the weak boundary layer^{56,64}. Although, not strictly a theory of adhesion, it does provide an explanation for why joints fail. It must be noted that physical adsorption is always present when there is intimate contact between molecules⁶⁴. In addition to these well known theories there are some more recent models for adhesion⁵⁷. However, there are two prime theories are apparent in the heat sealing of blister foils. The primary theory being chemical adsorption, but also physical adsorption is present.

Chemical Adsorption

Only covalent bonding, hydrogen bonding and van der Waals interactions are present in organic coatings^{56,64}. Of the three types of bonds, chemical covalent bonds correspond to the highest interaction energies ($60\text{--}700\text{ kJ mol}^{-1}$) and van der Waals, or physical bonds, interactions produce the weakest bonds ($2\text{--}40\text{ kJ mol}^{-1}$). Based on this information any adhesion due to the formation of chemical bonds at the interface will be strong⁵⁷.

Adhesion by chemical bonding is frequently the foremost adhesion mechanism in the case of polymer-metal interfaces⁶⁴. From a structural point of view, the creation of such interfaces involves the passage from a crystalline metal structure to a complex molecular polymer structure^{58,64}. Chemical bonds are

formed at the interface, usually as a result of a charge transfer from the metal to the polymer^{58,64}.

Physical Adsorption

Adhesion by this mechanism is attributed to surface chemical forces, and the chemisorption or physisorption of atomic and molecular species^{58,64}. The attractive forces working across two surfaces include weak dispersion forces and stronger forces attributed to hydrogen, covalent and ionic bonding^{58,64}. Work conducted by Zisman and colleagues⁶⁶, demonstrated that van der Waals dispersion and polarisation forces are more than adequate to account for the observed strengths of adhesive joints. The types of bonds formed between two surfaces depend upon the chemical structure of the interface⁵⁹. In order for chemisorption or physisorption processes to occur across the interface it is imperative that the adsorbate wet the substrate^{56,64,37}. In general, for spontaneous wetting, the surface energy of the solid must be greater than that of the liquid^{56,64}.

2.2.10 Stress Distribution

The strength of a joint is determined by a number of different material characteristics, namely force, stress, strain, ultimate tensile strength, modulus, toughness, and brittle, elastic and plastic behaviour⁵⁷. The distribution of stresses within the system can be considered on different scales. For instance, on the largest scale the flexibility or rigidity of the adherends will determine the array of stresses operating in this region⁵⁷.

2.2.11 Stresses in the Adherend

The ultimate method of testing the strength of adhesive joints is to measure the force or energy required to break a joint⁶⁷. Where at least one adherend is flexible, peel tests are conducted where the flexible member is peeled from the

rigid adherend at a defined angle⁶⁷. The T-peel configuration is used where both adherends are flexible. Peel stresses are to be avoided at all costs when developing the adhesive joint. Adhesive lap joints at low loads are largely in shear, and peel configurations experience predominantly transverse, tearing loads⁶⁸. For this reason peel joints are not intended to bear loads⁶⁸. There are many energy dissipating processes associate with peel such as work of adhesion (W_A) or cohesion (W_C), plastic deformation of the adhesive close to the fracture surface, viscoelastic dissipation as the peel front advances causing the adhesive to be stressed and then relaxed and for plastic and / or viscoelastic losses in bending the freed strip through the peel angle⁶⁸. The Imperil College London has developed peel test protocols to determine the stresses in lap joints, these protocols will be used to calculate the stresses within the MDPI laminate. The results are detailed in **Chapter 4**.

2.2.12 Stresses within the Adhesive

The requirement for an adhesive is that it is strong enough to withstand stresses to which the object is normally exposed⁵⁷. In the event of a failure it is preferable for the joint to break within the adhesive itself or at an interface between the adhesive and adherend⁵⁷. In addition there is the conflict between the need for the adhesive bonding to be strong enough to do its job and to last, yet weak enough to be dismantled should there be a need to take the joint apart⁵⁷. If it is assumed that bonding conditions are such that joint strength is determined solely by bulk adhesive properties, it is not uncommon to find tremendous discrepancies between the strength of a joint and the bulk properties of the adhesive⁵⁶. For example, the tensile strength of a butt joint may be many times as great as the tensile strength of the adhesive. Alternatively the joint strength may be much less than the strength of the adhesive⁵⁶.

2.2.13 Summary

Adhesion is a complex phenomenon which cannot generally be interpreted using a single theory to explain bonding given the broad range of both processes and materials which may be used in the bonding system. The main and established theories, put forward by various authors, for explaining the adhesion phenomenon are: mechanical interlocking; diffusion; physical adsorption; chemical adsorption and the acid-base theory, often all grouped together under the umbrella of adsorption theory; electrostatic; and weak boundary layer. However, for the purpose of this study we are only concerned with the physical and chemical adsorption theories. The theories discussed appear to differ from one another, however, there are premises that bind them all together. It has been stated that in order to obtain a strong adhesive bond intimate molecular contact must be achieved through spreading and wetting, also chemical bonds must be established. The latter condition ensures the formation of strong cohesive and interfacial bonds, thus, all of the theories discussed aim to fulfill these two pre-conditions.

As discussed the most critical part of the blister sealing process is the function of the heat seal adhesive on the lidding foil and the compatibility with its corresponding sealing surface. However, it was essential to understand the theories of adhesion, the types of adhesives that are commercially available and the important characteristics and properties of adhesives. This will assist my research into developing new adhesives and structures to achieve a higher degree of protection and containment within the blister pack. There are many types of test geometries available to test for adhesive strength and compatibility. However, the present study will focus upon peel behaviour of blister materials by determining the theoretical peel force of the MDPI sealed blister strip using the Imperial College London Protocols to determine the adhesive fracture toughness of adhesive Joints and compare to actual peel force values from studies to introduce a new heat seal lacquer detailed in

Chapter 4.

Chapter 2 Section 3

Literature Review

2.3 *Strength of Adhesive Joints*

2.3.1 *Introduction*

The aim for any adhesive is to give joints that are fit for their intended purpose⁵⁹. The ideal test for adhesive strength is to measure the force or total energy needed to break a joint⁵⁶. Bonded materials are subjected to various stresses⁵⁶, so to fully evaluate a bonded system a number of different test methods are necessary to gauge the relative durability of both the materials and the processes used. The most common test configurations in the adhesives industry are the single lap joint, the double lap joint, the cylindrical butt joint and the peel joint^{67,68}. However, we are primarily interested in the peel joint for the purpose of analysing MDPI blister strip. There are five main purposes for adhesion tests⁵⁸:

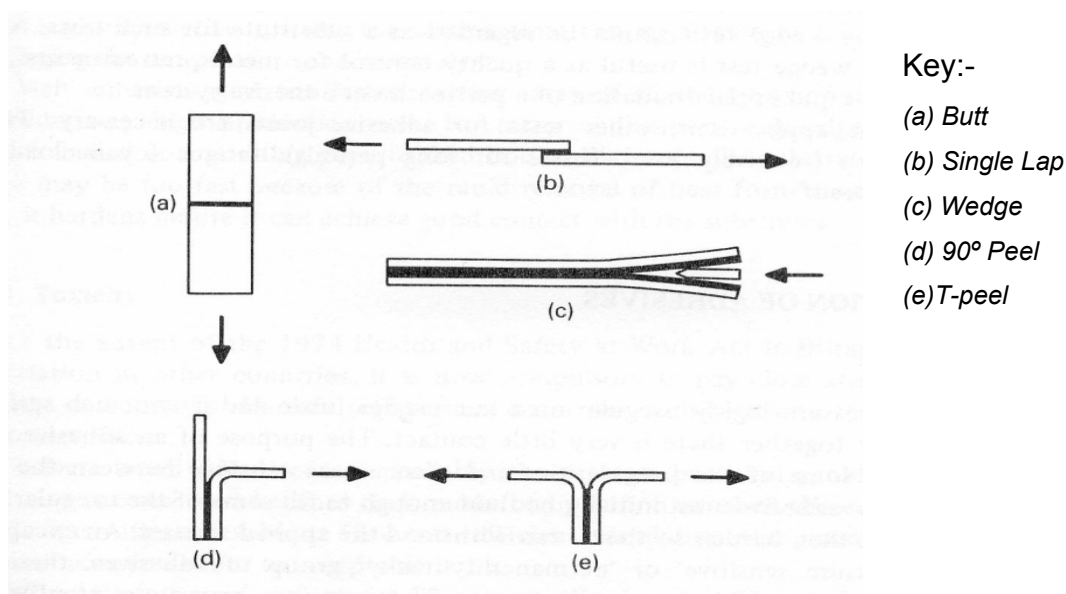
1. To check the quality of an adhesive to see if it falls within defined limits.
2. To determine the effectiveness of a surface pretreatment.
3. To gather data for the prediction of joint performance.
4. To select an adhesive from a group for a specific application.
5. To evaluate the effect of ageing.

2.3.2 *Peel Test*

There are many types of joints, however, the Fixed Arm peel test was the primary test method for adhesion in this study as both adherends were flexible aluminium foil and the adhesive was pressure and heat activated^{67,68}. The

aluminium base foil was adhered to a fixed base plate rendering the aluminium foil non flexible.

Figure 18 - Common Joints, Configurations for Adhesive Strength Tests⁵⁷.



The adhesive strength between the flexible laminates of the MDPI blister strip is of considerable practical importance. Generally, it would be important to maximise the adhesive strength of a given structure²⁷, however, in the case of the MDPI flexible laminates it is a requirement to be able to peel both laminates apart within the inhaler to expose the blister pocket. However, it was paramount to compare the peel strength of the modified heat seal lacquer with standard lidding foil samples and to show how the adhesive fracture toughness (also known as the adhesive strength or interfacial work of fracture) can be determined from the peel strength^{67,68}.

There are important distinctions between peel strength and adhesive fracture toughness, in that peel strength indicates how difficult it is to peel one substrate from another, but adhesive fracture toughness is fundamentally a mechanical property of the adhesive⁵⁶.

The results of a peel test are defined as the average peel force per unit width of the strip peeled. In a peel test, the force is applied so that a flexible member is peeled either from a rigid plate or a second flexible member⁵⁷. The force recorded gives a measure of adhesion⁵⁷. There are variations on this test, such as the 180° peel test, however the test that has been used in this study is depicted in Figure 18, (d), the fixed arm 90° peel test.

In peel tests the substrate is more often rigid and the flexible member is peeled at a defined angle. The advantage of the peel test over other adhesion tests is that each strip peeled yields a trace which shows how the force varies along the whole distance peeled, whereas other adhesion tests only give a single estimate of strength from each piece tested, for instance, the ultimate stress at failure in shear tests and tensile tests⁵⁷. Furthermore, laminates that can be peeled are classified into two types. Firstly, where there is minimum or negligible adhesive thickness, such as where the polymer films are welded together. Secondly, where the adhesive layer is not negligible and its deformation must be taken into consideration during the peel bending process^{67,68}. Both types can be accommodated by these peel tests. In the case of the MDPI laminate we do not need to consider the adhesive layer as the thickness is negligible, but we do need to consider the material structures, that include the aluminium and polymer type layers.

Figure 19 - Analysis of the Fixed Arm Peel Test^{67,68}

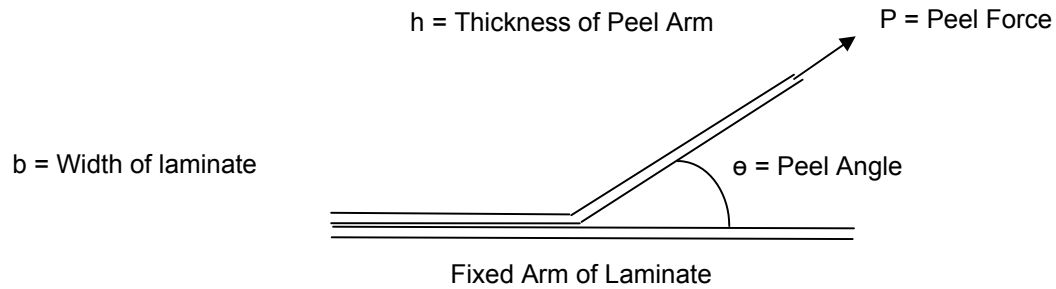


Figure 19 shows the peel of a laminate at a peel angle of θ with a force P acting on the peel arm (laminate width b , peel arm thickness h). For all peel tests on flexible laminates, adhesive fracture toughness (G_A) is obtained by measuring the external energy (G_E) to conduct peel of the laminate whilst making allowance for the plastic bending energy in the peel arm (G_p). A global energy analysis then provides a determination of adhesive fracture toughness [1]^{67,68}.

$$G_A = G_E - G_p \quad (1)$$

For many peel methods, including fixed arm, the peel strength (peel force per unit width of specimen) is measured as well as the stress-strain behaviour of the peel arm. This enables G_E and G_p to be calculated. G_E is determined from the peel strength (P/b) and peel angle (θ), and assuming negligible tensile deformation [2]^{67,68}.

$$G_E = \frac{P}{B} (1 - \cos \theta) \quad (2)$$

In order to calculate the plastic deformation energy (G_p) associated with the peel arm, it is first necessary to have knowledge of the tensile-strain characteristics of the peel arm material. This will include an initial elastic deformation but also a subsequent work hardening and plastic deformation. The plastic bending in the peel tests may then be modeled using large displacement beam theory with modifications for plastic bending^{67,68}.

Solutions have been formulated for bilinear and power law work hardening for the peel arm [3, 4]. Using the terms defined below and when $\varepsilon = \varepsilon_y$

$$\sigma = E \varepsilon \quad [3]$$

However, in both cases where $\varepsilon > \varepsilon_y$ the following equations can be derived:

$$\sigma = \sigma_y \left(\frac{\varepsilon}{\varepsilon_y} \right)^N \quad \text{Power law work hardening model.} \quad [4]$$

And:

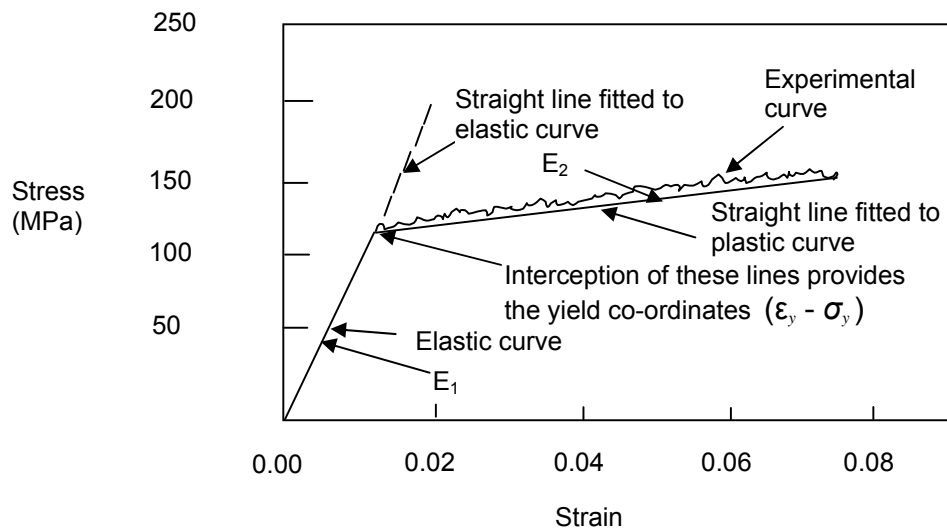
$$\sigma = \sigma_y + \sigma' E (\varepsilon - \varepsilon_y) \quad \text{Bilinear model.} \quad [5]$$

Where N is a constant, σ' is the ratio of plastic modulus to elastic modulus, i.e. E_2 / E_1 , σ_y is yield stress and ε_y is yield strain, N and σ' are the respective work hardening coefficients for power and linear work hardening^{67,68}.

For laminates where the adhesive layer thickness (h_A) is very small ($h = 0$) there is no requirement to consider the deformation in the adhesive in conducting the calculations of adhesive fracture toughness [1]^{67,68}. However, where $h_A > 0$ the deformation in the adhesive layer should be included in the analysis for which it will be necessary to have a knowledge of the modulus of the adhesive material (E_A). In all, these calculations can be complex and whilst a theory analysis is

given in reference [2], software is available to conduct analysis using equations [4, 5]^{67,68}.

Figure 20 – Definition of Yield Co-ordinates (bilinear)

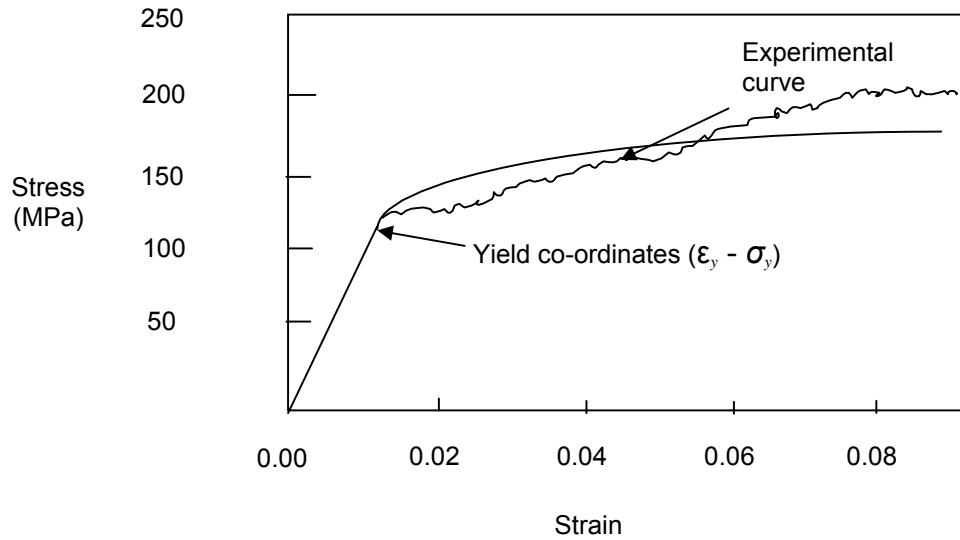


In order to determine G_A without neglecting any of the elastic or plastic deformations, two experiments are required:

- (a) The peel test with a control of the peel angle.
- (b) A tensile stress-strain measurement of the peel arm fracture.

The measured stress-strain curve is modeled to either a bilinear form, as shown in Figure 20, or a power law form as shown in Figure 21.

Figure 21 – Definition of Yield Co-ordinates (power law)



Dependant on the materials being tested one fit may be better than the other, however, for the purpose of the current studies the stress-strain measurements were extracted from the tensile testing equipment then input into the equations to calculate the adhesive fracture toughness. Critical to the analysis is the definition of the yield co-ordinates ($\epsilon_y - \sigma_y$). These can be obtained from the experimental data by the intersection of the plastic and elastic region straight lines^{67,68} as shown in Figure 20. The fitted curves must comply with these co-ordinates as indicated in equations 3 – 5. Therefore, once the yield co-ordinates are defined, then the elastic portion for both models is the line between the origin and these co-ordinates^{67,68}. The plastic region then starts beyond the yield co-ordinates, but for both types of model the fitted curve must pass through the yield co-ordinates^{67,68}.

In general, net stress (force / original cross sectional area) and net strain (increase in length / gauge length) are used. However, if the strain exceeds 10% then a true stress should be used (true stress = net stress [1 + strain])^{67,68}.

Adhesive fracture toughness is determined according to equation 2. Ideally, the corrections for plastic deformation should not be large otherwise errors for the

determination of adhesive fracture toughness will become significant^{67,68}. The size of the correction is given by:

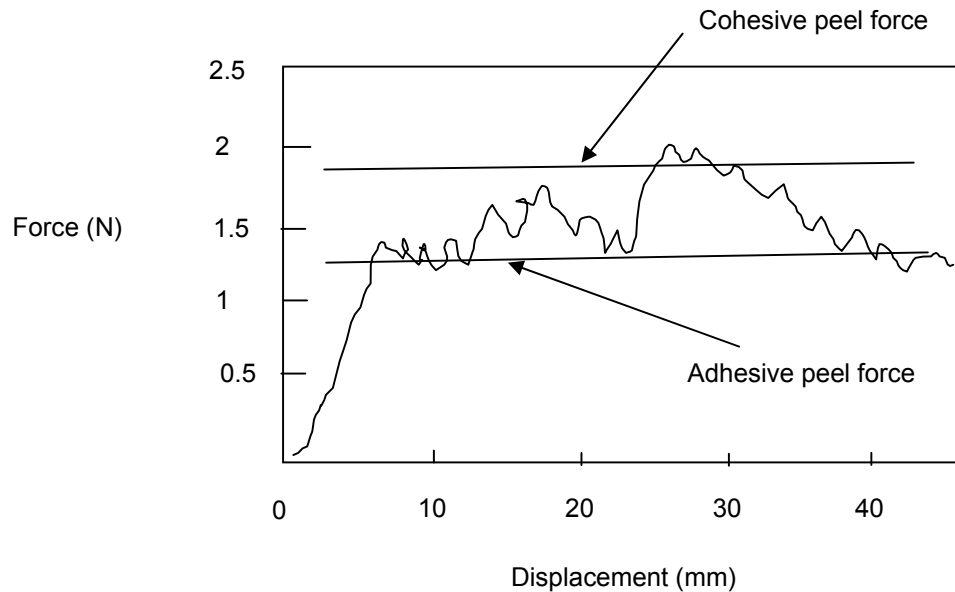
$$\left(\frac{G_p}{G} \right) \times 100\% - \text{The smaller the correction the better} \quad (6)$$

2.3.3 Experimental Procedures in the Fixed Arm Peel Test:

The choice of peel apparatus should incorporate a number of facilities. Firstly, the apparatus should be able to select the peel angle in the range of up to 180°. Secondly, the jig is attached to the Instron or similar instrument such that as peel occurs the angle is maintained constant as the jig moves along a low frictional bearing system. Thirdly, only one side of the laminate is allowed to be the peel arm in the test. Adhering one side of the laminate to the table is critical to the process. If this layer can separate from the table during the test then the energy exerted within the process will increase the measured adhesive fracture toughness to an erroneously high level⁵⁷. The means of gluing the laminate to the table must therefore, be reported⁵⁷. The substrate used for the peel arm should also be reported, as should the length, width and thickness dimensions of the specimen (h and h_A where h is the thickness of the substrate, without any coatings and h_A is the thickness of the adhesive). For the purpose of my protocol a 90° peel angle was chosen with a peel crack speed of 12 mm/min measured from the crosshead.

To determine the adhesive and cohesive fracture toughness it is necessary to plot a force verses displacement curve, this will determine the average peel force; unless there is a combination of adhesive and cohesive fracture, or stick-slip as shown in Figure 22. For these occasions, both the mean lowest and highest force values should be used to determine the adhesive and cohesive fracture toughness values.

Figure 22 – Peel Force versus Deflection in a Fixed Arm Peel Test



In order to conduct the corrections it is necessary to obtain a stress – strain plot on the material of the peel arm. This will need to be described either as a bilinear function or as a linear elastic power law function to accommodate analytical methods to determine the plastic work in the bending peel arm^{67,68}. The tensile test should be conducted at the same speed as the peel test.

To conduct a bilinear elastic fit for the stress / strain curve the following parameters are required:

Data from the tensile test on the peel arm material:

Test speed (mm/min)

E_1 = Elastic modulus, as defined by using small accurate strains at small deformations.

E_2 = Plastic modulus, defined by allowing the tensile specimen to continue its extension for as long as possible.

σ_y = Yield stress

ϵ_y = Yield strain

O' = Modulus of elasticity (E_2 / E_1)

Data from peel test: Peel angle: ($^{\circ}$)
Test speed: (mm/min)
Specimen dimensions: L (mm) b (mm)
Peel arm thickness: h (μm) Substrate only
Thickness of adhesive layer: h_A (μm)
Peel strength (P/b) (N/mm)

Note; if $h_A > 0$ then calculations should be conducted for h_A , using the Modulus of the adhesive E_A (GPa).

Derived results by calculation to the stress / strain data: G_p (J/m²); G_A (J/m²); G_E (J/m²) and Correction factor (%).

Results should be presented for each specimen.

The report should include a plot of the peel curve, 'force verses displacement' in the peel test. The length of peel growth should be marked on the curve and how the peel force used to determine peel strength is derived from the plot. Figure 22 gives a representation of this requirement. The tensile stress-strain plots should also be determine using either the bilinear and / or power law fits^{67,68}.

Chapter 2 Section 4

Literature Review

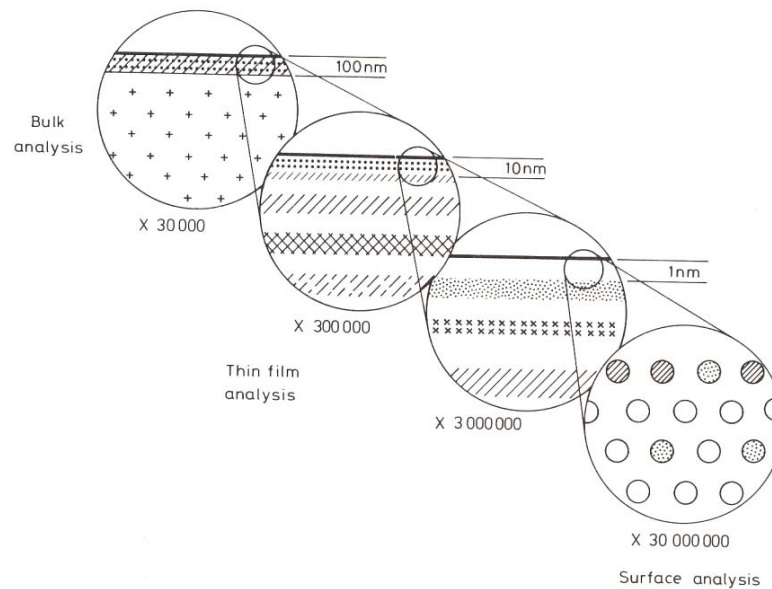
2.4 Material Characterisation and *Surface Analysis*

2.4.1 Introduction

To ensure the materials and adhesives used in the manufacture of blister packs are compatible with the blister sealing equipment, it was essential to gain knowledge of the surface and material characteristics of the sealing layers. By using a number of surface analysis techniques this was achievable.

Surface analysis uses chemical and physical probes to give information about the surface region of a sample⁶⁹. The area probed may be the extreme top layer of atoms or it may extend up to several microns beneath the sample surface, depending on the technique used⁶⁹. The analysis is performed to provide information on such characteristics as the chemical composition, the level of trace impurities or the physical structure of the sampled region⁶⁹. Figure 23 demonstrates the transition from bulk to surface analysis.

Figure 23 - Area of Interest in Surface Analysis⁵⁷.



The most commonly used surface analytical techniques for chemical analysis are X-ray Photoelectron Spectroscopy (XPS), Auger Electron Spectroscopy (AES), and Secondary Ion Mass Spectrometry (SIMS)⁶⁹. Surface topography or texture is most usually studied using SEM or Atomic Force Microscopy (AFM). Related techniques such as profilometry can also be used to provide quantitative data over a macroscopic area⁵⁷. Table 7 provides a summary of the main parameters of these test methods⁵⁷.

Table 7 - A Comparison of Surface Analytical Techniques⁵⁷

Parameter	AES	XPS	SIMS
Excitation source	Electrons	X-rays	Ions
Species detected	Electrons	Electrons	Ions
Spatial resolution	100nm	100µm 10µm (imaging)	1µm (SSIMS) 20nm (imaging)
Sampling depth	2-5nm	2-5nm	0.1nm (SSIMS)
Depth profile	Yes	Yes	Yes
Quantitative	Yes	Yes	Yes
Compound information	Limited	Yes	Yes
Sensitivity	>0.1%	>0.1%	0.1% (SSIMS) ppm (DSIMS)
Elemental range	Li-U	Li-U	H-U
Sample types	Metals, ceramics, flat glasses, limited data from polymers	All solids	All solids

2.4.2 Principle Techniques Employed in this Research Study

The principle surface technique employed in this research was SEM and the techniques used to analysis the material characteristics were FTIR Spectroscopy and DSC.

Fourier Transform Infrared Spectroscopy

FTIR is sensitive to the presence of chemical functional groups in a sample⁶⁹. Once the wave number positions of the bands of a functional group are known, the information can be used to identify that functional group in many samples via appropriate data compilations or obtained from the published literature⁶⁹. FTIR spectra can also be used to confirm molecular identities⁶⁹. This involves comparing the spectra of two samples to each other to determine whether the samples have the same composition. Finally, the peak intensities in an infrared spectrum are proportional to concentration, so FTIR spectra can be regarded as semi-quantitative and used to measure concentrations^{57,69}.

The capability of FTIR to detect chemical functionalities makes it a useful technique in adhesion studies especially when investigating joint durability. In such cases studies where many functionalities maybe present, as a result of hydration or due to the presence of coupling agent or primer that sustain adhesion in adverse conditions, FTIR has proved to be invaluable⁵⁷. Metals are often chemically pretreated so that joints are able to sustain their strength in adverse conditions. These pretreatments enhance bonding by chemically modifying the surface of the adherend⁵⁷. Fondeur and Koenig⁷⁰ used FTIR to characterise the surfaces of aluminium after various pretreatments. FTIR was able to distinguish between the different forms of oxide produced by the pretreatments.

FTIR spectra can be plotted in transmission or absorbance. However, for spectra being used in quantitative analysis, such as measuring concentrations, absorbance must be used⁶⁹. This is because Beer's Law states that absorbance and concentration are linearly proportional⁵⁷. Transmittance and concentration are not linearly proportional, making transmittance spectra ill-suited for quantitative analysis⁵⁷.

As the strength of the absorption is proportional to the concentration FTIR can be used for quantitative analysis. By maintaining constant sample geometry and keeping the infrared optics the same for all measurements, a linear relationship can be observed between the infrared absorption and the peak areas or heights from a particular sample⁶⁹.

In this study, FTIR absorbance spectra has been used successfully to confirm the identity of polymeric layers within new and existing blister laminates. The results of which are documented in **Chapter 4**.

General Introduction to Differential Scanning Calorimetry

DSC is a technique used to study the thermal transitions of polymers⁷¹. DSC experiments measure how much more heat has to be supplied to a sample material in order to maintain a constant rate of heating between the sample material and the reference⁷¹. In the most common DSC design, two pans sit on a pair of identically positioned platforms connected to a furnace by a common heat flow path. The polymer sample goes in one pan. The other pan is known as the reference and is left empty. The experimental conditions, such as heating rate and temperature are then programmed into the computer, which turns on the furnace⁷¹. So the computer turns on the furnace and tells it to heat the two pans at a specific rate, usually at 10°C per minute. The computer can maintain a constant heating rate throughout the experiment⁷¹. More importantly, it ensures that the two separate pans heat at the same rate as each other. DSC is used to determine thermodynamic properties of polymers, such as heat capacity, glass transitions, melting and crystallisation temperatures⁷¹. It can also be used to detect kinetic processes such as cure and physical ageing⁷¹. In this study, DSC has been used successfully to confirm the melting points of polymeric layers within new and existing blister laminates. The results of which are documented in **Chapter 4**.

Scanning Electron Microscopy

Electron microscopes have been developed to exploit the imaging and analytical capability which results from elastic and inelastic scattering of electrons within materials⁷². The information gained from effects can include:

- High resolution imaging of thin sections of material.
- Characterisation of surfaces by secondary and backscattered electrons.
- Crystallographic information via electron diffraction data.
- Photoelectron and Auger electron characterisation of surfaces.

The components of the scanning microscope include an electron source using, for example conventional tungsten filaments, a condenser lense system to focus the fine beam of electrons onto the specimen surface, a scanning system to translate the electron beam over a selected area of the specimen, and a detection facility to collect an image from the specimen and to control image contrast⁷². The magnetic condenser and objective lens serve to reduce the image to a final spot size on the sample of 1 to 200nm⁷². The interactions of a solid with an electron beam can be divided into two categories, elastic interactions that affect the trajectories of the electrons without altering their energies significantly, and inelastic interactions, which result in the transfer of part or all of the energy of the electrons to the solid⁷². The excited solid then emits secondary electrons, Auger electrons, X-rays and longer wavelength photons⁷².

Table 8 – Advantages and Disadvantages of SEM⁷²

Advantages	Disadvantages
Provides morphologic and topographic information.	The interaction of the electron beam with the specimen can be affected by the specimen's chemical composition, topography, and the magnetic and electrical properties.
Knowledge of the physical nature and chemical composition of a surface.	Restricted sample area.
Versatile and simple technique.	
Easy sample preparation.	
Good sensitivity.	

In this study, SEM has been used successfully to confirm that the heat seal lacquer from the MDPI lidding foil had penetrated sufficiently into its opposing sealing layer (base laminate) to guarantee that a good hermetic seal had been achieved. The results of which are documented in **Chapter 4**.

Chapter 2 Section 5

Literature Review

2.5 Heat Transfer into Blister Strips

2.5.1 Introduction

To determine the temperature of the filled active product in the blister filled strip it was essential to understand the basic laws of thermal transfer, heat transfer mechanisms and the flow of heat through the blister foil laminate during the platen sealing process.

2.5.2 Basic's of Heat Transfer

In the simplest terms heat transfer is concerned with temperature and the flow of heat⁷³. Temperature represents the thermal energy available, whereas heat flow represents the movement of energy from place to place⁷³.

On a microscopic scale, thermal energy is related to the kinetic energy of molecules⁷⁴. The greater the materials temperature, the greater the thermal agitation of its constituent molecules, manifested both in linear motion and vibrational modes⁷⁴. It is natural for regions containing greater molecular kinetic energy to pass this energy through regions with less kinetic energy⁷³.

Several material properties serve to modulate the heat transfer between two regions at differing temperatures⁷³. Examples include thermal conductivities, specific heats, material densities, fluid velocities, fluid viscosities and surface emissivities. Taken together, these properties serve to make the solution of many heat problems a very complex process⁷³.

Heat Transfer Mechanisms^{75,76,77,78}

Heat transfer mechanisms can be grouped into three broad categories:

- 1) **Conduction:** Regions with greater molecular kinetic energy will pass their thermal energy to regions with less molecular energy through direct collisions, a process known as conduction. In metals a significant portion of the transported energy is also carried by conduction band electrons. To simplify, the heat is transferred by means of molecular agitation within a material without any motion of the material as a whole. If one end of a rod is at a higher temperature, then energy will be transferred down the rod towards the cooler end because the higher speed particles will collide with the slower ones. The rate of conduction heat can be described by using either formulae (7) or Fourier's law of heat conduction:

$$\frac{Q}{t} = \frac{kA(T_{hot} - T_{cold})}{d} \quad (7)$$

Q = Heat transferred in time = t

K = Thermal conductivity of the barrier

A = Area

T = Temperature

D = Thickness of barrier

Fouriers Law of Heat Transfer by Conduction – States that:

$$q_{conv} = -k A \nabla T \quad (8)$$

Where; q_{conv} = Heat flow (W), $-k$ = Thermal conductivity ($Wm^{-1}K^{-1}$),
 A = Area (m^2), ∇ = Gradient in Temperature (K)

This equation determines the heat flux vector q for a given temperature of specific thermal conductivity k . The minus sign ensures that heat flows down the temperature gradient.

- 2) **Convection:** When heat conducts into a static fluid it leads to a local volumetric expansion. As a result of gravity induced pressure gradients expanded fluid parcel becomes buoyant and displaces, thereby transporting heat by fluid motion, termed 'convection'. Such heat induced fluid motion in initially static fluids is known as 'free convection'.

For cases where the fluid is already in motion, heat conducted into the fluid will be transported away, primarily by fluid convection. These cases are known as forced convection. This requires a pressure gradient to drive the fluid motion, as opposed to a gravity gradient to induce motion through buoyancy. The rate of convection can be described by Newton's law of heat convection:

Newton's Law of Heat Transfer by Convection – States that:

$$q_{\text{conv}} = h_c AT \quad (9)$$

Where; q_{conv} = Heat flow (W), h_c = *Convective heat transfer coefficient* ($\text{Wm}^{-2}\text{K}^{-1}$), A = *Area* (m^2), Δ = *Differential in Temperature* (K)

- 3) **Radiation:** Radiation is the only form of heat transfer that can occur in the absence of any form of medium, thus it is the only means of heat transfer through a vacuum. Thermal radiation is a direct result of the movement of atoms and molecules in a material. Since these atoms and molecules are composed of charged particles (protons and electrons), their movements result in the emission of electromagnetic radiation, which carries energy away from the surface. At the same time, the

surface is constantly bombarded by radiation from the surroundings, resulting in the transfer of energy to the surface. Since the amount of emitted radiation increases with increased temperature, a net transfer of energy from higher temperatures to lower temperatures results. The rate of radiation can be described by Stefan-Boltzmann law for radiation:

Stefan-Boltzmann Law for Radiation – States that:

$$q_r = \sigma A \varepsilon (T_1^4 - T_2^4) \quad (10)$$

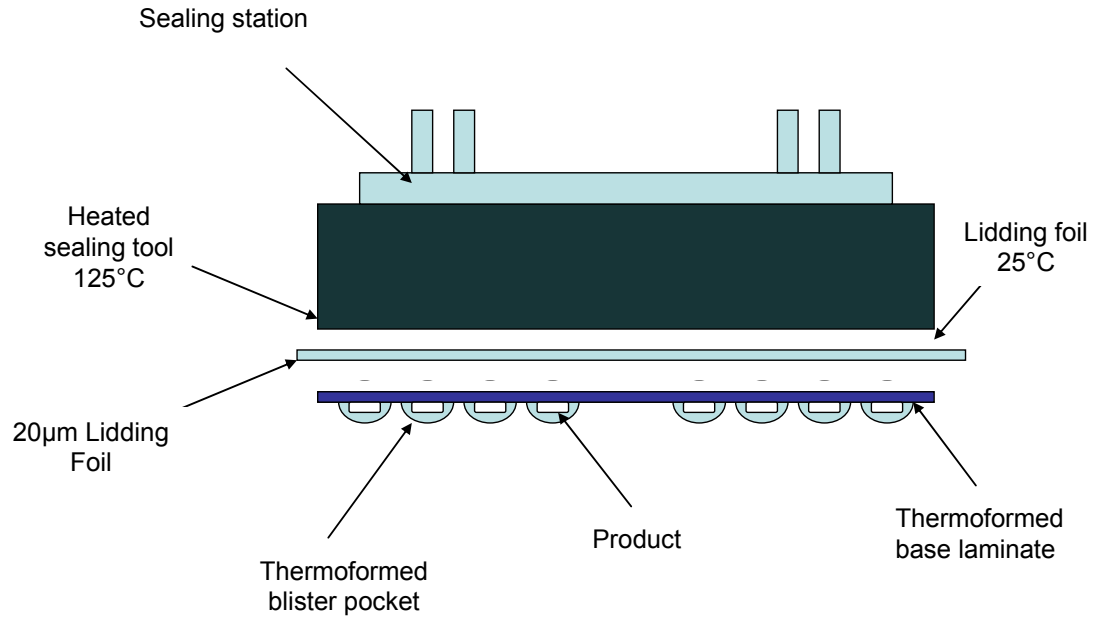
Where;

- q_r = Radiated heat
- σ = Stefan-Boltzmann constant ($\text{Js}^{-1} \text{m}^{-2} \text{K}^{-4}$)
- ε = Emission of object (ratio, no units)
- A = Area (m^2)
- T = Temperature (K)

2.5.3 Introduction into Heat Flow Equations^{75,76,77,78,79,80}

To model the heat flow within the platen heat sealing tool we are concerned with one main types of heat transfer, 'conduction'. The following heat transfer equations will be used as starting points to determine the required equations to determine the transfer of heat from the sealing surface plate to the product as depicted in Figure 24.

Figure 24 – Schematic of the Platen Sealing Station



Heat Equation (Temperature Determination)⁷⁸

The temperature profile within a body depends upon the rate of its internally-generated heat, its capacity to store some of this heat, and its rate of thermal conduction to its boundaries (where the heat is transferred to the surrounding environment). Mathematically this is stated by the Heat Equation:

$$\nabla^2 T - \frac{1}{\alpha} \frac{\partial T}{\partial t} = -\frac{1}{k} q_{gen} \quad (11)$$

along with its boundary conditions, equations that prescribe either the temperature T on, or the heat flux q through, all of the body boundaries Ω :

$$T(\Omega_a) = T_{prescribed} \quad (12)$$

$$q(\Omega_b) = q_{prescribed} \quad (13)$$

$$\Omega_a \cup \Omega_b = \Omega \quad (14)$$

In the heat equation, the power generated per unit volume is expressed by q_{gen} . The thermal diffusivity α is related to the thermal conductivity k , the specific density ρ by:

$$\alpha = \frac{k}{\rho c} \quad (15)$$

For steady state problems, the heat equation then simplifies to:

$$\nabla^2 T = -\frac{1}{k} q_{gen} \quad (16)$$

Derivation of the Heat Equation

The heat equation follows from the conservation of energy for a small element within the body.

$$\begin{array}{ccccccc} \text{Heat} & & \text{Heat} & & \text{Heat} & & \text{Change in} \\ \text{conducted in} & + & \text{generated} & = & \text{conducted} & + & \text{energy stored} \\ & & \text{within} & & \text{out} & & \text{within} \end{array}$$

We can combine the heats conducted in and out into one net heat condition to give:

$$\begin{array}{ccccc} \text{Net heat} & & \text{Heat} & & \text{Change in} \\ \text{conducted} & = & \text{generated} & - & \text{energy stored} \\ \text{out} & & \text{within} & & \text{within} \end{array}$$

Mathematically, this equation is expressed as:

$$\nabla \cdot \mathbf{q} = q_{gen} - \frac{de}{dt} \quad (17)$$

The change in energy e is related to the bodies ability to store heat by raising its temperature, given by:

$$\left(\frac{de}{dt} \right) = \rho c \left(\frac{dT}{dt} \right) \quad (18)$$

One can substitute for \mathbf{q} using Fourier's law of heat conduction from above to arrive at the heat equation then becomes:

$$\nabla (-k \nabla T) = q_{gen} - \rho c \left(\frac{dT}{dt} \right) \quad (19)$$

$$-k\nabla^2 T + \rho c \left(\frac{dT}{dt} \right) = q_{\text{gen}} \quad (20)$$

$$\nabla^2 T - \frac{1}{\alpha} \frac{\partial T}{\partial t} = -\frac{1}{k} q_{\text{gen}} \quad (21)$$

Understanding of the heat equations and modes of heat transfer were essential to enable the modelling of the platen sealing process. The process is mainly heated by heat conduction through heating elements inside the sealing tool assembly, see Figure 24.

In summary, **Chapter 2** details the relevant literature to the study of blister pack formulation including a consideration of the materials, processes and adhesion mechanisms. Consideration has also been given to the fundamentals of heat flow relevant to blister packaging. Importantly, a number of issues relating to the use of new materials and processes have been described. In the present study we will address issues concerned with the introduction of new materials and provide a scientific understanding of their performances. The new material studies include;

- New heat seal lacquers to give improved sealing characteristics.
- New primary contact materials with improved barrier to moisture.
- New base laminate that is more resistant to delamination.
- The heat transfer through primary contact blister foils.
- The peel characteristics of different blister packs.
- Development and qualification of new sealing tools.

This thesis also includes in **Chapter 7** details on Future Development opportunities that can now be researched and progressed following the results and conclusions from this study.

Chapter 3 details the experimental methodology and the test procedures used during this study.

Chapter 3 Section 1

Experimental

3.1 Methodologies and Procedures used during this Study of Blister Sealing

This section details the test methodologies and procedures used in the present study.

3.1.1 Introduction

Pharmaceutical packaging requires more attention to detail than most other types of packaging due to the critical nature of the materials required to protect the active product throughout its shelf life^{2,18,55,81}. The types of packaging material / design can also be influenced by the respective markets and heavily regulated by the authorities^{2,18,54,82}. The pharmaceutical pack must protect the product against mechanical, climatic, microbiological and human hazards, it may require child resistance and / or pilfer-resistance, it must also be compatible with the product^{4,54,81,82}. The selection of the materials depend on the chemical and physical barrier demands of the pharmaceutical product^{4,81,82}. The more moisture sensitive the product, the better the moisture vapour transmission barrier properties must be^{2,54,81,82}. Other considerations are machinability, production rates, depth of the blister, wall thickness, uniformity of the blister and sealing properties to the lidding stock⁸. Expensive and time consuming testing must therefore take place to verify the integrity of the blister pack and confirm the suitability of the chosen material²⁷, because any failure of the packaging system may result in ultimate failure of the active product to administer its required dose²⁷.

The following section details the types of testing required to confirm material suitability and pack integrity, and also gives an example of the experimental methodology used to introduce new materials into the pharmaceutical industry.

3.1.2 Protection Against Moisture

Introduction to Moisture Permeation in Pharmaceutical Blister Packs

Stability testing demonstrates the physical and chemical stability of drug products at a variety of environmental conditions including temperature, humidity and light⁸². Requirements for stability studies are defined in a number of ICH guidelines, including and storage conditions of 25C/60%RH, 30C/60%RH and 40C/75%RH⁸³.

The challenge for any moisture sensitive compound is to demonstrate stability at the accelerated condition of 40C/75%RH for 6 months. Many compounds are moisture sensitive and exposure at the accelerated condition results in significant product degradation⁵⁴. This part of the present study will determine the moisture content of a number of thermoform and cold form blister laminates that have been introduced by using the moisture content of the packaged product, and the moisture permeation rate of the blister laminate to predict the stability of the packaged product.

In the pharmaceutical industry the preferred package options are bottles or blisters⁵⁴. The most common blister materials are PVC, PVdC, Aclar PCTFE, aluminium foil and more recently, COCs⁸⁴. PVC is often preferred for drug products primarily due to its low cost and ease of processability⁸⁵. However, a disadvantage of PVC is that it has minimal moisture barrier properties⁸⁴. Aclar, comprised of laminated PVC, has superior moisture protection properties than either PVC or PVdC^{84,85,86}. Another disadvantage of PVC is the environmental issues associated with the disposal of films containing PVC, due to the chlorides present in the polymer matrix⁸⁵. A relatively new environmentally

acceptable blister film is copolymer of ethylene and COCs^{84,85,86}. The most impermeable moisture barrier is provided by coldform aluminium foil^{8,10}.

The usual practice of producing blisters and placing them on test in a chamber at 25°C/75%RH and 40°C/75%RH to test for moisture ingress, may produce very misleading results, particularly if a moist environment readily flows around the blister^{2,18}.

In actual practice blisters may be enclosed in a carton, and possibly over-wrapped, cartons are then placed in an outer corrugated case, and the case loaded on a pallet that is over-wrapped. All of these activities reduce the flow of moist air around the pack and provide a series of moisture barriers. It therefore, may not be surprising to find that in 24 – 48 months storage of a pallet that there is no actual moisture change in the product. Over-wrapping of individual cartons or the outer can therefore, significantly increase the shelf life of the product when stored on a pallet in a warehouse or as outers in a wholesalers or in a pharmacy^{2,27}. The predicted shelf life from a chamber test may therefore, carry an unnecessary safety factor or even indicate that a blister pack would not be suitable, when under actual conditions it could be acceptable^{2,18}.

Determination of Moisture Permeation of Blister Laminates.

The moisture permeability of a number of blister packs was determined according to the Containers Permeation Procedure⁸⁷. Blisters containing a hygroscopic lactose were stored at 23°C/75%RH and monitored for weight gain at four intervals over a period of 28 days. The weight gain was used to determine the moisture permeability through the container and was expressed as mg/per blister/per day⁸⁸. The theoretical moisture ingress can then be calculated by the United States Pharmacopeia (USP) 671 or 661 Containers-Permeation test⁸⁸ and compared to the actual results using the materials permeation rates as indicated for MDPI sealed blisters in Table 9.

Table 9 – USP Container-Permeation Results

Material	Container-Permeation (mg/blister/day)
Aluminium coldform blister	0.001
polyvinyl chloride	0.259
cyclic olefin copolymer	0.040

As expected, the aluminium foil gives the lowest permeability rate compared to all blister materials as detailed in Table 9. The aluminium foil had a Containers Permeation value of 0.001 mg per blister per day, which compared to PVC having a containers permeation value of 0.259 mg per blister per day, approximately a 200-fold difference. The new COC material container's permeation value is nearly seven times lower than that of PVC at 0.040 mg per blister per day.

Moisture Vapour Transmission Rate for Coldform Blisters

The decisive criterion for the impermeability of the pack to water vapour is the tightness of the seal⁸⁹. In the case of a tightly sealed blister, atmospheric moisture can only penetrate either through the seal, or the PVC layer⁸⁹, see Figure 25. A desiccant, 'generally calcium chloride' is filled into the blister pockets prior to sealing. Blisters are then stored at 40°C/75RH for 28 days and tested at various time-points⁸⁹. This procedure was performed in studies detailed in **Chapter 4** for the development of blister foils.

Figure 25 – Moisture Diffusion through the Seal^{4,8,10}

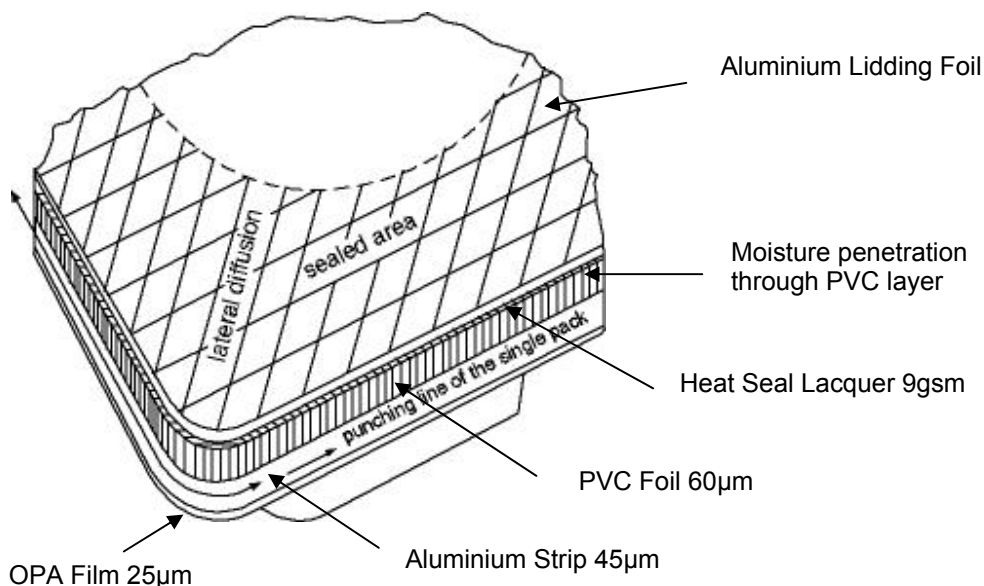
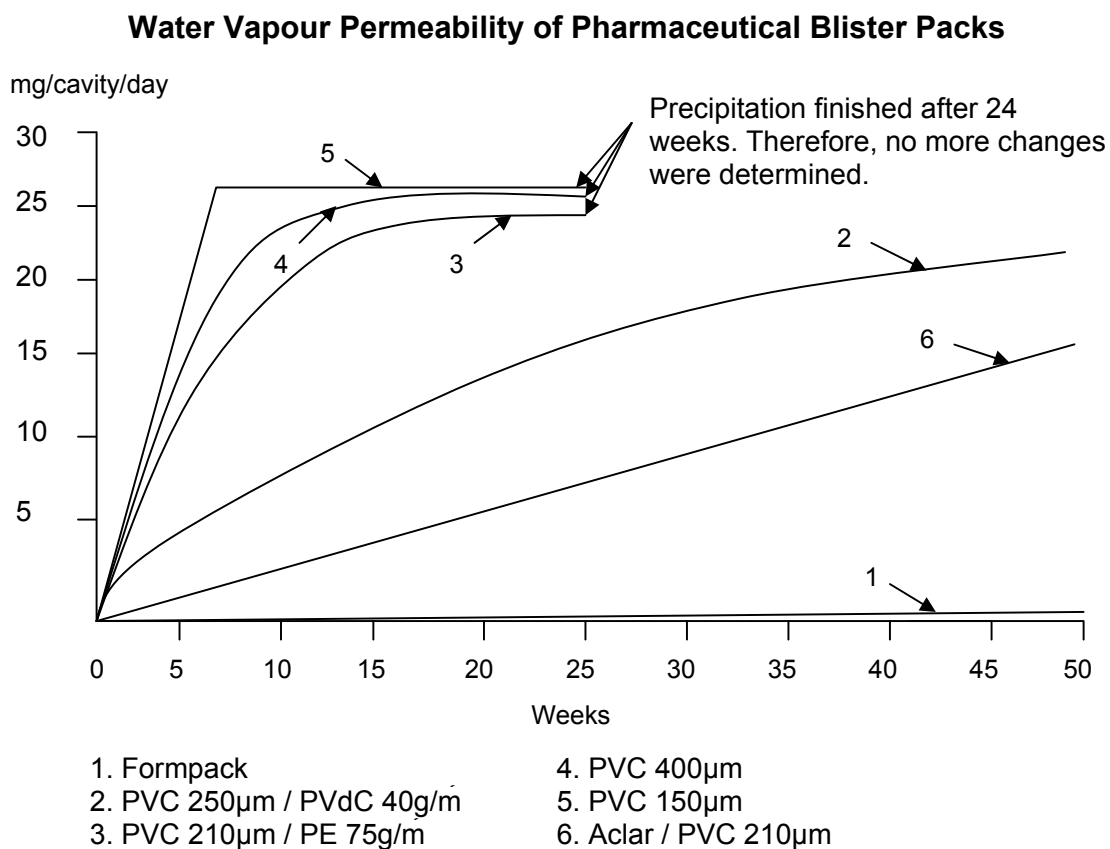


Figure 26 shows the water vapour permeability of pharmaceutical blister packs. Only the Formpack material does not show significant absorption of water vapour after 52 weeks testing at ambient conditions⁸⁹. The slight increase is due to the cross diffusion through either the PVC or the seal through the unsealed areas (land areas) or the edge of the blister into the cavity, see Figure 25. Although, this diffusion is almost negligible it is however, the decisive factor for products that are moisture sensitive and therefore, require a cold-form aluminium / aluminium blister²⁴. To further increase the barrier to diffusion, the distance, cavity to land area can be increased, resulting in decreased quantities of water vapour which might diffuse into the cavity^{8,24}.

Diffusion across the land area, perforation into the cavity and moisture uptake of the product can be calculated^{8,24}. To carry out this calculation the adsorption isotherm of the material, the length of the non-sealed area and the ratio of the perforation (length of cuts) are required⁸. In this study, the permeation rate of MDPI blisters was successfully calculated using this method. The results are documented in **Chapter 4**.

Figure 26 – Permeation Rates of Pharmaceutical Blisters



3.1.3 Process Leak Testing

Leak testing is generally carried out on a blister from each position on the sealing station, at the beginning and end of each work period, and at prescribed intervals throughout the run^{1,18,20}. Tests are normally conducted on filled as opposed to empty blisters, as misaligned tablets or undersized blisters can result in leaks. It is strongly recommended that non-destructive methods are used rather than using empty blister in a destructive test. It should be noted that these methods will not normally identify pocket-to-pocket leakage, and so must be supplemented by close visual examination for other critical defects; especially micro-channelling⁸.

Leak testing was conducted on all sealed blister laminates introduced as part of the present research studies to ensure that a sufficient seal will be formed between the lidding foil and the base laminates using the methylene blue dye test.

Dye Bath Test (Destructive test, pack needs to be opened)

Samples are placed in a bath of dye, typically methylene blue, within a vacuum chamber which is first evacuated to 51×10^3 Pa of mercury and held for 60 seconds, and then equilibrated to ambient pressure²⁰. If there is a leak, headspace is drawn out of the samples and replaced by dye²⁰. After washing and drying, the samples are opened and the contents / inner surfaces visually examined for ingress of dye. This is the most widely used leak test, but there is very little quantitative data to define its detection limits, this has been investigated as part of this study. There are many instances where products have failed stability trials due to moisture ingress, but the dye bath test has shown no defects. The pharmaceutical industry has recognised this and a number of companies are currently evaluating various non-destructive blister leak test methods.

Burst / Seal Strength

It is important to ensure that handling and shipping does not destroy the blister strip, which has left the site without leaks. It must remain sealed to maintain adequate shelf life and / or the desired quality when it reaches the consumer²⁰. Air pressure is introduced into the package until it bursts. The burst point pressure is held so that it can be recorded. This burst test should be repeated several times to get an average. Analysis of this data would be required if damaged packages were discovered by a consumer.

Thermal Conductivity Detector

A tracer gas, such as helium, carbon dioxide, or butane, is pressurised in the package, and a probe senses change in gas thermo-conductivity as the tracer gas enters the probe^{8,42}. This method does detect the leakage point, however, it is also highly operator dependent because if the probe is moved too fast or too far away from a hole, nothing will be detected¹.

Helium Leak Detector

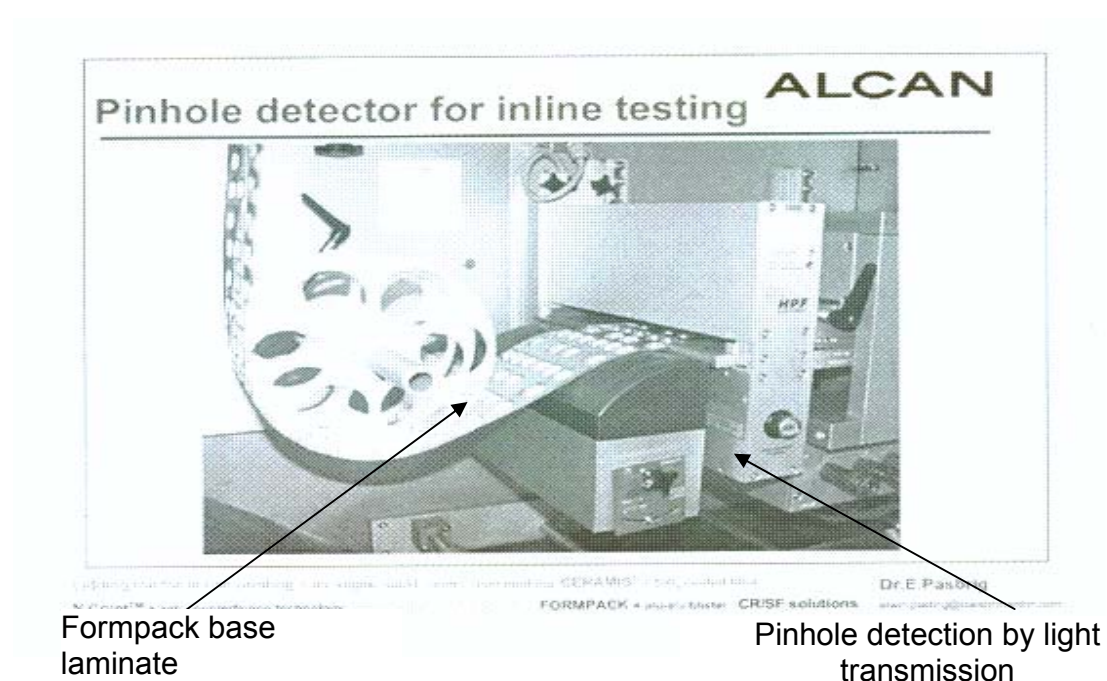
This has the greatest sensitivity²⁴. Firstly, the package is inflated (pressure) with helium. A detection probe is then used to sniff around the package to find any leaks²⁴. The major disadvantages are:

- 1) High operator dependence.
- 2) High initial cost (for supplies, etc.) and unit maintenance.
- 3) Time consuming to rectify faults.

Pinhole or Split Detection

After the base foil has been through the pocket forming station the web is constantly monitored for pinholes or splits that may have occurred as a result of either the foil manufacturing process and / or the laminating process or the blister forming process⁸. This is normally achieved by applying a high intensity light source to one side of the foil, whilst sensitive detectors scan the other side for light transmitted through imperfections⁸, see Figure 27. The technique can be shown to be capable of detecting the equivalent of a 100µm hole, but is not sensitive enough to detect all faults likely to affect product quality. There is also a risk that the lidding foil may be defective, but as this material is not inspected on line, we are relying on the control and efficiency of the lidding foil manufacturing and printing process and finished product stability data.

Figure 27 – Pinhole Detector for Inline Testing⁸



Tracer gas (e.g. Mocon) (non-destructive)

The principles are basically similar to the dye bath test, but utilise a suitable tracer gas such as CO₂ which can then be automatically detected^{8,42}. The techniques have been shown to be more sensitive and reproducible than the dye bath and have the major advantage of being non-destructive^{8,42}. However, there is a relatively high equipment cost, and some concerns as to its robustness for routine production use^{8,42}.

Pack Deformation (non-destructive test)

In this technique the pack is subjected to a cycle of pressurisation and / or evaluation⁴². The surface of the lidding foil is monitored at the centre of each blister pocket and the amount of movement between the maximum and minimum pressure points across the blister is measured⁴². In principle leaking blisters will exhibit little or no movement of the lid surface compared to non leaking blisters. Manual and automated systems are available and more

sensitive detection techniques are being developed including laser displacement for intricate items^{20,42}.

3.1.4 Seal (peel) Strength Test

Seal strength of the lidding materials are tested against the standard Formpack base material.

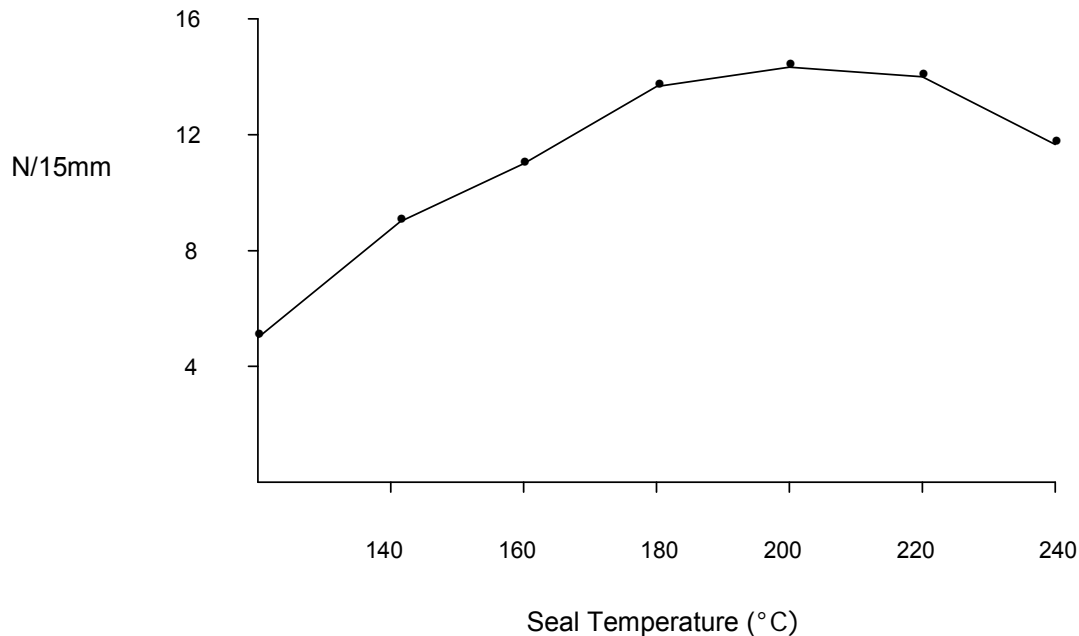
Test procedure:

- a) By means of a suitable cutting device strips of bottom and lidding web, 15 mm long, are cut in the machine direction.
- b) Strips are then, put together with the heat-sealed surfaces facing each other and are sealed:
 - Jaw temperature = 160 °C +/- 5°C
 - Jaw surface = smooth
 - Initial pressure = 25 N/cm²
 - Initial dwell time = 3 x 1 second
- c) After cooling down to ambient temperature, sealed strips are inserted in a tensile tester:
 - Separation speed = 100 – 120 mm/min
 - Separating angle = 180°

Seal Strength Testing of Formpack Material

To confirm the seal tightness of the standard Formpack material tests were carried out at Alcan Packaging. Figure 28 shows that a strong seal is achieved at between 180°C to 220°C.

Figure 28 - Standard Heat Seal Lacquer (LA723), Sealed against Standard PVC within Formpack Base Material²⁵



The sealed strips are pulled apart by means of a Variable Angle Peel Tester (VAPT), the average of the peeling force is given in N/15 mm. There is no national or international standard for the sealed seam strength of push-through foils²⁵. Nevertheless, the following unwritten limits are accepted in Europe: the value should not be below 7 N/15 mm. For peelable openings there are no set values, generally they range between 3 to 8 N/15mm.

3.1.5 Device Indexing Force Testing (Torsion Hub)

To ensure any functional changes to the equipment and any material changes within the Multi-Dose Powder Inhaler do not impact the performance of the device the Torsion Hub test was devised. Both individual and mean operating forces within the device are determined by fixing devices in a locating assembly and automatically indexing them. The design intent range for individual operating forces is between 3 – 15N; and the mean design intent range is between 5 – 10N.

3.1.6 Coating Weight of Heat Seal Lacquer

The coating weight of the heat seal lacquer on the lidding stock is generally determined during lacquer application at the end of the reel on the left and right edges⁹⁰. Additional manual measurements across reel length are not possible. To do this, the process would have to be stopped, lose its stability and additional waste would be created⁹⁰. Although, recent developments in Infrared (IR) technology have lead to the installation of IR cameras to continuously monitor lacquer weight transversally across the reel width⁹⁰.

3.1.7 Accelerated Shelf-life Tests

Accelerated shelf-life tests may be necessary to check out certain packs, especially where uncertainty exists with relation to creases (possible capillary type ingress / egress) and the presence of pinholes / perforations in the main body of the pack⁴. Extremes of temperature, and RH, and cycling conditions may be used⁴.

3.1.8 Experimental Techniques used to Investigate Bond Formation

A variety of factors affect the quality of adhesively bonded MDPI blister strip, for example surface preparation and the strength of the adhesive itself, therefore it requires a number of sophisticated analytical techniques to solve any adhesion problems.

Initially, the strength of the adhesive was measured and compared to a standard material, and this will be achieved primarily using the Fixed Arm peel test^{67,68}. As described in Section 3.1.4, this test was also used as a way of identifying any unsealed areas of the MDPI Lidding foil with the new heat seal lacquer. The new foil was investigated using surface analysis techniques such as SEM to identify any differences in bond formation along the length of the MDPI blister strip. The experimental techniques outlined in Table 10 were

described in greater detail in terms of their basic principles, advantages and limitations, and their use in this study in Section 2.4. Table 10 also summarises the purpose of each experiment.

Table 10 ***A Summary of Experimental Techniques and their uses in the Present Study***

Experiment	Function
Fixed Arm Peel Test	Measure adhesive strength.
Surface analysis - SEM	Failure mode analysis.
Kinetic analysis - DSC	Identify the thermal transitions of polymers.
Kinetic analysis - FTIR	Identify chemical functional groups, and molecular identities for good bond formation.
Tensile test	Effect of the modified heat seal lacquer on bulk adhesive mechanical properties.

What follows are the results of studies incorporating these experimental techniques in the order they were carried out in this research.

Chapter 4 - Results

Introduction

Following are the results of studies into the critical aspects of the blister sealing process. The primary objective being to achieve a good hermetic seal and ensure total product protective by controlling the heat flow of constant temperature at the sealing medium; preventing any moisture ingress into the blister pack and guarantee consistency of peel force of lidding and base laminates. Initially, the heated platen sealing process has been modelled. Furthermore to this, the moisture ingress into sealed blisters has been calculated and the theoretical and actual peel force values for a number of blister formats has been determined.

Additional to the aforementioned studies, a number of new materials have been introduced using the techniques and test procedures described in **Chapter 3**, such as:

- Introduction of a robust MDPI lidding foil.
- Development and introduction of a new rotary sealing tool.
- Introduction of an alternative adhesive and primer system in an aluminium cold form base laminate.
- Introduction of a new heat seal lacquer in the MDPI lidding foil.
- Introduction of an alternative clear polymer base laminate.

The aim of each study being to provide critical information on the blister sealing process.

Chapter 4 – Section 1

4.1 Modelling of the Heated Platen Sealing Process

4.1.1 Introduction

By understanding the modes of heat transfer and the equations relating to each mode combined with the knowledge of the platen sealing process it can be derived that the principal mode of heat transfer is conduction. Therefore, as the heat flow distribution is under a steady state condition, in a one dimensional plane, the appropriate equation to use to determine the heat transfer to the packed product is Fourier's equation [8]:

$$q = -k A \frac{\nabla T}{x} \quad (8)$$

q = Heat Transferred per unit time (W)

k = Thermal conductivity ($Wm^{-1} \cdot K^{-1}$)

A = Heat transfer area (m^2)

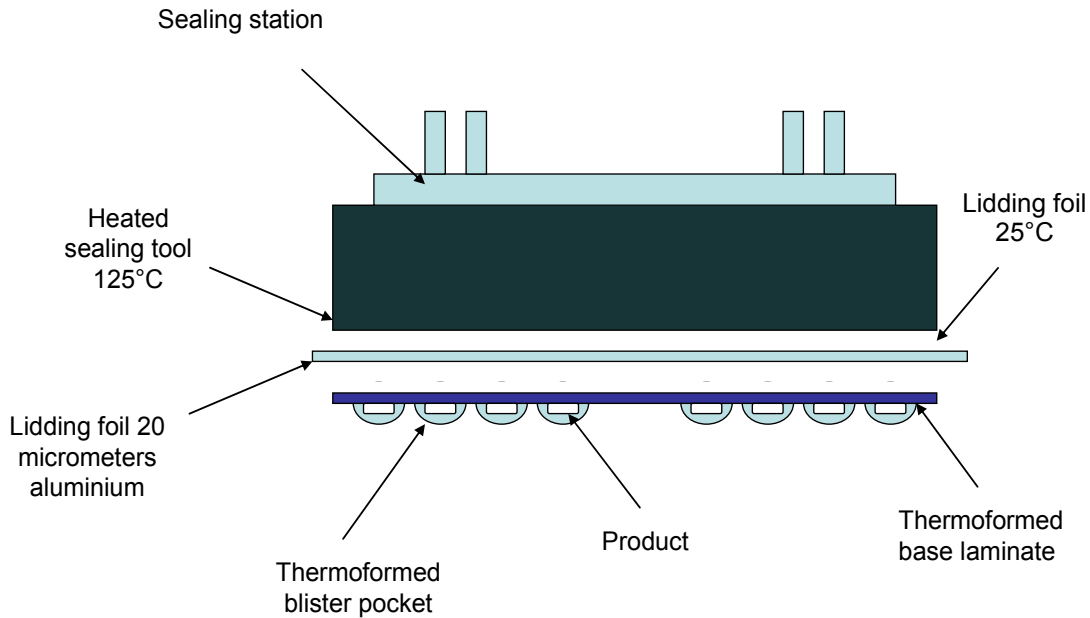
∇ = Gradient in Temperature (C)

x = Material thickness (m)

Firstly, the heat transfer per unit time (q) must be calculated using equation [8]: Figure 29 illustrates the platen sealing station and the critical parameters required to calculate the heat transfer.

The solution to the heat equation is based on the boundary conditions. In the case of platen sealing as depicted in Figure 29, the conditions are 125°C, which is the temperature of the sealing tool and the surface of the lidding foil of 25°C.

Figure 29 – Schematic of the platen sealing station



q = Heat Transferred per unit time (W)

k = Thermal conductivity of aluminium at 125°C = 255 Wm⁻¹· K⁻¹.

A = Heat transfer area = area of sealing tool directly over product = 0.00015m²

∇ = Gradient in Temperature = (sealing temp 125°C – air temperature 25°C)

X = Aluminium material thickness = 0.000020m

$$q = 225 \times 0.00015 \times \frac{125 - 25}{0.00002}$$

$$q = 168.75 \text{ kw}$$

Now that the heat transfer per unit time is known the heat flow through the aluminium foil into the product can now be calculated using the following equation:

$$\frac{q}{t} = \frac{KA (T_{\text{hot}} - T_{\text{cold}})}{d} \quad (7)$$

q = Heat Transferred per unit time = 168.75 KW

k = Thermal conductivity of aluminium at 125°C = 255 Wm k

A = Heat transfer area = area of sealing tool directly over product = 0.00015m²

∇ = Gradient in Temperature = (sealing temp outside 125°C – inside temp)

$$\frac{168750}{2.5} = \frac{255 \times .00015 (125 - T_{\text{cold}})}{0.00002}$$

$$\frac{168750 \times 0.00002}{2.5 \times 255 \times .00015} = (125 - T_{\text{cold}})$$

$$88.12 = (125 - T_{\text{cold}})$$

$$T = 125 - 88.12$$

Temperature of packed product = 36.88°C, for a sealing time of 2.5 seconds

It can be concluded from the study that by using the conventional conductive heat transfer process, combined with the technical parameters of the platen sealing process the product would be exposed to a maximum temperature of 36.88°C for a dwell time of 2.5 seconds. This is worst case, as in reality the heat is transferred through the lidding foil over 2.5 seconds, so the maximum temperature of 36.88°C will be reached in a time of <2.5 seconds. This will have no adverse effects on the drug product, in terms of degradation of the active ingredient and / or on the therapeutic effects on the patient. This is validated by all pharmaceutical packed products being exposed to accelerated ICH conditions of 40%RH/75°C for a period on 6 months during development of the product, and then being placed on a controlled stability program at 30°C / 65%RH for up to 3 years.

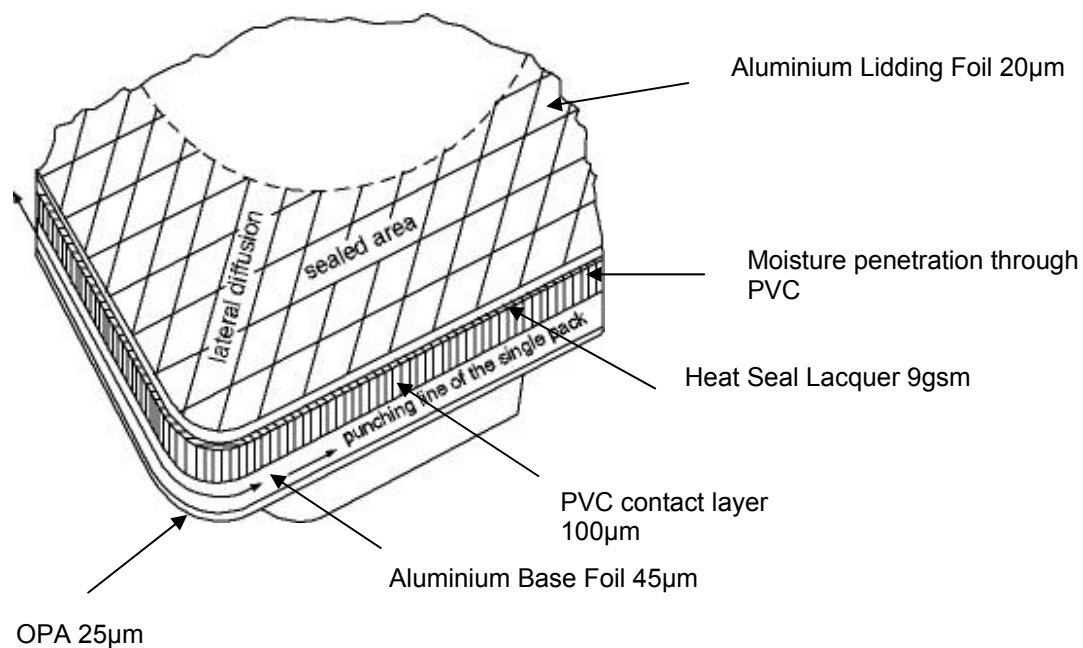
Chapter 4 Section 2

4.2 A Study of the Moisture Vapour Transmission Rate of MDPI Coldform Blisters

4.2.1 Introduction

The decisive criterion for the imperviousness of the pack to water vapour is the tightness of the seal⁸⁹. In the case of a tightly sealed blister, atmospheric moisture can only penetrate either through the seal, or the PVC layer^{91,92,93}, see Figure 30.

Figure 30 – Moisture Diffusion through the Seal⁸



The purpose of this study is to determine the potential moisture ingress through the PVC layer within the MDPI blister. The two materials which could potentially allow moisture ingress into the MDPI strip cavities are:

- Heat Seal Lacquer
- PVC Layer

Either side of these layers is the aluminium foil which provides a high barrier to moisture. The MDPI sealing process has been fully qualified to ensure a good seal is achieved at the specified sealing parameters. This study is to review the worst case for ingress of moisture through the PVC layer.

4.2.2 PVC Moisture Vapour Transmission Rates

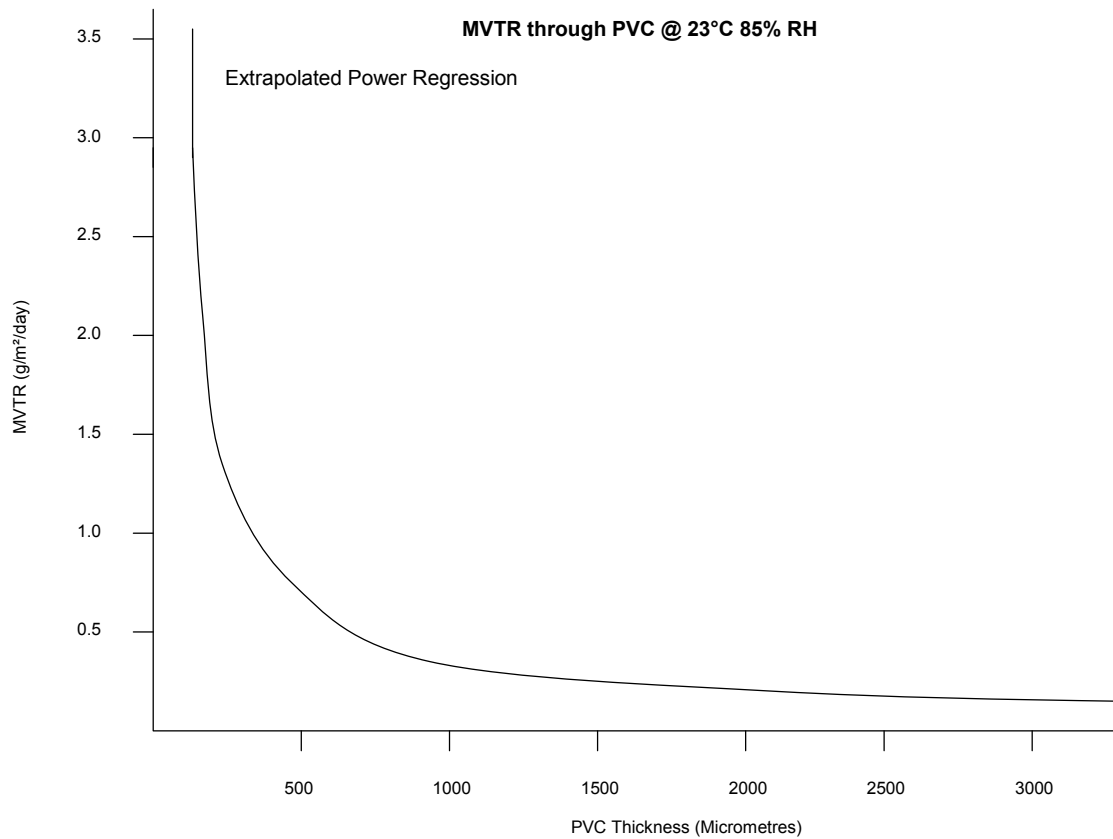
The following MVTRs Were obtained from Alcan Packaging Singen (APS), these values were used to calculate potential moisture ingress into the MDPI seal strip through the PVC layer, using the procedure detailed in Section 3.1.2⁹².

Table 11 – MVTR Data through PVC

PVC Thickness (Micrometres)	MVTR Results (g/m²/day)	
	23°C/85%RH	38°C/90%RH
250	1.0	-
200	-	5.0
100	2.2	-
60	3.6	-
25	-	35.0

From the data detailed in Table 11 a graph has been produced at 23°C/85%RH to determine the theoretical moisture ingress through 3mm of PVC into the blister, reference Figure 30. This 3mm distance represents the shortest distance through which moisture must penetrate through the seal in the MDPI strip to reach the active drug in the individual blisters.

Figure 31 – MVTR through PVC @ 23°C/85% RH



The graph is a first order power regression, obtained from data where MVTRs have been determined over a range of PVC thicknesses. This has been extrapolated to provide an indication of the MVTR through 3mm thickness of PVC⁹².

Dimensions

The following dimensions have been used to calculate the theoretical moisture ingress.

- Width of pocket = 3.5mm
- Distance of edge of pocket to edge of strip = 3.0mm
- Thickness of PVC = 100µm

$$\text{Theoretical Moisture Ingress (g)} = \text{Theoretical MVTR for 3mm PVC} \times \text{Surface Area of exposed PVC} \times \text{Time} \quad (22)$$

From the graph, the theoretical MVTR for 3mm of PVC is 0.1g/m²/day

$$\begin{aligned} \text{Surface Area of PVC} &= 0.0035\text{m} \times (100 \times 10^{-6})\text{m} \times 2 \\ &= 7 \times 10^{-7}\text{m}^2 \end{aligned}$$

Note- The surface area calculation is multiplied by 2 to cover both sides of the foil strip

Time = 2 years shelf life, i.e. 730 days

$$\begin{aligned} \text{Theoretical Moisture Ingress into pocket (g)} &= \frac{0.1\text{g}}{\text{m}^2/\text{d}} \times 7 \times 10^{-7}\text{m}^2 \times 730 \\ &= 5.11 \times 10^{-5}\text{mg} \end{aligned}$$

Percentage moisture per blister after 2 years based on 13.5mg of product inside blister

$$= \frac{0.0511\text{mg}}{13.5\text{mg}} \times 100 = 3.84\%$$

It can be concluded from this study that the potential ingress of moisture into the drug product (3.84%) is considered acceptable as most products are stable with up to 5.0% moisture content and therefore, moisture at these levels will not adversely affect the stability of the product. This is based on the fact that free moisture in the lactose can alter by $\pm 0.5\%$. This lactose has been routinely used in stability studies, which have demonstrated a stable product is produced containing this range of moisture. This study has also shown that by increasing of the distance between the blister pocket to any non sealed areas and edge of the blister strip will increase the barrier for diffusion and will result in decreased quantities of water vapour which could diffuse into the blister pocket. It is also advisable as part of any development program with new blister materials to calculate the theoretical moisture ingress, and compare to the actual experimental results when determining the moisture ingress of sealed blisters using calcium chloride desiccated granules. This approach to blister development has been adopted when qualifying new blister materials and new sealing processes.

Chapter 4 Section 3

4.3 Peel Testing of MDPI Blister Strips

4.3.1 Introduction

There are many types of joints, however, the fixed arm peel test was the primary test method for adhesion in this study as both adherends were flexible aluminium foil and the adhesive was pressure and heat activated.

The adhesive strength between the flexible laminates of the MDPI blister strip is of considerable practical importance. Generally, it would be important to maximise the adhesive strength of a given structure, however, in the case of the MDPI flexible laminates it is a requirement to be able to peel both laminates apart within the inhaler to expose the blister pocket. However, it was paramount to compare the peel strength of the New Robust Lidding Foil (NLF) with the standard lidding foil samples tested as part of the study detailed in section 4.6, and to show how the adhesive fracture toughness (also known as the adhesive strength or interfacial work of fracture) can be determined from the peel strength.

As previously described, the results of a peel test are defined as the average peel force per unit width of the strip peeled. In the peel test, the force is applied so that the flexible member (lidding foil) is peeled from a rigid plate. The force recorded gives a measure of adhesion. The test configuration used in this study is detailed in Figure 32.

As previously indicated in **Chapter 2**, laminates that can be peeled are classified into two types. Firstly, where there is minimum or negligible adhesive thickness, where the polymer films are welded together, resulting in a very thin layer of adhesive film. Secondly, where the adhesive layer is not negligible and

its deformation must be taken into consideration during the peel bending process. Both types can be accommodated by this test. However, in the case of the MDPI NLF and base foil laminates the adhesive layer is negligible and therefore, does not need to be considered. The equations and experimental method to determine the fracture toughness of the MDPI heat seal lacquer and the theoretical peel force are described in **Chapter 3**.

Figure 32 - Illustration of the Fixed Arm Peel Test

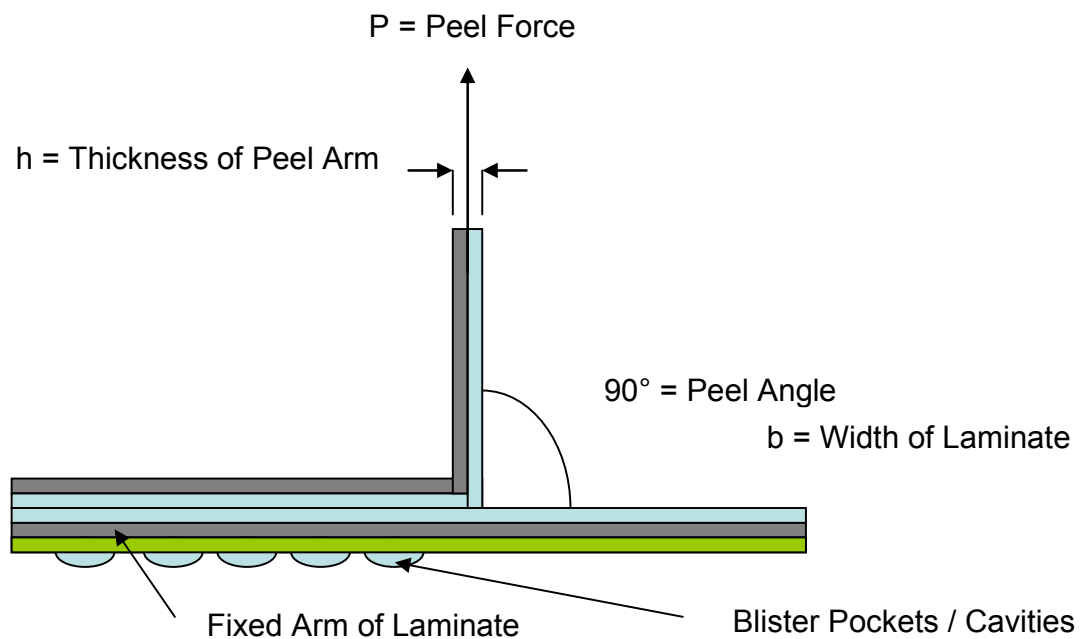


Figure 32 shows the peel of a laminate at a peel angle of 90° with a force P acting on the peel arm (laminate width b , peel arm thickness h).

Parameters:

b = Width of MDPI base laminate = 12mm

h = Thickness of MDPI NLF = $50\mu\text{m}$

Peel Angle = 90°

As described in **Chapter 2**, adhesive fracture toughness (G_A) is obtained by measuring the external energy (G_E) to conduct peel of the laminate whilst making allowance for the plastic bending energy in the peel arm (G_p), according to equation [1].

To calculate G_E this is determined from the peel strength (P/b) and peel angle (θ), and assuming negligible tensile deformation, as indicated in equation [2].

In order to calculate the plastic deformation energy (G_p) associated with the peel arm, it is first necessary to have knowledge of the tensile-strain characteristics of the peel arm material (lidding foil).

For laminates where the adhesive layer thickness (h_A) is very small ($h = 0$) there is no requirement to consider the deformation in the adhesive in conducting the calculations of adhesive fracture toughness. The thickness of the heat seal lacquer used as the sealant layer within the lidding foil is negligible therefore, will not be considered.

In order to determine G_A without neglecting any of the elastic or plastic deformations, two experiments are required:

- (a) The peel test with a control of the peel angle.
- (b) A tensile stress-strain measurement of the peel arm fracture.

Experimental Procedures in the Fixed Arm Peel Test:

A jig adapted purely for the measuring of MDPI lidding foil (peel arm) was attached to the Instron. The jig maintained a constant speed moving across low frictional bearings to achieve the 90° peel angle over the length of the MDPI sealed strip. The base laminate was fixed to the jig using 3M type sealing tape.

Peel arm (lidding foil) = 55 μ m x 12mm wide

Base laminate = 170 μ m x 12mm wide

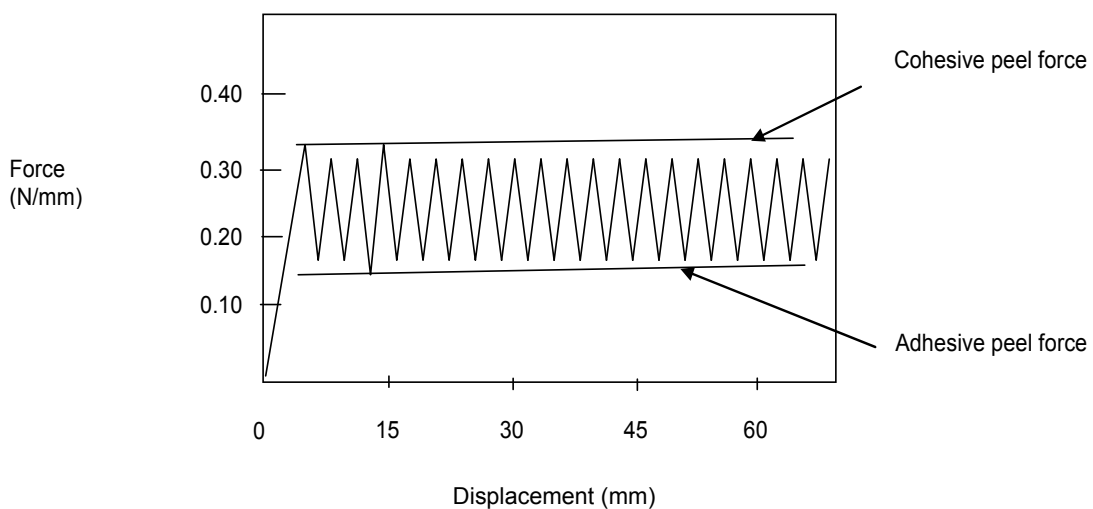
Length of strip = 150mm

Peel angle = 90°

Peel crack speed = 100 mm/min

To determine the adhesive and cohesive fracture toughness it was necessary to plot a force Vs displacement curve, this determined the average peel force. However, the graph in Figure 33 shows that there was a combination of adhesive and cohesive fracture. For this reason, both the mean lowest and highest force values were used to determine the adhesive and cohesive fracture toughness values, respectively.

Figure 33 – Peel Force versus Deflection in the Fixed Arm Peel Test

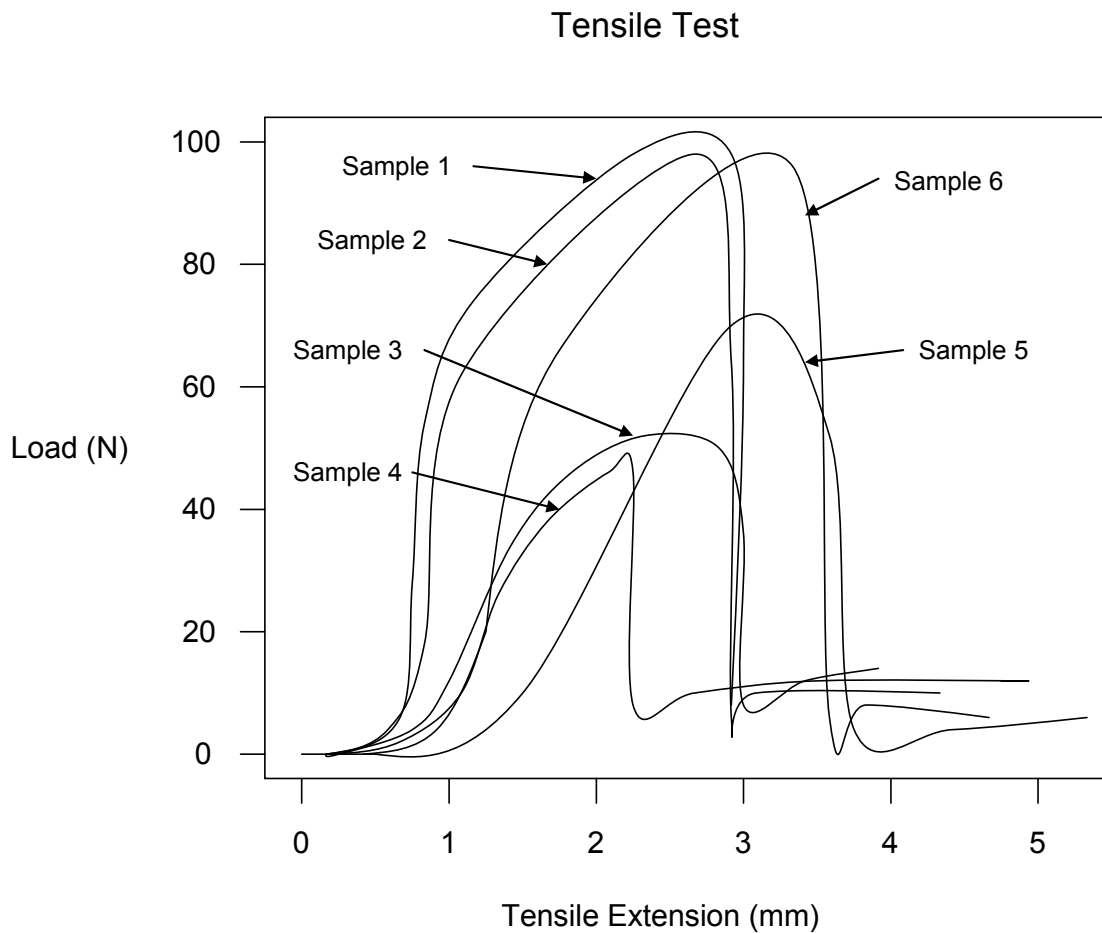


From the peel force calculations depicted in Figure 34 the average peel force is 0.25 N/mm.

In order to conduct the corrections summarised in Equations 1-2 it is necessary to either obtain a stress – strain as described in **Chapter 3** or a Load / Extension plot on the material of the peel arm. For the purpose of the study and

the availability of the equipment a Load / Extension plot was performed on six samples as detailed in Figure 34.

Figure 34 – Load versus Extension to Calculate Stress / Strain Behavior in the Tensile Test



To get a more representative determination of peel force a sealed MDPI blister strip was taken from each sealing station on the rotary sealing tool. The sealing tool seals two blister strips at the same time, termed lane (a), and lane (b), and 3 strips per revolution. Therefore 6 blister strips were taken to get an accurate indication of peel force.

Table 12 – Results from Tensile Testing on MDPI Samples

Sample	Maximum Load (N)	Extension at Break (mm)	Tensile Strain (mm/mm)	Tensile Stress (Mpa)	Bending Energy (J)	Time (sec)
1	93.32	2.98	0.06	1.23	0.14	1.72
2	90.52	2.84	0.06	1.21	0.14	1.70
3	48.25	3.66	0.07	0.064	0.07	2.19
4	47.48	2.14	0.04	0.063	0.04	1.28
5	68.93	3.18	0.06	0.92	0.08	1.91
6	94.41	3.15	0.06	1.26	0.13	1.89
Mean	73.81	2.99	0.06	0.93	0.09	1.80
S,D	22.15	0.50	0.01	0.30	0.04	0.34
Minimum	47.48	2.14	0.04	0.63	0.04	1.28
Maximum	94.41	3.66	0.07	1.26	0.14	2.19
Range	46.92	1.52	0.03	0.63	0.09	0.91

The tensile test was conducted at the same speed as the peel test, i.e. 100m/min. The data extracted from the tensile tester and the graph depicted in Figure 34 is detailed in Table 12, thus a stress / strain graph is not required. Firstly, because there was minimal elongation of the samples and therefore, the elastic deformation was negligible and secondly because the computer program gave a readout of the stress / strain results.

It can also be observed from Table 12 that the standard deviation is very high. This is due to the variation of seal temperature, and pressure around the circumference of the rotary sealing tool giving a range of peel forces.

To determine the fracture toughness of the adhesive (G_A) we now need to determine the plastic bending energy (G_p). The plastic bending energy is the work done (W) in fracturing the MDPI lidding material, and is measured in joules. This can be calculated using the following equation:

$$W = \frac{1}{2} \times \sigma \varepsilon \quad (23)$$

σ_y = yield stress = 0.93 (MPa)

ε_y = yield strain. = 0.06

$$W = \frac{1}{2} \times 0.93 \times 0.06$$

$$W = 0.027 \text{ J}$$

We now need to use equation [2] to determine the external energy:

$$G_E = \frac{P}{b} (1 - \cos \theta) \quad (2)$$

By inserting values gives:

$$G_E = \frac{0.25}{12} (1 - \cos 90) \quad \mathbf{G_E = 0.128J}$$

We can now use equation (1) to determine adhesive fracture toughness, where:

G_A = Adhesive fracture toughness; G_E = External Energy = 0.128J

G_p = Plastic bending energy = 0.027J

$$G_A = G_E - G_p \quad (1)$$

$$G_A = 0.128 - 0.027 = 0.1 \text{ J}$$

In summary the adhesive fracture toughness of the NLF (G_A value) is:

$$\mathbf{G_A = 0.1J/mm^2}$$

It can be concluded from the study that the theoretical adhesive fracture toughness can be calculated using the critical factors in achieving precise functionality of the MDPI, as in peel strength, width of strip and the tensile behaviour of the lidding foil. The adhesive used to bond the lid and base foil laminates is a peelable adhesive that cannot exceed an adherence fracture toughness of 0.2 J/mm^2 , and a peel force of 0.48 N/mm . If these figures are exceeded the lever force within the device increases to $\geq 15 \text{ N}$, resulting in the MDPI devices being rejected at the test machine. The results confirmed that the adhesive fracture toughness of the NLF was 0.1 J/mm^2 . Furthermore, it can be deduced from the results that the NLF gives a slightly higher peel force value of 0.25 N/mm compared to the standard lidding foil of 0.20 N/mm deduced from the study in section 4.6. Therefore, it can be concluded that the NLF is an acceptable alternative in terms of peel strength properties to the current lidding foil.

Chapter 4 Section 4

4.4 A study into an Alternative Lidding Foil Structure for MDPI Blister Strips

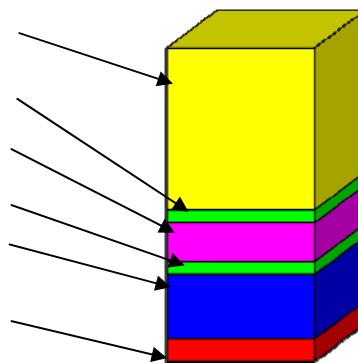
4.4.1 Introduction

The current lidding foil used in MDPI as detailed in Figure 35, uses a combined structure of paper (outside laminate) – polyester – aluminium – heat seal lacquer (inside laminate). There have been a number of market complaints with the foil splitting during actuation of the device by the patient⁹⁴, as detailed in Figure 36. The splitting occurs when the blister strip has been damaged during assembly resulting in small tears on the side of the strip. To overcome this problem a more robust lidding foil has been developed^{95,96,97,98}. The following section details the development of this material, starting with the initiation of the project, the equivalency and material analysis carried out and the conclusions and recommendations of the study.

Figure 35 - Existing Lidding Foil for MDPI

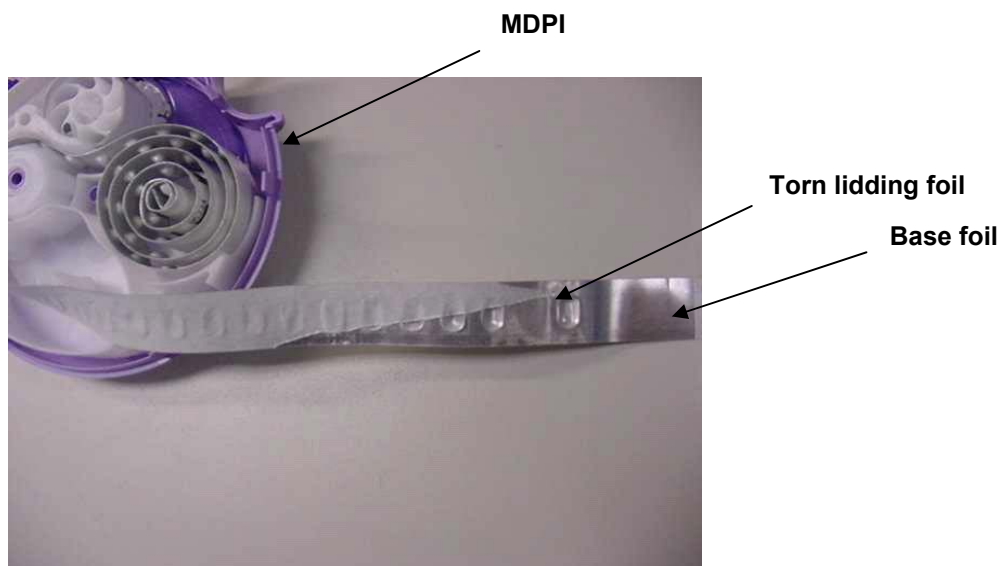
Existing lidding foil:

Paper	50gsm
Adhesive	4gsm
PET-film	12 μ m
Adhesive	4gsm
Aluminium	20 μ m
Peelable heat-seal lacquer (LA2475)	7gsm



Total weight = 135.8gsm Total thickness = 102 μ m

Figure 36 – Torn Strip Customer Complaint⁹⁴



A strip failure results in a situation where the patient is both unaware and unable to access the next dose of medication from the MDPI strip within the Diskus[®] device^{96,97,98}. This situation arises because the lid foil of the strip breaks and is therefore, not peeled from the blister pockets and thus not allowing the powder to be presented to the airflow port of the device^{96,97,98}. However, the counter on the device remains operational, compounding the failure by indicating that the device is working^{96,97,98}.

A stronger lid foil has been developed by APS⁹⁵. In order to demonstrate the superior performance of the new foil, data will be presented in three ways.

1. Physical data generated on the material of choice, MVTR, peel strength and tear resistance.
2. Practical evaluation of the new lid foils by running the materials on the industrial filling lines, using a modified recessed land area change part to allow higher sealing wheel temperatures to achieve a tighter more uniform seal, without the strip sealing in the non-sealed land area of the strip.

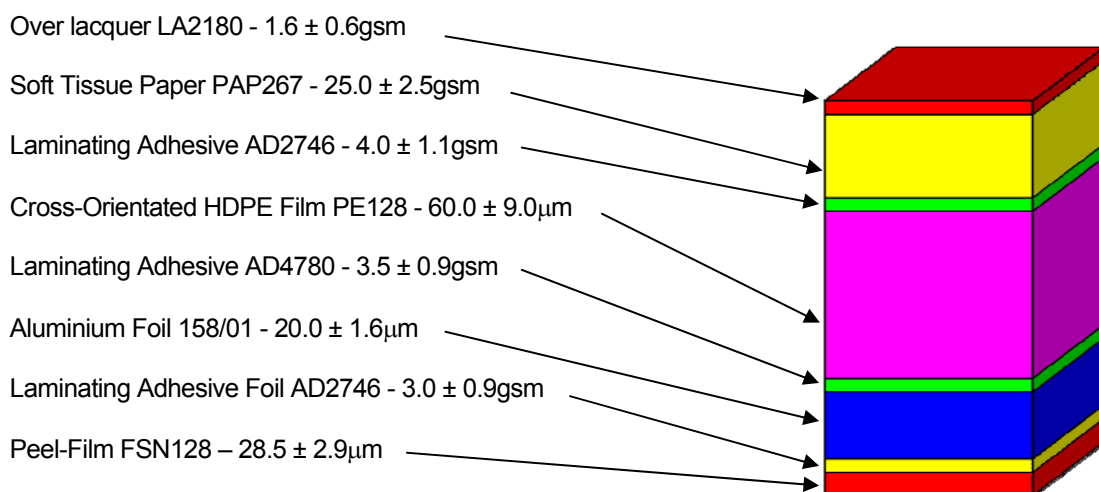
3. Adding defects to represent the types of damage the manufacturing process can inflict, and thereafter testing those strips within Diskus[®] devices.

Note: - The non-sealed land area on the strip is required to allow the lid and base laminates to be separated on the assembly machine prior to insertion into the sub-assembly, reference Figure 36.

The focus of this study is a new generation lidding foil developed by APS⁹⁵, which is detailed in Figure 37.

The aim of this study is to confirm that the New Lidding Foil (NLF) is more resilient to the production and assembly processes and that it has higher resistance to tearing should damage to the lid foil occur. The new foil will be evaluated on the filling line. The aim of the manufacturing trial will be to ascertain that the new lid foil will successfully run on each type of form-fill-seal line. Subsequently that it is possible to coil, insert and assemble the strips into Diskus[®] devices. A control strip using the current lid foil will be used throughout the trials for comparison.

Figure 37 – Proposed New Robust Lidding Foil Structure⁹⁸



Optimisation Study

The study assessed the performance of the NLF at full and half processing speed using a range of operating parameters, such as top and bottom sealing wheel temperatures, sealing wheel pressure and linear speed. The study also assessed the performance and capability of the strip on the assembly line.

The machine parameters were selected based on their potential impact on strip performance and therefore significance in defining optimum process conditions for NLF. The study was performed at full and half speed, 210 and 105 Strips Per Minute (SPM) respectively.

Materials

The materials used during the study are defined in Table 13.

Table 13 - Details of Materials used during Trials

Item code	Material	Description
15284	Lactose	LACTOSE FOR MDPI (GRADE 4) LACTOHALE
F902611	Base Foil	LAM OPA / AL / PVC 40MM
40000000007090	Lid Foil	O/LAC PAP-25 / VALERON-60 / AL-20 / PEEL LACQUER

Experimental Method

The study was performed to identify the optimum settings and a working range for pressure and temperature of the upper and lower sealing wheels at full and half speed.

Spools manufactured were progressed through the Sortimat Gemini assembly line to be assembled up to the completion of coiling. The spools progressed were selected based on peel force, dye test and appearance results generated following the filling stage. Filled strip samples were tested using Gemini lever force, tear strength, peel strength, dye tests, torsion hub and defect inspection methods.

Full Speed Conditions

The settings for the full speed trial at 210 Strips per Minute (SPM) are defined in Table 14.

Table 14 - Settings used during Full Speed Trials

Run	Temperature Upper Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Temperature Lower Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Pressure ($\pm 10\text{N}$)
1	120	55	225
2	125	60	235
3	130	60	235
4	130	70	265
5	135	65	250
6	135	70	265
7	135	75	280
8	140	70	265
9	145	70	265
10	145	80	295
11	150	80	295
12	150	85	305
13	155	85	305
14	155	55	225
15	155	55	300
16	155	85	225
17	150	75	295
18	145	70	280
19	140	65	300
20	140	75	265
21	150	65	265
22	165	65	265
23	175	65	265
24	135	55	235
25	145	65	265
26	155	75	295

Half Speed Conditions

The settings for the half speed trial at 105 (SPM) are defined in Table 15.

Table 15 - Settings used during Half Speed Trials

Run	Temperature Upper Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Temperature Lower Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Pressure ($\pm 10\text{N}$)
1	105	50	210
2	110	55	220
3	115	65	250
4	120	60	235
5	120	65	250
6	120	70	265
7	125	65	250
8	130	65	250
9	130	75	280
10	135	80	290
11	140	85	300
12	130	75	260
13	140	75	260
14	150	65	280
15	135	70	295
16	130	75	295
17	125	60	265
18	120	65	265
19	115	50	235
20	110	55	235

Acceptance Criteria and Sampling Regime

The measurement of quality and general acceptance criteria for this study assessed the strip from each spool manufactured against dye test, bulk weights, visual assessment, running issues, and strip length, using the number of samples for each test as defined in Table 16 – *Filling IPC Sampling Regime*. Additional samples were also tested as defined in Table 17 – *Device Testing Sampling Regime*, using the procedures detailed in **Chapter 3**, and assembled to completion of coiling on the Sortimat Gemini assembly line, using the number of samples for each test as defined in Table 18 – *Gemini Assembly IPC Regime*.

Table 16 - Filling IPC Sampling Regime

Description of Test	Reason for Test	Quantity to Inspect
Dye Test – Seal integrity uncoiled	To guarantee seal integrity of the uncoiled strip prior to assembly.	5 single strip from each lane
Dye Test – Seal integrity	To guarantee seal integrity of the uncoiled, un slit double strip prior to slitting.	5 double strip
Dye Test – Seal integrity coiled	To guarantee seal integrity of the coiled strip prior to assembly.	5 single strip from each lane
Lid foil checks – witness marks or damage	Lid foil checks – witness marks or damage.	5 double strip
Centrality	To ensure the blister pocket is central to the strip to ensure maximum seal area around the pocket.	5 double strip
Seal and registration	To ensure the maximum seal area around the pocket and that the pocket is aligned with the sealing tool.	5 double strip
Free from damage and dents	To ensure all the product will e evenly dispensed from the pocket.	5 double strip
Edges burr and curl free	To ensure the strip is of good quality so that it functions satisfactorily in the device.	5 double strip
Unsealed land area separates freely	To ensure the strips separate freely so they can be separated by the coiling machine prior to insertion in the device.	10 double strip
*Bulk Weight (target 12.5 – 13.5 mg)	To ensure there is sufficient powder in the pockets for dye testing.	1 double strip

*- For information only

Table 17 – Device Testing Sampling Regime

The following tests will be performed using the procedures detailed in **Chapter 3**.

Description of Test	Reason for Test	Quantity to Inspect
Tear test	To ensure the new robust lidding foil has an acceptable tear resistance so it will withstand the forces within the device.	1 double strip
Peel Strength	To ensure the peel strength is equivalent to the current lidding material.	6 double strip
Dye test	To guarantee seal integrity of the uncoiled strip.	200 double strip from filling
Dye test	To guarantee seal integrity of the assembled strip.	200 coiled strip from each lane of the Sortimat
Gemini Torsion hub test	To confirm the operating force of the device.	5 Double strip
Defect resistance	To ensure the new robust lidding foil does not get damaged through routine use.	50 double strip

Table 18 - Gemini Assembly IPC Regime

Description of Test	Reason for Test	Quantity to inspect
Visual inspection for strip separation	To ensure the strips separate freely so they can be separated by the coiling machine prior to insertion in the device.	100 strip from start of spool 100 strip from end of spool
Visual inspection for slitting	To ensure the strip is of good quality so that it functions satisfactorily in the device.	100 strip from start of spool 100 strip from end of spool
Dye testing	To guarantee seal integrity of the assembled strip.	Min 12 dye test
Loop weld test	To ensure the loop weld is strong enough to withstand the force exerted when the device is indexed.	Min 2 loop weld test
Land area not separating %	To ensure the strips separate freely so they can be separated by the coiling machine prior to insertion in the device.	100% inspection

Results and Discussion

The results in this section detail the findings of the trial and provide the basis of the trial recommendations and conclusions. On completion of the filling trials spools were selected and progressed for coiling on the Sortimat Gemini assembly line based on their potential impact on strip performance and therefore, significance in defining optimum process conditions for NLF. Strip was then coiled in order to assess the performance of the strip in its coiled state. Samples from each run were also tested for strip performance and coiled strip testing.

Full Speed Filling Trials (210 SPM)

The full sets of results at full speed are documented in Table 19. During the study individual fill weight was not performed. These tests were not considered significant in demonstrating strip quality. All key quality indicators were performed, i.e. (dye test, un-sealed land area and visual assessment).

Results

Table 19 - Results of Appearance Checks – Full Speed

Run No. (Recorded in the order they were run)	Central*	Strip Length	Average Bulk Weight Lane A	Average Bulk Weight Lane B	Seal & Registration*	Free from Damage & Dents	Edges Burr & Curl Free	Unsealed Area Separates Freely	Comments
Start up Challenge	S	325.0	13.0	13.1	S	S	S	S	
1	S	325.0	13.0	12.8	S	S	S	S	
2	S	325.0	13.0	12.9	S	S	S	S	
3	S	325.0	13.3	13.1	S	S	S	S	
4	S	325.0	12.9	12.8	S	S	S	S	
13	S	325.0	12.7	12.4	S	U	S	U	Separated freely with minor manipulation
12	S	325.0	12.4	11.9	S	S	S	U	Separated freely with minor manipulation
11	S	325.0	12.9	12.2	S	S	S	S	
10	S	325.0	12.7	11.4	S	S	S	S	
9	S	325.0	12.9	13.1	S	S	S	S	
8	S	325.0	12.8	13.0	S	S	S	S	
7	S	325.0	12.8	13.0	S	S	S	S	
6	S	325.0	12.8	13.0	S	S	S	S	
5	S	325.0	12.6	12.8	S	S	S	S	
14	S	325.0	12.7	12.8	S	S	S	S	
15	S	325.0	12.7	13.0	S	S	S	S	
16	S	325.0	12.7	13.1	S	S	S	S	

Results

Table 19 continued - Results of Appearance Checks Continued – Full Speed

Run No. (Recorded in the order they were run)	Central*	Strip Length	Average Bulk Weight Lane A	Average Bulk Weight Lane B	Seal & Registration*	Free from Damage & Dents	Edges Burr & Curl Free	Unsealed Area Separates Freely	Comments
17	S	325.0	12.7	12.9	S	S	S	S	
18	S	325.0	12.7	12.9	S	S	S	S	
19	S	325.0	12.8	12.9	S	S	S	S	
20	S	325.0	12.8	12.9	S	S	S	S	
21	S	325.0	12.8	12.9	S	S	S	S	
22	S	325.0	12.5	12.7	S	S	S	S	
23	S	325.0	12.8	12.9	S	U	S	U	Strip appearance failed due to creasing of lidding foil and wrinkling in land area
24	S	325.0	12.8	12.9	S	S	S	S	
25	S	325.0	13.0	13.0	S	S	S	S	
26	S	325.0	12.9	13.1	S	S	S	S	

Note - Reference Table 16 for number of samples tested S = Satisfactory or U = Unsatisfactory

Observations at Full Speed (210 SPM) – Filling Trials

During the start of batch a low level of lactose residue (powder spatter) was observed on the strip, see Appendix 4 – *Images*. The strip was visually inspected and it was concluded that the residual powder was consistent with the levels observed during routine production. Furthermore, that any dye test failure during the study caused by powder spatter would not be considered significant to the outcome of the trial as failure caused by powder spatter is an occurrence when using un-blended lactose and is not a consequence of the NLF. It was however, decided to monitor the strip quality throughout the trial and only take action if the strip quality deteriorates to an unacceptable level.

Runs 1, 2, 3, 4, 5, 6, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25 and 26 were manufactured in accordance with the protocol, all settings produced satisfactory results and met all protocol acceptance criteria.

Full Speed Strip – Assembly Trials

On completion of the filling trials, spools were selected based on their potential impact on strip performance, and therefore significance in defining optimum process conditions for NLF. The selected spools at full speed were supplied to the Sortimat Gemini assembly line to be coiled and measured, using the number of samples for each test as defined in Table 18. The full set of results at full speed are documented in Table 20.

Results Table

Table 20 *Results of Seal Integrity Tests – Full Speed*

Run No. (Recorded in the order they were run)	Seal Integrity - Double strip (5 tested)		Seal Integrity - Single Coiled (5 tested per lane)		Seal Integrity - Single Uncoiled (5 tested per lane)		Comments
	Lane A	Lane B	Lane A	Lane B	Lane A	Lane B	
Start up challenge	S	S	S	S	S	S	
1	S	S	S	S	S	S	
2	S	S	S	S	S	S	
3	S	S	S	S	S	S	
4	S	S	S	S	S	S	
13	S	S	S	S	S	S	
12	S	S	S	S	S	S	
11	S	S	S	S	S	S	
10	S	S	S	S	S	S	
9	S	S	S	S	S	S	
8	S	S	S	S	S	U	Failure caused by over sealing on lactose
7	S	S	S	S	S	U	Failure caused by pinhole through lidding foil
6	S	S	S	S	S	S	
5	S	S	S	S	S	S	
14	U	S	U	S	S	S	Genuine dye test rejects

Note- Test pocket failure on each strip tested

S = Satisfactory or U = Unsatisfactory

Results Table

Table 20 continued *Results of Seal Integrity Tests – Full Speed*

Run No. (Recorded in the order they were run)	Seal Integrity - Double strip (5 tested)		Seal Integrity - Single Coiled (5 tested per lane)		Seal Integrity - Single Uncoiled (5 tested per lane)		Comments
	Lane A	Lane B	Lane A	Lane B	Lane A	Lane B	
15	S	S	S	S	S	S	Failure caused by over sealing on lactose
16	S	S	S	S	S	S	
17	S	S	S	S	S	S	
18	S	S	S	S	S	U	Failure caused by over sealing on lactose
19	S	U	S	S	S	U	Failure caused by over sealing on lactose
20	S	S	S	S	S	S	
21	S	S	S	S	S	S	
22	S	U	S	U	S	S	Failure caused by over sealing on lactose
23	S	U	S	U	S	S	Failure caused by over sealing on lactose
24	S	S	S	S	S	S	
25	S	S	S	S	S	S	
26	S	S	S	S	S	S	

Note- Test pocket failure on each strip tested

S = Satisfactory or U = Unsatisfactory

Observations from Full Speed Strip – Assembly Trials

Strip samples from each lane were inspected for strip separation and slitting quality. It was observed during inspection that the edge of the strip on top of lane A and bottom of lane B was not a clean cut, giving a “feathered” type appearance, reference Appendix 5 – *Images*. The strip was inspected and it was concluded that it was consistent with strip quality observed during routine production and therefore, recorded as satisfactory. All spools were tested in accordance with the protocol and produced satisfactory results and met all protocol acceptance criteria.

Table 21 *Satisfactory Full Speed Settings Concluded from Filling and Assembly Trials*

Run	Temperature Upper Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Temperature Lower Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Pressure ($\pm 10\text{N}$)
1	120	55	225
2	125	60	235
3	130	60	235
4	130	70	265
5	135	65	250
6	135	70	265
7	135	75	280
8	140	70	265
9	145	70	265
10	145	80	295
11	150	80	295
15	155	55	300
16	155	85	225
17	150	75	295
18	145	70	280
19	140	65	300
20	140	75	265
21	150	65	265
22	165	65	265
24	135	55	235
25	145	65	265
26	155	75	295

Half Speed Filling Trials (105 SPM)

The full set of results at half speed are documented in Table 22. During the study individual fill weight was not performed. These tests were not considered significant in demonstrating strip quality and were used for information only. All key quality indicators were performed, i.e. (dye test, un-sealed land area and visual assessment).

Results Table

Table 22 *Results of Appearance Checks – Half Speed*

Run No. (Recorded in the order they were run)	Central*	Strip Length	Average Bulk Weight Lane A	Average Bulk Weight Lane B	Seal & Registration*	Free from Damage & Dents	Edges Burr & Curl Free	Unsealed Area Separates Freely	Comments
1	S	325.0	13.6	12.9	S	S	S	S	
2	S	325.0	12.8	12.8	S	S	S	S	Slight crease lane B station 0
3	S	325.0	12.9	12.8	S	S	S	S	As above
4	S	325.0	12.7	12.4	S	S	S	S	
5	S	325.0	12.9	12.7	S	S	S	S	
6	S	325.0	12.7	12.6	S	S	S	S	
7	S	325.0	12.7	12.7	S	S	S	S	Slight crease lane B station 0
8	S	325.0	12.8	12.7	S	S	S	S	
9	S	325.0	12.7	12.6	S	S	S	U	Strip separated with minor manipulation
12	S	325.0	12.8	12.6	S	S	S	U	As above
13	S	325.0	13.0	13.0	S	S	S	U	As above
11	S	326.0	13.1	12.9	S	S	S	U	As above
10	S	326.0	13.0	12.9	S	S	S	U	As above
14	S	326.0	13.0	12.8	U	U	S	U	Appearance failures on due to poor registration Strip separated with minor manipulated
15	S	326.0	12.6	12.6	S	S	S	U	Strip separated with minor manipulated
16	S	326.0	12.7	12.6	S	S	S	U	As above
17	S	326.0	12.9	12.8	S	S	S	S	

Results Table

Table 22 continued

Results of Appearance Checks Continued– Half Speed

Run No. (Recorded in the order they were run)	Central*	Strip Length	Average Bulk Weight Lane A	Average Bulk Weight Lane B	Seal & Registration*	Free from Damage & Dents	Edges Burr & Curl Free	Unsealed Area Separates Freely	Comments
18	S	325.0	12.9	12.9	S	S	S	S	
19	S	325.0	12.8	12.7	S	S	S	S	
20	S	325.0	12.8	12.8	S	S	S	S	

Note - Reference Table 16 for number of samples tested S = Satisfactory or U = Unsatisfactory

Observations at Half Speed (105 SPM) - Filling Trials

Runs 1, 4, 5, 6, 8, 17, 18, 19 and 20 were manufactured in accordance with the protocol, all settings produced satisfactory results and met all protocol acceptance criteria.

Runs 2, 3, and 7 were manufactured in accordance with the protocol the settings produced satisfactory results and met all protocol acceptance criteria. However, a slight crease was also observed on all spools on lane B station 0, reference Appendix 6 – *Images*. Because this minor defect was not causing any dye test or strip appearance failures, and a good quality seal was achieved at the settings used for runs 2, 3 and 7, it was agreed that the settings would be recommended for subsequent studies, and any repeat runs using conditions from runs 2, 3 and 7 would not be required.

Runs 9, 10, 11, 12, 13, 14, 15 and 16 were manufactured in accordance with the protocol. However, it was observed during the appearance checks that there was slight sticking in the land area. As previously stated the settings used during runs 9, 10, 11, 12, 13, 14, 15 and 16 were part of the process stretch and there was an expectation that the higher process temperature and pressure settings could be unsatisfactory for the land area. It was concluded that the sticking in the land area was caused by higher sealing temperatures and pressure settings of the sealing wheels.

During IPC testing all dye tests performed failed on the test pocket. Following review of this failure during previous studies it was concluded that the probable causal factor was the reduced length of the sealed area between the test pocket and the unsealed land area. Therefore, for the purpose of these trials dye test failure of the test pocket is not considered significant.

Half Speed Strip – Assembly Trials

On completion of the filling trials spools were selected based on their potential impact on strip performance and therefore significance in defining optimum process conditions for NLF. The selected spools at half speed were coiled and measured using the number of samples for each test as defined in Table 18. The full set of results at half speed are documented in Table 23.

Results Table

Table 23 *Results of Seal Integrity Tests – Half Speed*

Run No. (Recorded in the order they were run)	Seal Integrity - Double strip (5 tested)		Seal Integrity - Single Coiled (5 tested per lane)		Seal Integrity - Single Uncoiled (5 tested per lane)		Comments
	Lane A	Lane B	Lane A	Lane B	Lane A	Lane B	
1	S	S	S	S	S	S	
2	S	S	S	S	S	S	
3	S	S	S	S	S	S	
4	S	S	S	S	S	S	
5	S	S	S	S	S	S	
6	S	S	S	S	S	S	
7	S	S	S	S	S	S	
8	S	S	S	S	S	S	
9	S	S	S	S	S	S	
12	S	S	S	S	S	S	
13	S	S	S	S	S	S	
11	S	S	S	S	S	S	
10	S	S	S	S	S	S	
14	S	S	S	S	S	S	
15	S	S	S	S	S	S	

Note- Test pocket failure on each strip tested

S = Satisfactory or U = Unsatisfactory

Results Table

Table 23 continued *Results of Seal Integrity Tests – Half Speed*

Run No. (Recorded in the order they were run)	Seal Integrity - Double strip (5 tested)		Seal Integrity - Single Coiled (5 tested per lane)		Seal Integrity - Single Uncoiled (5 tested per lane)		Comments
	Lane A	Lane B	Lane A	Lane B	Lane A	Lane B	
16	S	S	S	S	S	S	
17	S	S	S	S	S	S	
18	S	S	S	S	S	S	
19	S	S	S	S	S	S	
20	S	S	S	S	S	S	

Note- Test pocket failure on each strip tested

S = Satisfactory or U = Unsatisfactory

Observations from Half Speed Strip – Assembly Trials

Strip samples from each lane were inspected for strip separation and slitting quality, all samples inspected produced satisfactory results and met all protocol acceptance criteria.

Table 24 *Satisfactory Half Speed Settings from Filling and Assembly Trials*

Run	Temperature Upper Sealing Wheel (±5°C)	Temperature Lower Sealing Wheel (±5°C)	Pressure (±10N)
1	105	50	210
2	110	55	220
3	115	65	250
4	120	60	235
5	120	65	250
6	120	70	265
7	125	65	250
8	130	65	250
17	125	60	265
18	120	65	265
19	115	50	235
20	110	55	235

Gemini Device Testing

On completion of the filling trials spools were selected based on seal integrity (dye tests) and strip appearance results generated following the filling stage. The parameters used to produce these spools are expected to provide a solid indication of an optimal operating window.

Filled strip samples were then tested for peel strength, seal integrity, Gemini lever force / torsion hub and defect inspection tests. The number of samples for each test are defined in Table 17. The full set of test results from samples produced at full speed are documented in Tables 25 - 26 – *Results Table*.

Dye testing and subsequent examination of dye test failures was carried out on the selected strip runs that had been coiled using the Gemini Sortimat assembly equipment. The strips were coiled and ends formatted, prior to being released into collection bags (rather than insertion into Gemini devices). The results are documented in Table 27.

Results Table

Table 25 *Device Testing Seal Integrity Results – Full Speed*

Run No.	% Seal Integrity failures (Double Filled strip) 100 Tested		% Seal Integrity failures (Single Coiled) 100 Tested		Seal Integrity (Single Uncoiled)		Comments
	Lane A	Lane B	Lane A	Lane B	Lane A	Lane B	
3	0	0	7	1	*	*	All 8 strips were popping related dye test failures.
24	0	2	2	7	*	*	All Filled/uncoiled strip failures caused by low level lactose on strip. 4 filled coiled strips failed due to low level of lactose on strip, 5 filled coiled strips were popping related dye test failures.
5	8	31	*	*	*	*	All Filled/uncoiled strip failures caused by low level lactose on strip.
8	2	11	3	8	*	*	All Filled/uncoiled and coiled strip failures caused by low level lactose on strip.
25	1	3	0	2	*	*	All filled/uncoiled strip failures caused by low level lactose on strip. 1 filled coiled strip low level lactose on strip.
11	4	8	1	3	*	*	All Filled/uncoiled and coiled strip failures caused by low level lactose on strip.
26	2	5	2	1	*	*	All filled/uncoiled strip failures caused by low level lactose on strip. 1 filled coiled strip failed due to low level of lactose on strip, 2 filled coiled strips were popping related dye test failures.

Note - * Indicates tests not performed

Results Table

Table 26 *Device Testing Strip Performance Results – Full Speed*

Run No.	Tear Test (N/mm)	Peel Test (N/mm)	Gemini Torsion Hub Test Individual Operation Force Range Design Intent = 3 - 15N		Gemini Torsion Hub Test Mean Operation Force Design Intent = 5 - 10N		Edge cut defect Testing with 135° 1.25mm cut (50 samples tested)	Comments
			To design intent	14% Weaker Torsion	To design intent	14% Weaker Torsion		
1	*	0.28	*	*	*	*	*	
2	*	0.24	*	*	*	*	*	
3	*	0.25/0.27	*	*	*	*	*	
4	*	0.27	*	*	*	*	*	
5	*	0.27	*	*	*	*	*	
6	*	0.31	*	*	*	*	*	
7	*	*	*	*	*	*	*	
8	*	0.32	*	*	*	*	*	
9	*	0.32	*	*	*	*	*	
10	*	0.31	*	*	*	*	*	
11	*	0.33	6.8 – 11.3N	6.0 – 9.7N	8.4 – 9.5N	7.3 – 8.3N	*	
12	*	0.33	*	*	*	*	*	
13	*	0.31/0.30	*	*	*	*	*	
14	*	0.30	*	*	*	*	*	
15	*	0.28	*	*	*	*	*	
16	*	0.29	*	*	*	*	*	

Note - * Indicates tests not performed - Reference Table 17 for number of samples tested

Results Table

Table 26 continued *Device Testing Strip Performance Results – Full Speed*

Run No.	Tear Test (N/mm)	Peel Test (N/mm)	Gemini Torsion Hub Test Individual Operation Force Range Design Intent = 3 - 15N		Gemini Torsion Hub Test Mean Operation Force Design Intent = 5 - 10N		Edge cut defect Testing with 135° 1.25mm cut (50 samples tested)
			To design intent	14% Weaker Torsion	To design intent	14% Weaker Torsion	
17	*	0.29	*	*	*	*	*
18	*	0.31	*	*	*	*	*
19	*	0.26	*	*	*	*	*
20	*	0.31	*	*	*	*	*
21	*	0.30	*	*	*	*	*
22	*	0.30	*	*	*	*	*
23	*	0.30	*	*	*	*	*
24	*	0.27	*	*	*	*	*
15	*	0.29	*	*	*	*	*
26	*	0.35	7.0 – 11.2N	6.2 – 9.4N	8.7 – 9.6N	7.7 – 9.5N	All tests satisfactory, no tears propagated.
Current lidding Foil	*	*	7.3 – 9.8N	5.4 – 7.9N	8.3N	6.8N	*

Note - * Indicates tests not performed - Reference Table 17 for number of samples tested

Table 27 *Results of Gemini Assembly Strip Performance Testing – Full Speed*

Run No.	Visual Inspection for Strip Separation (200 Strip)		Visual Inspection for Slitting (200 Strip)		Dye Testing (20 Samples)		Loop Weld Test (2 Samples)		Land Area Not Separating (100% Inspection)	
	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory
1	200	0	200	0	20	3	2	0	*	n/a
3	200	0	200	0	20	0	2	0	*	n/a
5	200	0	200	0	20	2	2	0	*	n/a
8	200	1	200	0	20	2	2	0	*	n/a
9	200	0	200	0	20	0	2	0	*	n/a
11	200	0	200	0	20	0	2	0	*	n/a
12	200	2	200	0	20	1	2	0	*	n/a
19	200	0	200	0	20	0	2	0	*	n/a
20	200	0	200	0	20	0	2	0	*	n/a
24	200	0	200	0	20	0	2	0	*	n/a
25	200	0	200	0	20	0	2	0	*	n/a
26	200	0	200	0	20	0	2	0	*	n/a

Note - * This data could not be collated as the Operational Equipment Efficiency recording data was not active

Observations from the Seal Integrity Testing at Full Speed

As recorded in Table 25, dye test failures on samples from run 3 were observed. On inspection the failures indicated that they were genuine seal integrity rejects, as blister 30 from each strip had popped open. The settings used during run 3 will therefore, not be recommended for future development studies.

Dye test failures on samples from runs 24 and 26. On inspection a vast majority of rejects were genuine popping related rejects, therefore settings from these runs were not recommended for future development studies. However, on further analysis of the dye test failures it was evident that the sealed strip was misaligned due to the poor alignment of the top and bottom sealing wheels. All failed samples tested from runs 5, 8 11, and 25 were caused by low level lactose residue on strip, see Appendix 4 – *Images*. Previous results indicated that powder spatter is an occurrence when using un-blended lactose and not a consequence of the NLF. Therefore, settings from these runs will be recommended for future development studies.

Observations from the Coiled Strip Performance Testing at Full Speed

Samples from runs 11 and 26 were selected for Gemini Lever force testing using standard and 14% weaker torsion hubs. The 14% weaker torsion hub was used to demonstrate that the device would function with a strip that had a relatively high peel force (strip from run 11 = 0.33N.mm and strips from Run 26 = 0.35N/mm). All recorded results were within the individual operation force range design intent of 3 - 15N, and the mean operational force design intent of 5 – 10N. Results indicated that there was a 1N increase in lever force using NLF (for both standard and 14% weaker torsion hubs); compared to the Current Lidding Foil (CLF), reference Table 26. However, the 1N increase is not seen as significant, as the recorded values are still within the specified limits.

Samples from run 26 were selected for defect testing. An edge cut was applied and strip inserted into the Gemini device. Following operation the device was

opened and the strip examined for evidence of tear propagation. All tests were satisfactory, no tears propagated, indicating that the slightly elevated temperatures (from previous testing) used did not degrade the tear resistance of the NLF, reference *Table 26 – Results Table*. Samples from all runs were selected for peel force testing. All tests were satisfactory, reference *Table 26 – Results Table*. The peel force results ranged from 0.24 N/mm to 0.35 N/mm, which is an equivalent peel force to the CLF as tested in section 4.6.

The results specified in Table 28 is a summary of the settings confirmed as satisfactory following R&D full speed testing.

Table 28 ***Satisfactory Full Speed Settings Following Filled Strip and Coiled Strip Testing***

Run	Temperature Upper Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Temperature Lower Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Pressure ($\pm 10\text{N}$)
5	135	65	250
8	140	70	265
11	150	80	295
25	145	65	265

Half Speed Seal Integrity Testing

On completion of the filling trials spools were selected based on seal integrity (dye tests) and strip appearance results generated following the filling stage. The parameters used to produce these spools are expected to provide a solid indication of an optimal operating window.

Filled strip samples were tested for peel strength, seal integrity, Gemini lever force / torsion hub and defect inspection tests. The numbers of samples for each test are defined in Table 17. The full sets of test results from samples produced at full speed are documented in Tables 29 - 30.

Dye testing and subsequent examination of dye test failures was carried out on the selected strip runs that had been coiled using the Gemini Sortimat assembly

equipment. The strips were coiled and ends formatted, prior to being released into collection bags (rather than insertion into Gemini devices). The results are documented in Table 31.

Results Table

Table 29 *Device Testing Seal Integrity Results – Half Speed*

Run No.	% Seal Integrity failures (Double Filled strip) 100 tested		% Seal Integrity failures (Single Coiled) 100 Tested		Seal Integrity (Single Uncoiled)		Comments
	Lane A	Lane B	Lane A	Lane B	Lane A	Lane B	
1	2	0	13	2	*	*	1 Filled uncoiled strip failure caused by low level lactose on strip, and 1 caused as a popping related dye test failure. 2 Filled coiled strip pockets failed due to low level of lactose on strip, 14 pockets of filled coiled strip was popping related dye test failures.
2	5	1	6	0	*	*	5 filled/uncoiled strip failure caused by low level lactose on strip, and 1 caused as a popping related dye test failure. 4 filled/coiled strip pockets failed due to low level of lactose on strip, 2 pockets of filled/coiled strips were popping related dye test failures.
5	1	0	4	1	*	*	Unknown why 1 filled/uncoiled strip failed (not popped). 5 filled/coiled strip pockets failed due to low level of lactose on strip.
9	0	0	*	*	*	*	No dye test failures on strips tested.
10	0	0	0	0	*	*	No dye test failures on strips tested.
20	0	0	27	4	*	*	All filled/coiled strips were popping related dye test failures.
18	*	*	0	0	*	*	No dye test failures on strips tested.
16	2	5	12	4	*	*	12 filled/uncoiled strip failure caused by low level lactose on strip. 2 pockets of filled/coiled strips were popping related dye test failures, 1 filled/coiled strip failed for unknown reason.
19	*	*	1	4	*	*	All filled/coiled strips were popping related dye test failures.
17	*	*	3	0	*	*	3 filled/uncoiled strip failure caused by low level lactose on strip.
15	*	*	1	22	*	*	1 filled/coiled strip pockets failed due to low level of lactose on strip. 22 filled/coiled strips failed due to shriveling of sealed strip (from elevated temperature settings).
14	*	*	13	37	*	*	1 filled/coiled strip pockets failed due to low level of lactose on strip. 49 filled/coiled strips failed due to shriveling of sealed strip (from elevated temperature settings).

Note - * Indicates tests not performed

Results Table

Table 30 *Device Testing Strip Performance Results – Half Speed*

Run No.	Tear Test (N/mm)	Peel Test (N/mm)	Gemini Torsion Hub Test Individual Operation Force Range Design Intent = 3 - 15N		Gemini Torsion Hub Test Mean Operation Force Design Intent = 5 - 10N		Edge cut defect Testing with 135° 1.25mm cut (50 samples tested)	Comments
			To design intent	14% Weaker Torsion	To design intent	14% Weaker Torsion		
1	*	0.28	*	*	*	*	*	
2	*	0.30	*	*	*	*	*	
3	*	0.31	*	*	*	*	*	
4	*	0.35	*	*	*	*	*	
5	*	0.32	*	*	*	*	*	
6	*	0.38	*	*	*	*	*	
7	*	0.37	*	*	*	*	*	
8	*	0.30	*	*	*	*	*	
9	*	0.30	*	*	*	*	*	
10	*	0.35	*	*	*	*	All tests satisfactory, no tears propagated.	
15	*	0.30	*	*	*	*	*	
16	*	0.30	*	*	*	*	*	
17	*	0.29	*	*	*	*	*	
18	*	0.31	*	*	*	*	*	
19	*	0.28	*	*	*	*	*	
20	*	0.29	*	*	*	*	*	

Note - * Indicates tests not performed - Reference Table 17 for number of samples tested

Results Table

Table 31 ***Results of Gemini Assembly Strip Performance Testing – Half Speed***

Run No.	Visual Inspection for Strip Separation (200 Strip)		Visual Inspection for Slitting (200 Strip)		Dye Testing (20 Samples)		Loop Weld Test (2 Samples)		Land Area Not Separating (100% Inspection)	
	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory	Number Tested	Number Un-satisfactory
1	200	0	200	0	20	0	2	0	*	n/a
2	200	0	200	0	20	0	2	0	*	n/a
5	200	0	200	0	20	0	2	0	*	n/a
6	200	0	200	0	20	0	2	0	*	n/a
7	200	0	200	0	20	0	2	0	*	n/a
8	200	0	200	0	20	0	2	0	*	n/a
9	200	0	200	0	20	0	2	0	*	n/a
10	200	0	200	0	20	0	2	0	*	n/a
14	200	0	200	0	20	0	2	0	*	n/a
15	200	0	200	0	20	0	2	0	*	n/a
16	200	0	200	0	20	0	2	0	*	n/a
17	200	0	200	0	20	0	2	0	*	n/a
18	200	0	200	0	20	0	2	0	*	n/a
19	200	0	200	0	20	0	2	0	*	n/a
20	200	0	200	0	20	0	2	0	*	n/a

Note - * This data could not be collated as the Operational Equipment Efficiency recording data was not active

Observations from the Seal Integrity Testing at Half Speed

All samples tested from runs 9, 10 and 18 were dye tested in accordance with the protocol, and produced satisfactory results.

Dye test failures on samples from runs 1, 2, 14, 15, 16, 19, and 20. On inspection a vast majority of rejects were genuine popping related rejects, therefore settings from these runs will not be recommended for future development studies. However, on further analysis of the dye test failures it was evident that the sealed strip was misaligned due to the poor alignment of the top and bottom sealing wheels. All failed samples tested from runs 5, and 17 were caused by low level lactose residue on strip, see Appendix 4 – *Images*. Previous results indicated that powder spatter is an occurrence when using un-blended lactose and not a consequence of the NLF. Therefore, settings from these runs will be recommended for future development studies.

Observations from the Coiled Strip Performance Testing at Half Speed

Samples from run 10 were selected for defect testing. An edge cut was applied & strip inserted into the Gemini device. Following operation the device was opened and the strip examined for evidence of tear propagation. All tests were satisfactory, no tears propagated, indicating that the slightly elevated temperatures (from previous testing) used did not degrade the tear resistance of the NLF, reference Table 30 – *Results Table*.

Samples from all runs were selected for peel force testing. All tests were satisfactory, reference Table 30 – *Results Table*, the peel force results ranged from 0.28 N/mm to 0.35 N/mm, which is an equivalent peel force to the CLF as tested in section 4.6.

The results specified in Table 32 is a summary of the settings confirmed as satisfactory following R&D half speed testing.

Table 32 ***Satisfactory half Speed Settings Following R&D Filled Strip and Coiled Strip Testing***

Run	Temperature Upper Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Temperature Lower Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Pressure ($\pm 10\text{N}$)
5	120	65	250
9	130	75	280
10	135	80	290
17	125	60	265
18	120	65	265

4.4.2 Conclusions and Recommendations from Production Study

It can be concluded from the study that the new recessed land area change parts inserted in the sealing wheel have provided a larger operating sealing range in terms of higher temperatures and pressures without sticking in the land area. It will therefore, be recommended that the recessed change parts be used during subsequent trials and any formal validation studies.

The recommended settings are influenced by the poor alignment of the upper and lower sealing wheels that has contributed to the unsealing (popping) issue seen particularly with pocket 30 during the dye test examination.

At half speed the more elevated seal parameters led to partial sticking of the unsealed land area. Further investigation / development will be required. Further work will also be carried out to assess the effect of seal alignment on the un-sealing (popping) issue. In addition a trial will be carried out in order to provide a direct comparison between the NLF and CLF. This will enable a comparison to be made of the NLF vs CLF ability to cope with product residue (spatter) between the sealing surfaces, as this was the most frequent cause of the observed dye test failures.

The satisfactory settings for half speed concluded from the findings of this study that should be referenced to evaluate NLF further are provided in Table 33.

Table 33 *Satisfactory Settings - Half Speed*

Run	Temperature Upper Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Temperature Lower Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Pressure ($\pm 10\text{N}$)
5	120	65	250
9	130	75	280
10	135	80	290
17	125	60	265
18	120	65	265

The recommended nominal sealing parameters for subsequent development trials at half speed are:

- Upper sealing wheel temperature 125-130°C.
- Lower sealing wheel temperature 70-75°C.
- Pressure of 260-275N.

The satisfactory settings for full speed concluded from the findings of this study that should be referenced to evaluate NLF further are provided in Table 34.

Table 34 *Satisfactory Settings - Full Speed*

Run	Temperature Upper Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Temperature Lower Sealing Wheel ($\pm 5^{\circ}\text{C}$)	Pressure ($\pm 10\text{N}$)
5	135	65	250
8	140	70	265
11	150	80	295
25	145	65	265

The recommended nominal sealing parameters for any subsequent development trials at full speed are:

- Upper sealing wheel temperature 140-145°C.
- Lower sealing wheel temperature 70-75°C.
- Pressure of 260-275N.

It can also be concluded that the NLF gave acceptable seal quality over a wide range of operating conditions. The NLF therefore, has demonstrated to be an acceptable alternative to the current foil, although further work would be required to validate these wider operating conditions. Furthermore, due to the NLF material structure it has an increase resistance to tear strength and for this reason it will eliminate any patient unaware defects.

Chapter 4 Section 5

4.5 A study into Developing a new Adhesive and Primer System within the MDPI Cold-Form Base Laminate

4.5.1 Introduction

As previously mentioned in Section 2.1, in addition to temperature, pressure and speed, consideration of the forming characteristics is also essential to the overall sealing operation^{24,99}. If the critical parameters of the forming operation have not been fully understood then delamination of the layers can occur under stressed conditions⁵⁰. Delamination can also occur if the humidity during the lamination process is low, thus reducing the bonding strength between, for example the OPA and aluminium layers^{50,100,101}. This phenomenon has been observed on MDPI blisters after 6 months storage at the accelerated ICH conditions for stability testing at 40°C/75%RH.

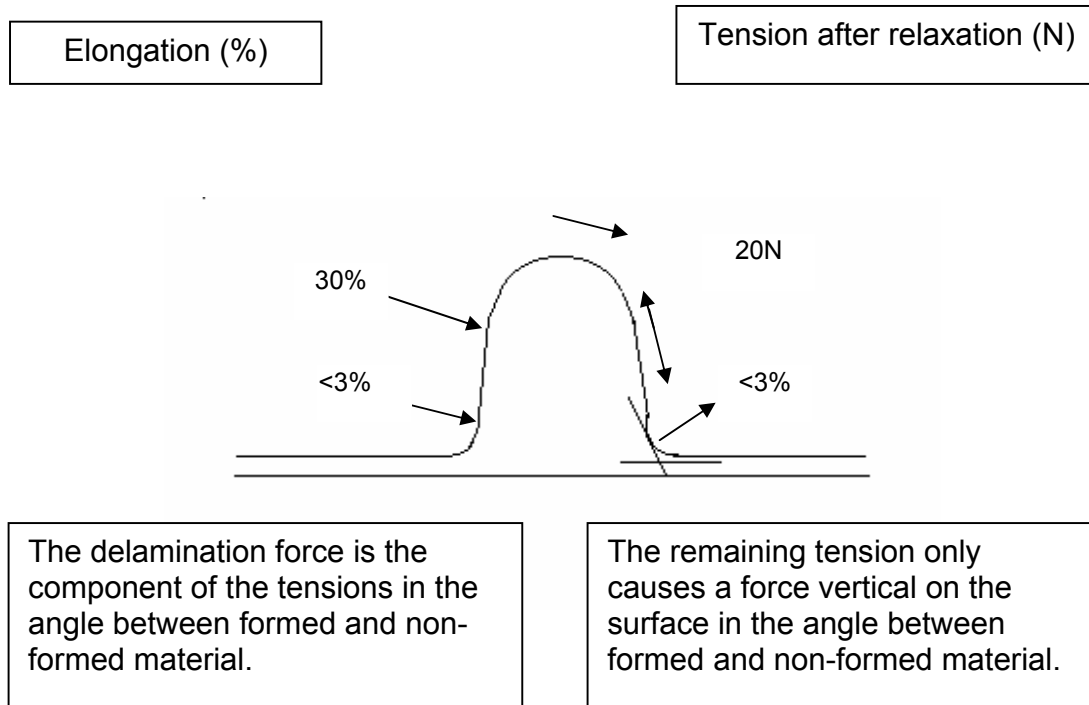
The delamination of the OPA layer means that there is no contact with the aluminium. The aluminium layer itself is still intact and not damaged nor impaired in anyway. Therefore, de-lamination has no influence over the barrier properties of the blister strip, and hence the containment and protection of the product is not compromised in anyway. However from a cosmetic point of view this is not acceptable and therefore requires investigating.

Also critical to the forming operation is the design of the forming tool, and the forming depth and pocket profile⁵⁰. If the radius of the forming tool is under 0.5mm and the depth and / or profile of the blister pocket has not been fully optimised, then the outside laminate (OPA) can be overstressed⁵⁰. This tension in the OPA can also lead to delamination⁵⁰, starting in the border between the cavity and the non-formed area (sealing area). The sealing layer will not show the same phenomenon and will not impact on the quality of the product,

because the humidity in the cavity is very low, due to the environmental conditions of 22°C / 40RH in the blister sealing room, which is not high enough to lead to a reaction with the adhesive⁵⁰. For a reaction to take place, it would have to start from the trimmed side and must continue through the sealed seam. Tests show that the bonding strength between the inner layer (PVC) and aluminium is not influenced by storage under stress conditions. Additionally, there is no remaining tension in the PVC after the forming, since a non-oriented film is being used^{49,50}.

Providing an optimum forming process is achieved and because of the fixation of the OPA on the aluminium by the adhesive, the tension should not affect the border between formed and non-formed areas of a blister, which is the only place where the tension in the film is creating a force perpendicular to the surface^{49,50}, as described in Figure 38. In this area, the elongation of the material is very low, typically less than 3%⁵⁰, and therefore, the force vertical to the surface is very low as well⁵⁰. However, in storage under stress conditions, the cohesive strength of the adhesive is slowly decreasing, which leads to delamination when the cohesion becomes lower than the delaminating forces^{49,50}, see Figure 38.

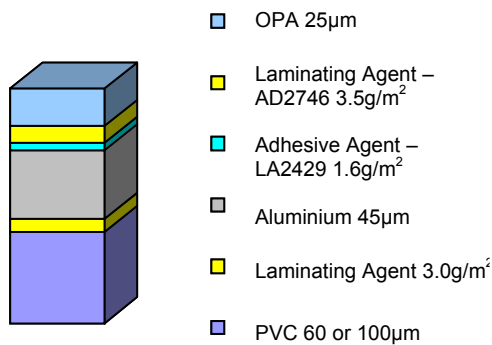
Figure 38 - Tension and Delaminating Forces in Base Material⁵⁰



APS who supply cold form base laminate for use in MDPI devices, have also observed that in conditions of high temperature and humidity, delamination of the OPA and aluminium layers occurred^{102,103}. The delamination is caused by the chemical and physical property of the primer and adhesive system between the OPA and aluminium layers under the influence of humidity and temperature. As a result APS have reformulated the adhesive and primer used to improve the adhesive bond between the aluminium and OPA layers, which is stable to delamination for a period of 26 weeks^{102,103,104}, stored at 40°C / 95%RH. This material is known as 'Quality Advanced 2', reference Figure 39.

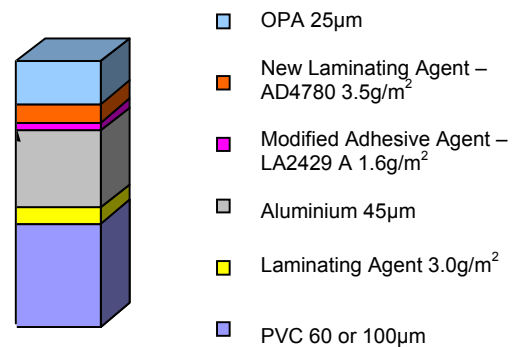
Figure 39 - Comparison of Current and New Base Laminates Details the Difference in Material Structures^{105,106,107,108,109}.

Current standard laminate for coldform blisters



Outside	Layer
	OPA 25µm
	Adhesive 3.5g/m ²
	Primer 1.6g/m ²
	Aluminium 45µm
	Adhesive 3.0g/m ²
Inside	PVC (60 or 100µm)

New laminate for coldform blisters



New laminate
As for standard laminate
New adhesive
Modified Primer
As for standard laminate
As for standard laminate
As for standard laminate

Material Descriptions

Both the new Quality Advanced 2 and current base laminates comprise of standard OPA, aluminium and PVC layers with the same adhesive and primer between the aluminium and PVC (product contact) layer.

- PVC is used to support the blister giving it more rigidity and provides a compatible surface to be sealed against the heat seal lacquer of the lidding foil.
- The aluminium provides the barrier properties of the blister strip.
- The OPA is used to support the aluminium whilst being formed into blister pockets.

Evaluation and Testing to Approve the new Adhesive and Primer System

As part of the evaluation of a new heat-seal lacquer documented in **Chapter 4.6** the new Quality Advanced 2 base laminate was tested alongside the current material to compare that the line performance and seal strength and to monitor the long term stability impact on the active product between the new and current materials. The exercise was also designed to investigate the degree of resistance of Quality Advanced 2 to delamination and compare to the standard cold form laminate. However, prior to testing it was imperative to understand the regulatory requirements for a primary contact component change. Firstly to ensure any changes in primary contact materials and coatings that are in direct contact with the drug product comply with the receiving market guidelines and regulatory requirements as detailed in Table 35. Secondly, that composition and testing of the final product is in accordance with the relevant directives for plastic materials, additives and surface coatings as detailed in Table 35. There are also guidelines on plastic immediate packaging materials that have been published by the European Medicines Evaluation Agency (EMA)¹¹⁰. The guideline applies to packaging materials intended to be in direct contact with the active substance or medicinal product. The materials may be part of the container, the closure or the seal. The guidelines set out to provide a list of test criteria to confirm the materials have no interaction with the drug product or any other material that combines to make up the container closure system that may have an adverse effect on the drug product¹¹¹. The data provided depends on the physical state of the active substance and the pharmaceutical dosage form and route of administration. Table 36 gives the full comprehensive list of the required tests and data that must be submitted for regulatory changes.

Table 35 – Regulatory Requirements for a Primary Contact Material
Change^{112,113}

Pharmacopoeia	Composition and Testing of the Final Article	
	Food Contact	Heavy Metals
- United States Pharmacopoeia (USP) 24 th Edition 1999.	- 21 CFR (US); plastics, additives paper etc.	- CONEG regulation and USP.
- Ph.Eur. 3 rd Edition 1997 & supplement 2001 European Pharmacopoeia (EP).	- Directive 90/128/EEC, plastic materials and articles.	- Directive 94/62/EEC and Ph. Eur.
- JP 3th Edition Japanese Pharmacopoeia (JP).	- Directive 7/142/EEC EU vinyl chloride monomer level.	
	- Resolution AP 96(5) EU surface coatings.	

Table 36 – Test Requirements for a Primary Contact Material

Change^{110,111,112}

Test	Rationale	Source of Testing
Compatibility	Proof that there is no interaction between container closure system and drug product that may impact stability or efficacy of the product.	Performed as part of GSK test regime detailed in section 4.5, and 4.6.
Extraction Studies	Exposing a sample of a component to an approved solvent system to maximize the amount of extractables from the packaging.	Performed by APS to support their proposal to switch to the new adhesive / primer system.
Interaction Studies	Studies to detect any effects that plastic packaging components have on the product leading to unacceptable change in the quality of the product under normal storage and or use.	Performed by APS to support their proposal to switch to the new adhesive / primer system.
Sorption Studies	Bonding of a solute to a plastic packaging component as a physicochemical phenomenon related to the properties of the packaging material and the chemical properties of the active substance or other soluble substances in the preparation.	Performed by APS to support their proposal to switch to the new adhesive / primer system.
Suitability	Assessment of the container closure system in regard to protection, safety, compatibility and performance (function).	Performed by APS to support their proposal to switch to the new adhesive / primer system.
Migration Studies	Release of substances (leachables) from the plastic component into the content of the container under conditions that reproduce those of the intended use.	Performed by APS to support their proposal to switch to the new adhesive / primer system.

Summary and Results of the Development Study to Introduce the new Adhesive and Primer System (Quality Advanced 2).

To qualify the new material a development study was performed which concluded that the delamination resistance is higher with Quality Advanced 2 compared to the standard material^{105,106,107}.

Section 4.6 documents the equivalence testing performed on filled MDPI lid foil containing SERETIDE® & FLOVENT® blends at several strengths (SERETIDE® 50/100, 50/250, 50/500 and FLOVENT® 100) with lid foil using replacement heat seal lacquer (HSL) that has been introduced as part of my studies which is documented in section 4.6. The testing covers both the qualification the Quality Advanced 2, and replacement HSL. The results of the study are documented in the following Tables 41 – 55.

The filled MDPI strip was subsequently manufactured into devices which were then sent to the GSK Packaging Evaluation Laboratory (PEL) at Barnard Castle for equivalence testing, including peel strength testing of MDPI strip, and lever force testing of MDPI devices. The PEL peel strength, and lever force data supports the choice of the new Quality Advanced 2 base laminate as an approved replacement to the current material. Furthermore, the compatibility testing at GSK Ware confirmed that the new Quality Advanced 2 base laminate was compatible with the production equipment. In addition, no seal integrity (dye test) failures were recorded during the filling of the FLOVENT® and SERETIDE® batches or any issues observed during subsequent assembly into devices.

It can be concluded from these studies that Quality Advanced 2 base laminate has performed comparatively or better than the existing base material used to manufacture MDPI sealed strip, and is the basis for GSKs instructions to switch to Quality Advanced 2.

Chapter 4 Section 6

4.6 A Study into Developing a new Heat Seal Lacquer for use in MDPI Sealed Blisters

4.6.1 Introduction

Degussa, a supplier to APS, manufacturers of MDPI lid foil have made changes to their manufacturing process of Poly Methyl Acrylate (PMA), a majority polymer constituent of the HSL that APS apply to the lid foil prior to supply to GSK^{114,115}. The PMA supplied to APS has changed from a solid form of polymer to a liquid form of polymer^{114,115}. When initially evaluated at labs in APS, slightly higher peel strengths were recorded^{114,115}. APS later developed an amended or 'balanced' formulation, which involved a minor change to the APS HSL recipe within the Drug Master File (DMF) range, which resulted in equivalent peel force results during APS lab testing^{114,115}.

This section documents the equivalence testing performed on filled MDPI lid foil containing SERETIDE® & FLOVENT® blends at several strengths (SERETIDE® 50/100, 50/250, 50/500 and FLOVENT® 100), with lid foil with replacement HSL from both the first 'unbalanced' formulation and the second 'balanced' formulation, manufactured with liquid PMA Polymer and 'Quality Advanced 2' MDPI base foil. This was run in parallel with filled MDPI strips containing current lid and base foil intended as "control" on Mk2 filling lines, GSK Ware.

The filled MDPI strip was subsequently manufactured into MDPI devices which were then placed on stability testing. The equivalence testing included peel strength testing of MDPI strip and also lever force testing of MDPI devices.

Summary of the HSL Material Equivalence Testing

The PEL peel strength data in Tables 41 – 44 support the choice of the unbalanced formulation over the balanced formulation as this shows average peel strength results closer to the ‘control’ formulation. The lever force test results performed in the production facility using both the unbalanced and balanced HSL formulation batches are observed to show equivalence to the current control formulation batch. The MK2 actives compatibility test results appear to show similar performance to those results previously observed for lactose filled MDPI strip and devices manufactured on MK2 and MK3 filling machines. In addition, no seal integrity (dye test) failures were recorded during the filling of the ADVAIR[®] and SERETIDE[®] batches or any issues observed during subsequent assembly into devices. It was therefore, recommended that both the balanced and unbalanced formulations are considered suitable alternatives to the current HSL. However, the final decision is to switch to the un-balanced formulation.

Production and Sample Details

The lid and base foil materials used and the batch details recorded during the study are defined in Tables 37 - 40 below:

Table 37 - Sample Material / Batch Details – SERETIDE® 50/100

	HSL status:	Control	Balanced'	Unbalanced'
Lid foil material	material code	1402168	40000000005924	40000000005940
	material description	LAM PA/PET/AL PEEL LID 40MM	NHC LAM PA/PET/AL	NHC LAM PA/PET/AL
	Batch no.	351812	362700	362702
	Alcan Ref	LA2475	LA2475A	LA2475B
Base foil material	material code	40000000003952	40000000003952	40000000003952
	material description	QUALITY ADVANCED 2	QUALITY ADVANCED 2	QUALITY ADVANCED 2
	Batch no.	374498	374498	374498
Filling stage	Line resource	RPSSFL15	RPSSFL15	RPSSFL15
	material code	40000000002193	40000000002193	40000000002193
	material description	STDE MDPI 50/100MCG 60D STP TRIAL	STDE MDPI 50/100MCG 60D STP TRIAL	STDE MDPI 50/100MCG 60D STP TRIAL
	process order no.	2000564149	2000564150	2000564151
	batch no.	R324293	R324295	R324297
	No. of Filling IPCs failed/tested	0/2	0/2	0/2
	No. of spools rejected / produced	0/3	0/3	0/3
	IPC Summary(Pass/Fail)	PASS	PASS	PASS
Assembly / Packing stage	Line resource	RPSUAL17	RPSUAL17	RPSUAL17
	material number	40000000002535	40000000002535	40000000002535
	material description	STDE MDPI 50/100MCG 60D DKUS TRIAL	STDE MDPI 50/100MCG 60D DKUS TRIAL	STDE MDPI 50/100MCG 60D DKUS TRIAL
	process order no.	2000579769	2000579772	2000579771
	batch no.	R330491	R330526	R330524
	No. of Assembly IPCs failed/tested	0/4	0/3*	0/3
	IPC Summary(Pass/Fail)	PASS	PASS	PASS

Table 38 - Sample Material / Batch Details – SERETIDE® 50/250

	HSL status:	Control	Balanced'	Unbalanced'
Lid foil material	material code	1402168	40000000005924	40000000005940
	material description	LAM PA/PET/AL PEEL LID 40MM	NHC LAM PA/PET/AL	NHC LAM PA/PET/AL
	Batch no.	351812	362700	362702
	Alcan Ref	LA2475	LA2475A	LA2475B
Base foil material	material code	40000000003952	40000000003952	40000000003952
	material description	QUALITY ADVANCED 2	QUALITY ADVANCED 2	QUALITY ADVANCED 2
	Batch no.	374498	374498	374498
Filling stage	Line resource	RPSUFL17	RPSUFL17	RPSUFL17
	material code	40000000002276	40000000002276	40000000002276
	material description	STDE MDPI 50/250MCG 60D STP TRIAL	STDE MDPI 50/250MCG 60D STP TRIAL	STDE MDPI 50/250MCG 60D STP TRIAL
	process order no.	2000564152	2000564153	2000564154
	batch no.	R324298	R324300	R324302
	No. of Filling IPCs failed/tested	0/2	0/2	0/2
	No. of spools rejected / produced	0/3	0/3	0/3
	IPC Summary(Pass/Fail)	PASS	PASS	PASS
Assembly stage	Line resource	RPSUAL17	RPSUAL17	RPSUAL17
	material number	40000000002537	40000000002537	40000000002537
	material description	STDE MDPI 50/250MCG 60D DKUS TRIAL	STDE MDPI 50/250MCG 60D DKUS TRIAL	STDE MDPI 50/250MCG 60D DKUS TRIAL
	process order no.	2000579778	2000579776	2000579773
	batch no.	R330544	R330534	R330529
	No. of Filling IPCs failed/tested	0/3	0/3	0/4
	IPC Summary(Pass/Fail)	PASS	PASS	PASS

Table 39 - Sample Material / Batch Details – SERETIDE® 50/500

	HSL status:	Control	Balanced'	Unbalanced'
Lid foil material	material code	1402168	40000000005924	40000000005940
	material description	LAM PA/PET/AL PEEL LID 40MM	NHC LAM PA/PET/AL	NHC LAM PA/PET/AL
	Batch no.	351812	362700	362702
	Alcan Ref	LA2475	LA2475A	LA2475B
Base foil material	material code	40000000003952	40000000003952	40000000003952
	material description	QUALITY ADVANCED 2	QUALITY ADVANCED 2	QUALITY ADVANCED 2
	Batch no.	374498	374498	374498
Filling stage	Line resource	RPSSFL09	RPSSFL09	RPSSFL09
	material code	40000000002495	40000000002495	40000000002495
	material description	STDE MDPI 50/500MCG 60D STP TRIAL	STDE MDPI 50/500MCG 60D STP TRIAL	STDE MDPI 50/500MCG 60D STP TRIAL
	process order no.	2000564155	2000564157	2000564159
	batch no.	R324303	R324304	R324305
	No. of Filling IPCs failed/tested	0/2	0/2	0/2
	No. of spools rejected / produced	0/3	0/3	0/3
	IPC Summary(Pass/Fail)	PASS	PASS	PASS
Assembly stage	Line resource	RPSUAL17	RPSUAL17	RPSUAL17
	material number	40000000002538	4000000000258	40000000002538
	material description	STDE MDPI 50/500MCG 60D DKUS TRIAL	STDE MDPI 50/500MCG 60D DKUS TRIAL	STDE MDPI 50/500MCG 60D DKUS TRIAL
	process order no.	2000579779	2000579781	2000579780
	batch no.	R330547	R330564	R330563
	No. of Assembly IPCs failed/tested	0/4	0/3	0/4
	IPC Summary(Pass/Fail)	PASS	PASS	PASS

Table 40 - Sample Material / Batch Details – FLOVENT® 100

	HSL status:	SERETIDE 50/100 Control	Balanced'	Unbalanced'
Lid foil material	material code	1402168	40000000005924	40000000005940
	material description	LAM PA/PET/AL PEEL LID 40MM	NHC LAM PA/PET/AL	NHC LAM PA/PET/AL
	Batch no.	351812	362700	362702
	Alcan Ref	LA2475	LA2475A	LA2475B
Base foil material	material code	40000000003952	40000000003952	40000000003952
	material description	QUALITY ADVANCED 2	QUALITY ADVANCED 2	QUALITY ADVANCED 2
	Batch no.	374498	374498	374498
Filling stage	Line resource	RPSSFL15	RPSSFL08	RPSSFL08
	material code	40000000002193	40000000005142	40000000005142
	material description	STDE MDPI 50/100MCG 60D STP TRIAL	FLUT 100MCG MDPI 60D STRIP TRIAL	FLUT 100MCG MDPI 60D STRIP TRIAL
	process order no.	2000564149	2000564223	2000564229
	batch no.	R324293	R324306	R324308
	No. of Filling IPCs failed/tested	0/2	0/3	0/2
	No. of spools rejected / produced	0/3	1/5*	0/3
	IPC Summary(Pass/Fail)	PASS	PASS	PASS
Assembly stage	Line resource	RPSUAL17	RPSUAL17	RPSUAL17
	material number	40000000003995	40000000001285	40000000001285
	material description	STDE MDPI 50/100MCG 60D DKUS TRIAL	FLUT 100MCG MDPI 60D FINISH PACK	FLUT 100MCG MDPI 60D FINISH PACK
	process order no.	2000579769	2000579497	2000579770
	batch no.	R330491	R330359	R330520
	No. of Assembly IPCs failed/tested	0/4	0/3	0/4
	IPC Summary(Pass/Fail)	PASS	PASS	PASS

Development and Equivalency Testing

Manufacturing Method

All the samples referenced in Section 4.6 were manufactured on MK2 Filling machines at GSK Ware (filling lines FL09, FL15 and FL17 during Oct - Nov 2007). The filling of the MDPI strip and subsequent assembly into MDPI devices was performed in accordance with the relevant local production procedures and batch documentation. MDPI strip samples were collected during the filling trials and sent to the PEL at Barnard Castle for Peel strength testing. For each strength variant, several MDPI spools were produced and assembled into DISKUS[®] devices as per routine production for use in lever force testing.

Due to insufficient available blend at the time of manufacture, the decision was taken to manufacture only the 'unbalanced' and 'balanced' HSL for the FLOVENT[®] 100 batches and to compare the peel strength and lever force data against one of the other SERETIDE[®] 'control' batches. (Table 37 contains the data for the SERETIDE[®] 50/100 batch as comparison).

Peel Strength Testing

The peel strength tests were performed using the PEL, GSK standards, see Tables 41- 44 for PEL references.

Each device was initially taken apart and the MDPI strip removed and the lane identification recorded (lane A or lane B). The MDPI strips were mounted on the VAPT and the MDPI strips peeled at test speeds of 100mm/min. The VAPT equipment allows the strip to be peeled in a horizontal position to prevent the powder from being tipped out. The angle of peel was maintained at 90 deg. Approx 50 pockets were peeled for each MDPI strip and the average peel strength was calculated. The peel strength calculation included the area around blisters with a seal across the full width of the strip, giving higher values, and

the area over the blisters where the seal is not across the full width of the strip, resulting in lower values.

Results

Table 41 - Peel Strength Test Results – SERETIDE® 50/100

Confidence limits ± 0.01 Nmm

PEL Test Ref	Peel Strength (Nmm)						
	R324293 (Control)		R324295 (Balanced)		R324297 (Unbalanced)		
	07/PEL/10/48F		07/PEL/10/46F		07/PEL/10/47F		
	lane A	lane B	lane A	lane B	lane A	lane B	Average
a) start of batch	0.17	0.16	0.16	0.16	0.16	0.17	0.16
	0.18	0.19	0.15	0.15	0.18	0.16	0.17
	0.18	0.19	0.16	0.16	0.17	0.17	0.17
b) middle of batch	0.19	0.18	0.17	0.16	0.18	0.18	0.17
	0.19	0.20	0.17	0.16	0.19	0.19	0.18
	0.18	0.18	0.16	0.17	0.18	0.18	0.17
c) end of batch	0.18	0.17	0.17	0.15	0.18	0.17	0.17
	0.20	0.17	0.17	0.16	0.19	0.18	0.18
	0.17	0.18	0.16	0.16	0.18	0.18	0.17

Table 42 - Peel Strength Test Results – SERETIDE® 50/250

PEL Test Ref	Peel Strength (Nmm)						
	R324298 (Control)		R324300 (Balanced)		R324302 (Unbalanced)		
	07/PEL/10/45F		07/PEL/10/43F		07/PEL/10/44F		
	lane A	lane B	lane A	lane B	lane A	lane B	Average
a) start of batch	0.18	0.18	0.15	0.15	0.17	0.17	0.17
	0.19	0.18	0.16	0.15	0.16	0.17	0.17
	0.18	0.18	0.15	0.15	0.16	0.16	0.17
b) middle of batch	0.20	0.19	0.17	0.17	0.18	0.18	0.18
	0.18	0.19	0.17	0.18	0.18	0.17	0.18
	0.18	0.19	0.17	0.17	0.18	0.18	0.18
c) end of batch	0.19	0.19	0.17	0.17	0.18	0.19	0.18
	0.19	0.19	0.17	0.17	0.19	0.17	0.18
	0.18	0.19	0.16	0.17	0.18	0.19	0.18

Table 43 - Peel Strength Test Results – SERETIDE® 50/500

PEL Test Ref	Peel Strength (Nmm)						
	R324303 (Control)		R32304 (Balanced)		R324305 (Unbalanced)		
	07/PEL/10/49F		07/PEL/10/55F		07/PEL/10/50F		
	lane A	lane B	lane A	lane B	lane A	lane B	Average
a) start of batch	0.22	0.19	--*	--*	0.19	0.16	0.19
	0.20	0.20	--*	--*	0.19	0.17	0.19
	0.19	0.20	--*	--*	0.19	0.17	0.19
b) middle of batch	0.20	0.19	--*	--*	0.19	0.18	0.19
	0.20	0.20	--*	--*	0.19	0.18	0.19
	0.21	0.21	--*	--*	0.19	0.19	0.20
c) end of batch	0.21	0.20	0.18	0.18	0.19	0.18	0.19
	0.20	0.19	0.17	0.18	0.20	0.18	0.18
	0.19	0.21	0.18	0.17	0.20	0.18	0.19

* - No data available, End of batch sample taken after trial completion.

Table 44: Peel Strength Test Results – FLOVENT® 100

PEL Test Ref	Peel Strength (Nmm)						
	R324293 (Control)		R324306 (Balanced)		R324308 (Unbalanced)		
	07/PEL/10/48F		07/PEL/10/46F		07/PEL/10/47F		
	lane A	lane B	lane A	lane B	lane A	lane B	Average
a) start of batch	0.17	0.16	0.16	0.15	0.17	0.16	0.16
	0.18	0.19	0.16	0.15	0.18	0.17	0.17
	0.18	0.19	0.15	0.15	0.18	0.17	0.17
b) middle of batch	0.19	0.18	0.17	0.16	0.19	0.17	0.18
	0.19	0.20	0.16	0.15	0.18	0.19	0.18
	0.18	0.18	0.17	0.16	0.19	0.18	0.17
c) end of batch	0.18	0.17	0.17	0.16	0.19	0.18	0.17
	0.20	0.17	0.17	0.16	0.19	0.18	0.18
	0.17	0.18	0.16	0.15	0.18	0.18	0.17

Summary of Peel Strength Results

SERETIDE® 50/100

Table 41 details the results of the balanced and un-balanced HSL formulations against the 'control' formulation. The 'unbalanced' formulation is found to show equivalence with current 'control' formulation while the 'balanced ' formulation

could not be shown to show equivalence. The practical difference between the balanced and unbalanced formulations and the current lid foil material is considered negligible.

SERETIDE® 50/250

Table 42 details the results of the balanced and un-balanced HSL formulations against the 'control' formulation. The 'unbalanced' formulation is found to show equivalence with current 'control' formulation while the 'balanced ' formulation could not be shown to show equivalence. Also both the replacement formulations are observed to record lower average peel strength values compared to the standard 'control' formulation. The 'unbalanced' formulation however, was observed to have a range of peel strength values closer to the current 'control' formulation.

SERETIDE® 50/500

Table 43 details the results of the balanced and un-balanced HSL formulations against the 'control' formulation. Neither the 'unbalanced' and 'balanced' formulation could be shown to show equivalence to the 'control' formulation. Again, both the replacement formulations are observed to record lower average peel strength values compared to the standard 'control' formulation, with the 'un-balanced' formulation closest to the control.

FLOVENT® 100

Tables 44 show the results of the balanced and un-balanced HSL formulations against the SERETIDE® 50/100 'control' formulation. The 'unbalanced' formulation appears to be equivalent with the SERETIDE® 50/100 'control' formulation while the 'balanced' formulation was not. Since no FLOVENT® 100 'control batch was available, both results are subject to interpretation. This

result is likely to be due to the variation in peel strength results observed across the 3 control batches.

Lever Force Testing

The device lever force tests were performed using a calibrated Salter EFG200 electronic force gauge. The results are detailed in Tables 45 - 55.

Each DISKUS[®] device was prepared for testing by removing the outer case and ensuring the number '60' appears in the dose indicator window. The device was placed in the test rig and the force gauge set to zero before the start of the test. The device was rotated clockwise to operate the dose release lever. The force gauge display was recorded in the record sheet. The device was removed from the test rig and the released powder was removed with the HEPA filtered vacuum system. The lever was pushed back towards the mouthpiece and the device was placed back into the test rig to test the lever force of the next blister pocket and so on.

For each device, the test was first carried out on pockets 60 to 55. Then for pockets 54 to 12, the device was indexed and powder extracted automatically to waste using the MDPI indexing machine. Lever force testing as described above was then completed on pockets 11 to 1.

Table 45 - Lever Force Test Results – Batch R330491 (SERETIDE® 50/100 Control)

Note: The lever force increases as the device is indexed through the device. For this reason averaging the results will not have any relevance on the study.

R330491	Dose indicator – All values in Newton's																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	21.1	13.5	11.0	10.4	9.4	6.9	9.6	11.9	11.1	10.7	11.4	11.3	14.3	13.4	15.5	15.8	13.4
Lane B (N)	11.1	10.6	8.5	7.8	7.5	6.9	9.9	11.1	11.7	12.5	11.0	11.3	15.0	14.6	14.7	18.7	14.1
Device 6																	
Lane A (N)	13.1	12.2	9.4	7.9	7.7	7.7	11.4	12.3	12.8	10.5	10.4	11.9	15.5	14.5	15.3	17.4	16.2
Lane B (N)	10.2	9.2	8.3	6.9	7.2	6.7	8.8	9.7	10.5	10.1	9.9	9.2	12.7	11.8	13.0	14.8	11.6
Device 9																	
Lane A (N)	14.8	11.2	10.4	8.4	8.2	6.0	9.3	10.8	12.4	12.1	11.8	11.1	14.7	15.1	14.3	16.7	12.8
Lane B (N)	9.1	9.1	8.4	7.6	6.6	5.8	8.9	11.2	10.6	11.2	9.8	10.5	13.3	11.4	13.4	15.5	13.5
Device 12																	
Lane A (N)	15.3	12.7	10.3	9.5	8.3	6.6	10.1	10.5	10.3	10.4	11.7	11.7	14.4	13.8	17.3	15.3	13.9
Lane B (N)	8.5	10.3	9.4	6.9	7.0	7.4	8.8	10.8	11.3	11.8	10.3	11.0	14.9	13.0	16.0	16.4	13.0
Device 15																	
Lane A (N)	13.6	12.3	9.6	9.3	7.9	7.4	8.9	10.9	10.9	11.4	10.6	10.4	14.7	13.9	15.2	14.7	13.0
Lane B (N)	10.5	10.1	8.2	7.7	7.1	7.7	8.2	9.8	10.9	11.2	10.8	11.4	14.7	12.9	15.4	14.7	12.9
Device 18																	
Lane A (N)	13.7	13.2	10.0	8.5	7.9	7.0	11.2	11.2	11.8	12.0	12.4	11.7	14.4	14.3	14.2	16.1	15.7
Lane B (N)	12.7	11.6	9.8	10.4	8.0	7.0	8.0	10.9	9.7	10.8	10.3	11.5	13.2	13.4	19.2	14.5	13.5
Device 21																	
Lane A (N)	14.0	13.2	10.6	9.4	6.3	6.1	9.6	8.5	9.5	11.8	10.3	11.5	14.9	14.2	15.3	16.2	13.9
Lane B (N)	11.0	10.3	8.3	6.6	6.5	6.7	10.1	10.1	9.4	10.5	9.2	10.3	13.4	11.8	14.8	14.3	13.1
Device 24																	
Lane A (N)	13.4	12.5	9.2	8.1	9.1	7.5	9.2	10.1	11.2	11.1	10.0	10.6	14.7	12.6	13.9	13.1	13.6
Lane B (N)	10.0	10.1	9.1	7.3	6.9	6.6	8.3	10.9	9.7	10.7	9.3	11.8	13.7	11.1	14.6	16.9	13.3

Table 46 - Lever Force Test Results – Batch R330526 (SERETIDE® 50/100 Balanced)

R330526	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	14.6	12.7	9.5	10.0	8.1	6.7	8.9	10.6	10.9	11.5	10.7	12.0	14.5	14.4	15.0	14.8	13.5
Lane B (N)	10.7	11.0	9.7	7.7	6.7	6.8	8.1	9.3	10.8	11.6	10.8	9.5	14.6	12.1	13.5	14.4	13.1
Device 6																	
Lane A (N)	14.9	13.6	9.9	8.0	7.5	7.0	8.4	9.4	9.5	10.3	10.6	9.9	12.9	13.0	13.6	15.6	13.2
Lane B (N)	8.1	8.7	8.5	6.6	7.1	7.0	10.2	10.3	11.1	12.1	10.1	10.1	14.1	12.7	14.7	18.2	14.9
Device 9																	
Lane A (N)	14.6	13.3	10.6	9.0	7.8	7.1	8.7	10.3	11.2	11.7	10.1	11.1	13.8	12.9	12.8	16.3	14.3
Lane B (N)	10.1	10.4	9.1	8.0	7.6	6.6	9.9	10.8	11.8	11.6	9.8	9.5	11.6	11.2	13.6	13.7	12.9
Device 12																	
Lane A (N)	9.8	9.2	8.1	5.4	6.7	6.5	9.1	10.1	11.2	10.2	9.6	11.1	13.8	12.9	12.3	16.6	13.6
Lane B (N)	9.4	10.0	8.3	6.8	6.5	7.0	9.0	10.3	10.2	11.5	10.2	10.9	15.9	12.6	15.3	14.0	13.3
Device 15																	
Lane A (N)	15.7	11.9	8.8	8.4	6.8	6.5	9.4	10.3	10.3	9.2	10.0	9.1	13.9	14.2	14.9	16.5	13.1
Lane B (N)	8.1	10.3	8.7	7.3	6.6	6.1	8.7	9.3	10.4	10.8	8.5	9.9	14.0	12.2	13.8	15.1	12.5
Device 18																	
Lane A (N)	9.9	8.6	6.9	6.1	5.7	6.2	8.5	9.4	10.1	10.0	9.0	10.4	12.7	11.6	12.5	15.5	11.6
Lane B (N)	9.3	9.2	7.5	6.9	5.8	5.7	9.6	10.5	10.8	11.1	9.9	10.6	14.9	12.5	14.6	12.3	11.9
Device 21																	
Lane A (N)	10.8	8.1	7.3	6.1	6.0	6.0	7.7	8.7	9.8	11.1	10.2	10.1	11.6	10.5	12.7	16.1	13.7
Lane B (N)	8.3	7.9	8.8	7.1	6.8	6.7	7.8	10.6	10.4	10.9	9.9	10.6	14.8	11.0	14.6	15.2	13.4
Device 24																	
Lane A (N)	12.2	11.5	9.8	7.1	8.1	7.3	7.1	8.3	10.5	9.5	9.2	9.8	12.2	12.0	13.5	14.8	13.4
Lane B (N)	9.7	9.8	8.7	7.3	6.0	6.9	8.2	10.0	11.4	11.3	9.8	10.5	11.9	12.5	14.6	14.3	13.6

Table 47 - Lever Force Test Results – Batch R330524 (SERETIDE® 50/100 Un-balanced)

R330524	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	11.0	7.8	7.1	7.0	6.1	5.1	8.5	10.3	10.9	11.8	11.1	11.6	13.6	13.2	14.0	15.1	12.1
Lane B (N)	12.0	9.8	8.5	7.7	7.5	6.6	9.4	9.5	11.3	12.6	8.5	10.3	14.5	12.5	15.5	15.5	13.3
Device 6																	
Lane A (N)	10.2	10.0	7.7	7.1	6.7	6.2	8.7	9.4	9.6	9.6	9.1	10.4	13.7	12.2	13.2	12.3	11.6
Lane B (N)	10.7	7.7	8.8	7.2	6.0	5.9	9.7	9.1	9.7	10.9	9.5	11.1	12.2	12.6	14.6	14.5	13.1
Device 9																	
Lane A (N)	15.0	12.0	10.2	8.7	7.0	6.8	8.6	10.3	10.9	10.7	9.4	9.7	12.8	12.7	13.2	14.6	12.1
Lane B (N)	9.7	8.4	9.3	6.1	5.6	6.5	9.2	10.7	10.2	10.6	9.4	9.0	12.5	13.1	14.4	15.6	13.2
Device 12																	
Lane A (N)	11.4	10.2	9.2	8.6	6.0	6.2	7.0	9.5	9.6	9.7	9.8	10.1	12.4	13.3	13.6	14.6	12.0
Lane B (N)	11.3	10.1	9.2	7.0	6.6	6.1	7.6	9.5	10.2	9.9	8.8	10.4	11.4	10.4	12.3	14.5	10.2
Device 15																	
Lane A (N)	10.4	9.0	7.7	6.7	6.0	5.0	8.6	10.4	10.5	11.5	10.1	10.6	14.2	15.6	15.0	18.6	16.2
Lane B (N)	10.7	11.2	8.9	7.9	7.7	6.5	11.4	10.9	10.3	10.3	10.5	10.0	13.8	13.0	14.2	15.0	12.0
Device 18																	
Lane A (N)	13.4	11.4	8.7	8.3	6.7	5.9	9.4	10.5	10.6	11.1	9.4	11.4	12.4	13.7	13.6	13.6	13.8
Lane B (N)	10.8	9.2	8.6	7.2	6.6	6.0	8.9	10.3	9.5	12.1	9.0	10.5	13.1	11.9	11.8	14.4	13.3
Device 21																	
Lane A (N)	8.4	8.1	7.5	5.7	6.0	6.3	7.7	10.7	10.1	10.2	9.2	9.2	10.1	12.1	13.0	12.9	13.0
Lane B (N)	9.0	10.1	8.5	7.0	6.1	6.9	10.2	10.6	10.1	11.5	10.5	10.3	12.1	13.4	13.5	17.7	14.2
Device 24																	
Lane A (N)	11.8	8.6	6.9	6.2	6.7	6.3	7.5	8.4	9.0	9.6	9.2	10.0	11.6	12.3	13.5	14.2	11.6
Lane B (N)	10.5	10.2	7.7	6.8	7.0	5.8	8.2	8.7	9.9	10.4	8.0	9.5	12.0	11.4	13.7	15.1	12.9

Table 48 - Lever Force Test Results – Batch R330544 (SERETIDE® 50/250 Control)

R330544	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	15.1	14.4	11.3	10.1	7.0	7.8	8.9	11.1	10.1	8.5	10.4	11.8	8.5	13.5	13.4	14.8	13.9
Lane B (N)	8.4	8.5	7.7	6.2	5.9	6.3	8.7	9.0	9.7	9.7	9.2	9.1	12.3	12.3	13.3	11.2	12.4
Device 6																	
Lane A (N)	10.5	6.7	8.3	6.6	5.9	5.6	8.4	10.3	9.9	9.2	7.4	8.9	10.4	11.9	13.3	11.9	12.7
Lane B (N)	11.7	9.5	8.3	7.4	6.1	6.2	6.4	7.5	7.8	8.6	7.5	8.5	10.4	9.5	9.6	9.3	10.4
Device 9																	
Lane A (N)	10.4	8.5	6.1	4.7	5.3	3.9	7.7	9.6	10.3	9.3	9.2	9.2	12.9	13.3	14.5	13.1	13.7
Lane B (N)	7.6	8.2	6.7	6.6	5.8	5.1	6.9	8.6	8.7	8.9	7.8	8.9	10.4	10.1	11.6	10.2	12.0
Device 12																	
Lane A (N)	14.4	9.9	10.0	9.8	9.1	6.9	8.1	9.6	10.0	10.5	9.0	10.5	10.6	13.8	13.9	12.1	13.9
Lane B (N)	11.7	10.4	9.0	6.7	7.2	5.5	8.3	9.0	8.7	8.8	7.4	8.3	10.2	12.1	13.1	13.1	11.5
Device 15																	
Lane A (N)	11.4	10.7	8.3	6.4	6.3	5.8	7.7	9.0	8.9	9.0	7.3	8.0	11.0	11.1	11.8	11.3	11.3
Lane B (N)	9.0	7.2	8.2	6.4	4.7	4.0	7.6	9.3	8.5	9.9	9.1	8.4	10.0	11.0	11.8	9.9	11.4
Device 18																	
Lane A (N)	13.4	10.3	9.2	7.8	8.2	6.6	8.0	8.8	8.1	7.5	7.5	7.8	10.5	10.7	11.0	10.2	10.8
Lane B (N)	11.8	11.6	9.1	9.0	7.4	6.1	7.2	9.2	8.2	8.6	7.9	8.4	11.7	10.6	12.2	12.0	11.7
Device 21																	
Lane A (N)	14.4	12.2	11.4	9.6	8.1	7.6	8.9	9.3	9.3	9.2	9.2	9.0	12.4	12.6	12.7	12.6	13.0
Lane B (N)	8.2	8.0	8.7	6.3	4.9	6.0	7.4	7.5	8.6	8.8	8.2	7.7	10.1	10.8	11.5	11.9	10.7
Device 24																	
Lane A (N)	13.8	10.7	10.5	8.8	9.2	7.5	7.1	8.9	9.9	10.3	8.1	8.2	11.8	12.5	12.1	12.9	11.9
Lane B (N)	10.4	10.2	8.7	6.8	6.1	5.3	8.4	8.2	8.9	8.8	7.9	7.0	10.2	10.9	12.4	11.8	13.3

Table 49 - Lever Force Test Results – Batch R330534 (SERETIDE® 50/250 Balanced)

R330534	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	14.0	11.2	10.0	7.6	8.3	6.5	8.6	8.6	10.6	10.7	8.7	9.6	14.1	11.8	12.6	13.8	13.7
Lane B (N)	9.0	9.4	7.1	6.8	4.8	5.4	9.6	8.0	9.3	9.9	7.9	9.5	12.6	11.5	13.2	14.1	12.1
Device 6																	
Lane A (N)	10.3	8.9	7.1	7.2	6.6	5.9	8.3	9.1	9.3	9.9	8.6	9.2	11.5	12.0	12.1	13.5	12.0
Lane B (N)	10.5	8.0	6.9	5.6	5.5	5.0	8.9	9.9	9.5	10.3	8.6	9.7	13.0	12.7	14.3	14.1	13.6
Device 9																	
Lane A (N)	14.5	12.3	9.7	8.8	7.5	7.1	9.3	8.2	9.7	10.5	9.1	10.6	12.6	12.3	12.2	11.5	12.5
Lane B (N)	9.8	9.2	7.1	5.9	6.0	5.4	6.9	9.4	8.1	9.5	9.1	9.8	12.9	12.5	13.7	12.3	13.3
Device 12																	
Lane A (N)	10.2	9.1	7.6	6.9	6.3	5.0	9.4	9.2	9.2	9.1	7.6	8.9	10.5	11.5	12.2	11.9	11.9
Lane B (N)	7.5	7.5	6.5	5.2	5.4	5.4	6.9	8.1	8.3	8.5	7.9	9.0	12.4	10.4	12.9	14.4	12.3
Device 15																	
Lane A (N)	14.2	12.4	9.7	8.9	8.3	9.4	9.1	9.6	9.0	8.6	8.4	9.0	11.4	12.1	12.6	12.9	13.4
Lane B (N)	9.5	8.2	8.0	7.1	6.1	5.6	8.5	8.7	9.3	8.6	7.8	9.0	11.2	10.4	12.3	13.3	11.3
Device 18																	
Lane A (N)	12.3	11.0	9.5	7.8	7.1	6.0	6.7	8.9	8.5	9.0	7.1	7.5	11.3	10.7	11.1	11.9	10.3
Lane B (N)	12.9	7.9	8.2	7.0	6.5	5.4	7.8	9.0	10.5	10.1	8.4	9.3	14.2	11.5	13.6	12.7	13.7
Device 21																	
Lane A (N)	12.3	11.0	9.5	7.8	7.1	6.0	6.7	8.9	8.5	9.0	7.1	7.5	11.3	10.7	11.1	11.9	10.3
Lane B (N)	12.9	7.9	8.2	7.0	6.5	5.4	7.8	9.0	10.5	10.1	8.4	9.3	14.2	11.5	13.6	12.7	13.7
Device 24																	
Lane A (N)	14.9	11.7	9.5	8.4	9.2	7.7	8.4	9.3	9.2	8.5	7.3	9.2	11.6	12.0	12.9	10.7	12.1
Lane B (N)	11.6	9.2	7.5	5.9	6.8	5.4	7.9	9.9	8.7	9.7	8.2	8.0	12.2	12.1	14.2	12.5	13.0

Table 50 - Lever Force Test Results – Batch R330529 (SERETIDE® 50/250 Un-balanced)

R330529	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	13.1	9.7	7.9	7.8	8.1	6.8	7.9	9.3	10.0	9.3	9.2	8.8	11.3	11.8	12.3	13.1	13.5
Lane B (N)	11.2	10.2	7.8	5.9	6.0	5.3	10.3	9.1	10.3	10.2	9.7	8.8	14.1	12.3	14.5	15.0	13.8
Device 6																	
Lane A (N)	15.1	12.2	10.9	9.5	9.9	6.6	8.3	8.8	10.9	10.2	9.3	9.6	11.7	10.3	12.4	13.6	12.0
Lane B (N)	10.1	9.4	7.7	6.2	5.6	6.0	8.4	9.2	9.3	9.0	8.2	7.9	10.2	11.4	12.0	14.1	12.0
Device 9																	
Lane A (N)	11.3	10.2	7.5	7.8	8.1	5.6	8.9	10.0	10.9	9.3	9.2	9.4	13.3	12.2	12.7	11.8	13.9
Lane B (N)	10.1	9.4	7.8	7.4	5.9	5.7	9.6	10.3	10.6	11.2	9.1	10.1	12.4	11.8	12.8	13.2	13.2
Device 12																	
Lane A (N)	10.2	8.7	7.1	6.5	5.7	6.6	7.4	9.4	9.8	9.3	8.3	8.4	11.0	11.4	11.5	13.2	12.2
Lane B (N)	13.0	11.8	10.0	7.9	8.5	6.0	9.1	10.1	10.4	10.3	8.3	9.4	11.8	12.7	13.7	14.3	13.7
Device 15																	
Lane A (N)	12.4	9.4	8.8	7.6	7.8	7.1	8.9	9.3	9.7	9.6	8.0	8.9	10.3	12.2	12.5	11.1	13.5
Lane B (N)	9.5	8.9	8.3	6.4	4.6	5.2	7.7	8.6	9.0	9.6	8.1	8.4	10.8	11.7	12.9	11.7	11.9
Device 18																	
Lane A (N)	11.1	9.8	8.7	6.7	6.0	6.1	9.0	10.0	9.1	10.0	8.3	8.9	11.4	11.9	12.6	11.5	12.0
Lane B (N)	9.5	8.4	6.9	5.8	5.6	5.0	8.4	8.8	10.1	9.1	7.7	8.6	11.1	11.7	11.9	12.8	11.8
Device 21																	
Lane A (N)	13.2	11.8	11.1	7.2	7.4	7.4	8.8	8.6	9.6	9.1	8.4	7.8	10.4	12.1	12.9	11.9	13.0
Lane B (N)	8.5	8.6	7.4	6.4	5.9	5.5	8.7	10.0	10.4	10.0	8.8	10.2	12.1	12.1	13.8	13.9	12.9
Device 24																	
Lane A (N)	12.2	13.1	9.7	8.0	7.3	6.9	8.7	8.7	9.2	9.5	8.6	8.3	11.2	11.3	11.0	10.4	11.4
Lane B (N)	9.9	8.7	7.6	6.7	5.7	5.2	7.8	9.5	9.5	9.2	8.7	9.4	11.3	11.9	12.5	13.5	12.4

Table 51 - Lever Force Test Results – Batch R330547 (SERETIDE® 50/500 Control)

R330547	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	11.7	8.6	7.3	5.7	5.3	4.9	7.0	9.3	8.7	9.3	8.7	8.2	10.7	9.8	10.7	11.3	11.3
Lane B (N)	8.4	8.4	8.1	6.4	6.4	5.9	8.0	8.3	8.8	9.1	7.9	7.6	11.0	9.7	11.4	11.5	11.1
Device 6																	
Lane A (N)	12.2	9.4	9.3	7.8	7.7	5.6	7.4	7.2	8.0	7.7	7.7	7.2	9.9	9.6	9.5	9.1	10.3
Lane B (N)	8.6	8.5	8.2	6.2	5.6	5.1	7.3	9.0	9.3	9.7	8.9	8.2	11.0	9.6	11.5	12.1	11.1
Device 9																	
Lane A (N)	11.1	10.3	7.3	5.5	5.6	5.8	7.7	7.5	7.4	8.7	8.1	7.8	8.8	9.6	10.6	11.5	10.0
Lane B (N)	8.3	7.7	7.2	5.6	5.4	5.6	8.0	7.9	8.0	8.8	8.7	8.6	11.9	9.9	11.0	12.4	10.8
Device 12																	
Lane A (N)	7.3	7.6	6.4	5.9	5.2	4.9	5.5	8.2	7.9	8.7	7.7	7.6	9.3	9.3	10.5	11.2	10.3
Lane B (N)	9.4	8.5	7.9	6.5	5.8	5.9	7.4	8.5	8.9	9.0	8.5	8.3	11.6	10.1	11.4	10.2	11.1
Device 15																	
Lane A (N)	10.7	9.6	8.1	7.1	7.2	6.1	7.8	8.7	9.1	8.3	8.3	8.1	11.2	9.9	11.4	12.2	11.8
Lane B (N)	8.7	7.7	7.4	7.1	5.8	5.5	7.3	7.9	9.1	9.4	8.5	7.8	11.4	9.6	11.7	12.8	11.8
Device 18																	
Lane A (N)	11.4	9.0	7.3	6.4	6.8	5.0	7.6	7.7	8.6	8.3	8.1	7.8	10.3	9.7	11.3	12.4	10.3
Lane B (N)	8.7	7.8	7.1	5.9	5.5	5.4	8.4	7.8	8.6	9.3	8.0	8.0	10.5	9.9	11.7	14.0	11.1
Device 21																	
Lane A (N)	14.9	10.6	9.4	9.0	8.4	6.3	7.8	9.3	9.6	10.0	8.7	9.3	11.6	10.4	13.1	12.0	12.6
Lane B (N)	9.0	8.1	7.2	6.0	5.5	5.0	7.5	9.2	9.6	9.3	8.3	8.6	12.1	11.1	12.1	13.4	11.1
Device 24																	
Lane A (N)	8.7	6.6	6.6	5.7	6.1	5.1	7.6	9.2	8.8	8.8	6.5	7.3	10.5	9.5	11.4	11.4	10.4
Lane B (N)	9.2	7.7	6.9	6.4	5.7	4.9	7.4	8.7	8.2	9.0	7.3	7.4	11.4	9.2	10.5	11.1	10.8

Table 52 - Lever Force Test Results – Batch R330564 (SERETIDE® 50/500 Balanced)

R330564	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	9.7	8.6	6.1	5.7	6.5	5.0	7.9	8.0	9.0	9.7	8.6	6.9	10.6	9.7	11.8	12.1	11.5
Lane B (N)	9.9	8.2	6.7	6.2	5.1	5.1	7.6	8.0	8.8	9.1	8.1	8.1	11.7	10.9	11.7	10.0	11.3
Device 6																	
Lane A (N)	11.6	9.4	7.2	6.1	6.2	5.6	7.6	7.9	8.0	7.9	7.7	8.6	10.4	10.5	11.1	10.7	10.6
Lane B (N)	8.5	8.7	6.7	6.1	5.7	5.4	7.4	8.2	8.6	8.5	7.8	8.3	11.7	9.8	11.7	11.2	10.0
Device 9																	
Lane A (N)	8.6	7.1	6.1	5.6	4.7	4.9	7.5	8.0	8.3	8.6	7.8	8.2	9.4	9.7	10.8	13.4	11.0
Lane B (N)	8.3	7.5	6.5	5.9	5.4	5.3	7.5	8.1	8.6	8.4	8.1	8.1	11.7	9.0	10.3	10.3	10.2
Device 12																	
Lane A (N)	12.3	10.9	9.2	8.1	8.1	7.2	8.7	9.6	8.8	8.6	8.0	8.6	11.2	10.4	11.0	13.2	11.1
Lane B (N)	8.5	7.7	7.9	6.0	5.4	5.7	6.7	8.5	8.3	8.9	7.8	8.4	10.7	9.7	10.8	10.6	11.7
Device 15																	
Lane A (N)	13.2	11.5	9.1	7.5	7.4	6.4	7.6	9.4	8.5	7.9	7.8	8.3	8.9	9.7	11.6	12.3	10.9
Lane B (N)	7.2	7.7	7.2	5.4	5.2	5.7	7.3	8.8	8.5	9.1	7.9	8.4	11.4	10.5	11.2	10.0	10.6
Device 18																	
Lane A (N)	11.4	10.3	8.7	7.6	6.8	6.7	7.4	7.2	8.7	8.5	7.8	8.5	10.0	9.7	11.2	12.6	10.2
Lane B (N)	10.7	10.3	7.6	6.9	6.4	5.9	6.8	7.6	8.7	8.7	7.7	7.9	10.7	9.2	10.5	10.1	9.8
Device 21																	
Lane A (N)	10.2	9.2	7.0	5.9	5.7	5.6	7.5	8.2	7.7	8.9	8.2	8.7	10.3	9.2	10.5	12.6	10.8
Lane B (N)	7.0	9.0	7.4	5.8	5.9	5.8	8.1	8.0	9.4	8.1	8.1	8.0	10.7	10.3	11.1	12.1	10.2
Device 24																	
Lane A (N)	8.8	8.8	7.9	5.8	5.6	4.8	7.8	8.8	7.8	8.3	7.2	7.6	9.8	10.0	13.2	13.0	10.2
Lane B (N)	7.7	9.0	8.6	6.4	5.6	5.7	7.1	8.5	9.6	8.4	8.0	8.3	11.0	9.9	12.1	11.5	11.4

Table 53 - Lever Force Test Results – Batch R330563 (SERETIDE® 50/500 Un-balanced)

R330563	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	11.2	8.5	7.5	6.8	6.2	5.3	7.9	8.0	8.4	8.8	8.4	8.3	10.0	10.7	11.1	12.2	11.1
Lane B (N)	8.3	8.2	6.9	5.3	5.7	5.6	7.7	8.5	9.3	8.9	7.4	8.1	10.3	9.9	11.1	12.6	11.2
Device 6																	
Lane A (N)	13.5	11.6	10.6	9.7	7.4	7.7	6.1	8.3	8.5	8.7	7.7	7.8	10.3	9.9	9.9	11.0	11.0
Lane B (N)	13.4	10.5	8.9	8.0	7.5	6.7	7.3	7.9	8.4	8.9	8.7	7.0	10.3	10.1	10.5	10.6	9.9
Device 9																	
Lane A (N)	11.9	9.4	8.4	7.6	6.0	4.7	8.2	8.9	9.8	9.5	8.5	8.6	10.2	9.9	11.3	13.1	13.2
Lane B (N)	7.8	8.5	7.9	6.2	5.2	5.2	7.8	9.0	10.1	9.6	7.1	8.4	10.9	10.5	11.7	13.0	11.8
Device 12																	
Lane A (N)	13.7	9.1	8.1	7.8	6.6	5.8	9.0	8.8	8.7	8.5	8.5	8.1	10.3	10.1	11.4	13.2	11.7
Lane B (N)	8.8	7.8	7.5	6.5	5.9	5.9	7.5	9.1	8.8	8.8	7.9	8.4	10.3	10.5	10.9	12.9	11.6
Device 15																	
Lane A (N)	14.2	11.1	9.6	8.1	6.6	6.5	8.3	9.0	9.1	9.0	8.2	8.0	9.5	8.9	10.7	12.5	12.7
Lane B (N)	10.1	9.2	8.7	7.7	6.7	5.7	7.9	8.4	10.0	10.2	8.1	8.7	11.0	9.2	10.6	12.0	11.4
Device 18																	
Lane A (N)	12.3	11.0	10.0	9.1	8.0	6.4	7.9	9.1	9.2	9.2	8.2	8.8	10.3	9.9	10.9	10.6	11.0
Lane B (N)	8.7	9.1	8.2	6.8	7.5	6.2	7.7	8.4	9.3	9.1	8.9	8.8	11.1	9.3	10.8	13.7	11.1
Device 21																	
Lane A (N)	12.0	10.2	8.6	7.3	6.8	7.0	8.0	8.8	9.3	8.9	8.7	8.4	10.5	10.0	10.6	12.1	10.9
Lane B (N)	7.8	9.6	7.9	5.5	6.0	5.0	6.9	8.3	9.4	10.0	7.4	8.4	10.3	10.0	10.1	11.2	12.5
Device 24																	
Lane A (N)	10.1	9.0	7.4	7.6	6.6	5.9	8.4	8.1	8.9	8.7	7.9	8.1	9.5	9.6	10.9	10.8	11.8
Lane B (N)	8.6	8.5	6.7	5.7	5.9	5.5	8.5	9.1	10.1	9.1	8.7	9.0	11.7	10.0	11.3	13.2	11.2

Table 54 - Lever Force Test Results – Batch R330359 (FLOVENT® 100 Balanced)

R330359	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	8.8	8.4	6.9	6.3	4.7	4.9	8.2	8.3	8.6	9.1	8.0	7.7	10.1	9.5	11.0	13.2	10.4
Lane B (N)	8.0	7.7	6.1	6.7	5.7	5.5	7.7	7.5	8.9	9.0	7.7	8.3	12.5	10.1	10.8	12.2	10.8
Device 6																	
Lane A (N)	10.5	8.9	7.2	6.5	5.2	5.5	8.3	8.7	8.5	9.2	7.6	8.3	11.3	9.4	11.7	12.1	11.1
Lane B (N)	8.7	8.5	7.2	6.1	5.1	5.9	8.2	9.3	8.7	7.7	6.3	8.3	11.0	9.9	11.8	10.7	10.6
Device 9																	
Lane A (N)	14.2	11.0	8.8	7.3	6.4	5.0	8.7	8.9	9.4	8.5	6.7	8.7	11.2	9.9	12.6	11.6	11.3
Lane B (N)	6.7	7.1	6.4	4.6	5.6	5.1	8.1	8.4	8.5	7.9	8.1	7.7	12.6	9.9	10.9	10.5	10.7
Device 12																	
Lane A (N)	11.2	8.9	6.7	6.9	6.4	5.7	7.7	8.1	8.7	9.4	8.2	9.1	9.5	9.9	11.4	11.7	10.2
Lane B (N)	6.9	7.6	5.5	5.2	5.5	5.4	7.8	8.0	8.6	8.7	7.7	7.2	12.9	9.3	10.4	9.7	9.4
Device 15																	
Lane A (N)	9.3	7.6	6.8	4.5	5.6	5.3	8.1	8.7	9.8	8.4	7.7	7.9	10.3	10.1	11.4	11.9	10.7
Lane B (N)	7.9	7.7	6.4	4.2	5.2	5.4	7.2	7.4	8.1	7.7	7.8	8.6	10.5	9.1	10.2	10.0	9.7
Device 18																	
Lane A (N)	8.5	8.1	6.5	5.5	5.2	6.0	7.3	8.6	8.9	9.5	8.3	8.6	9.8	9.8	11.6	12.0	10.5
Lane B (N)	6.6	5.7	5.9	5.2	4.5	5.5	7.4	7.3	9.0	8.3	7.1	8.4	10.2	9.8	11.2	10.4	11.5
Device 21																	
Lane A (N)	12.2	8.5	8.3	7.3	6.4	6.2	8.4	8.2	9.0	8.2	8.2	8.7	10.5	10.9	12.1	13.3	11.4
Lane B (N)	9.9	7.4	7.7	5.6	5.4	5.1	7.9	8.8	10.1	9.2	7.1	9.3	11.0	9.8	11.7	11.3	10.8
Device 24																	
Lane A (N)	11.7	8.8	7.8	8.1	7.1	5.7	7.9	8.5	10.2	9.8	8.5	7.4	10.4	10.7	11.9	12.3	11.6
Lane B (N)	8.6	6.3	7.6	5.6	5.5	5.5	7.6	8.4	9.4	9.0	8.1	8.2	12.5	10.0	12.2	13.9	11.0

Table 55 - Lever Force Test Results – Batch R330520 (FLOVENT® 100 Un-balanced)

R330520	Dose indicator																
Device 3	60	59	58	57	56	55	11	10	9	8	7	6	5	4	3	2	1
Lane A (N)	10.6	9.9	7.2	6.8	5.9	6.1	9.3	10.6	10.0	9.8	8.2	9.4	12.0	11.0	11.5	13.0	12.0
Lane B (N)	8.8	8.5	8.5	6.2	5.5	5.3	9.7	9.0	9.2	9.0	8.2	8.0	10.8	10.5	10.9	13.0	10.5
Device 6																	
Lane A (N)	12.2	10.8	9.4	8.5	8.4	7.1	8.6	9.6	9.4	8.9	8.2	8.0	10.9	10.2	12.3	11.9	11.6
Lane B (N)	8.8	7.6	7.4	6.2	6.2	5.3	9.4	9.3	9.1	9.0	8.5	8.2	11.6	10.7	12.5	12.1	11.7
Device 9																	
Lane A (N)	8.8	8.3	8.1	6.7	6.7	6.0	8.5	9.6	9.9	9.5	8.1	8.9	10.8	11.5	12.3	13.2	12.1
Lane B (N)	9.2	8.8	7.4	5.6	5.8	5.2	9.0	8.5	10.0	8.6	7.7	8.4	10.8	9.3	10.9	9.6	10.7
Device 12																	
Lane A (N)	13.0	10.5	8.8	9.0	7.0	7.0	8.3	9.2	10.1	9.1	8.7	9.3	10.7	10.8	10.7	12.2	11.0
Lane B (N)	8.6	7.6	6.2	6.9	5.5	5.6	8.4	9.4	9.4	10.2	8.9	8.9	11.4	9.8	11.9	11.4	12.1
Device 15																	
Lane A (N)	13.4	10.2	8.3	7.0	6.4	6.1	8.5	9.2	9.2	8.9	8.4	7.8	10.4	9.9	11.5	11.5	10.8
Lane B (N)	8.4	7.4	7.1	6.4	5.3	5.9	9.0	9.1	9.6	9.7	8.3	8.7	11.4	10.8	11.7	13.9	11.2
Device 18																	
Lane A (N)	14.1	11.5	9.4	8.7	8.4	6.2	7.0	9.1	10.1	8.7	8.7	9.5	10.3	10.1	11.5	13.4	10.9
Lane B (N)	8.5	8.5	7.3	6.2	5.8	5.7	7.9	9.0	8.6	9.3	8.8	8.7	9.8	9.6	10.1	11.0	11.1
Device 21																	
Lane A (N)	13.1	10.5	9.6	8.1	7.8	8.2	9.2	9.0	9.5	9.7	9.4	8.8	11.4	9.9	11.7	14.1	11.6
Lane B (N)	8.4	7.6	8.0	6.7	5.7	5.3	7.6	9.2	9.8	10.2	7.9	8.6	10.8	10.3	10.9	11.2	11.4
Device 24																	
Lane A (N)	7.8	7.5	6.2	5.2	5.4	5.9	7.8	8.8	8.9	8.2	8.0	8.2	10.0	9.3	11.8	10.5	11.0
Lane B (N)	6.6	7.3	6.8	5.8	5.0	4.7	7.5	8.6	9.1	9.2	8.7	8.9	10.0	9.9	11.1	10.8	13.2

Summary of Lever Force Results

SERETIDE® 50/100

Tables 45 – 47 show the results of the lever force data for the balanced and unbalanced HSL formulations against the ‘control’ formulation. Neither the ‘unbalanced’ and ‘balanced’ formulation lever force results were shown to be equivalent to the ‘control’ formulation lever force results. Although not equivalent, the practical difference between the ‘balanced’ and ‘unbalanced’ formulations and the current lid foil material is not considered significant.

SERETIDE® 50/250

Tables 48 - 50 show the lever force results. The ‘un-balanced’ and ‘balanced’ HSL formulations are observed to show equivalence to the current ‘control’ formulation batch.

SERETIDE® 50/500

Tables 51 - 53 show the results for the lever force data. Both the ‘un-balanced’ and ‘balanced’ HSL formulations are observed to show equivalence to the current ‘control’ formulation batch.

FLOVENT® 100

Tables 54 – 55 show the results for the lever force data. The ‘un-balanced’ and ‘balanced’ HSL formulations are observed not to be equivalent to the SERETIDE® 50/100 ‘control’ formulation batch. Since no FLOVENT®100 ‘control batch was available, both results are subject to interpretation. This result is likely to be due to the variation in lever force results observed across the three control batches as observed in Table 45, 48, 51 and 52. The only observation that can be made is that the lever force data from the ‘unbalanced’ formulation is slightly higher than the ‘balanced’ formulation.

Surface and Material Characterisation of the new HSL and Quality Advanced 2 Base Laminate

To confirm the new HSL had transferred successfully to the Quality Advanced 2 base laminate, SEM analysis was performed on peeled sealed strip. This was achieved by peeling the lidding and base foil laminates apart and performing the analysis on both the base and lidding foil laminates. The images confirmed that an effective seal was obtained, reference Appendix 7 for SEM images. Further analysis to confirm the molecular identity of both the inside (PVC) and outside (OPA) layers of the new Quality Advanced 2 base laminate was performed using FTIR. A trace was performed comparing against a standard spectrum from the existing base laminate. The results confirmed equivalence to the existing base laminate, reference Appendix 8.

Furthermore, to confirm the melting point of the PVC layer within the new Quality Advanced 2 base laminate had not changed following the modification of the primer and adhesive layers DSC analysis was performed. DSC is an effective technique that is used to study the thermal transitions of polymers, which measures how much heat has to be supplied to a sample material in order to maintain a constant rate of heating between the sample material and the reference. The results confirmed that the melting point of the new PVC layer was 84°C, identical to the current PVC layer, reference Appendix 9.

Summary

The PEL peel strength data supports the choice of the 'un-balanced' formulation over the 'balanced' formulation as this generally shows average peel strength results closer to the 'control' formulation.

In addition, the peel strengths results for both the balanced and un-balanced HSL formulations are consistently observed to be slightly lower than current 'control' formulation. While peel strength can be considered an indicator of seal quality, the current IPC test used in routine production to determine seal quality

is the dye test. No dye test failures were observed during the manufacture of the 11 batches during the filling stage, reference Tables 37 - 40. In addition, higher peel strength would potentially be of more concern as this could lead to increased lever force test failures during device assembly stage.

It can therefore, be concluded that the peel strength and lever force data recorded for the strips containing SERETIDE® and FLOVENT® blends supports the choice of the 'un-balanced' HSL formulation, as this is closest to the peel strength data for the 'control' HSL formulation.

Whilst the lever force test results for both the 'un-balanced' and 'balanced' formulation batches were not shown to be statistically equivalent, they can be shown to have no practical difference to the current 'control' formulation batches. In addition, no lever force IPC failures were observed during the production of the MDPI devices.

The conclusion of this study is that the MDPI lid foil containing the 'un-balanced' HSL manufactured with liquid PMA polymer, using Quality Advanced 2 is suitable as a replacement for the current lid foil containing HSL manufactured with solid PMA polymer, as both the lever force and peel strength data was closer to the control using the existing lidding foil. Furthermore, that no functionality problems on the production line were observed.

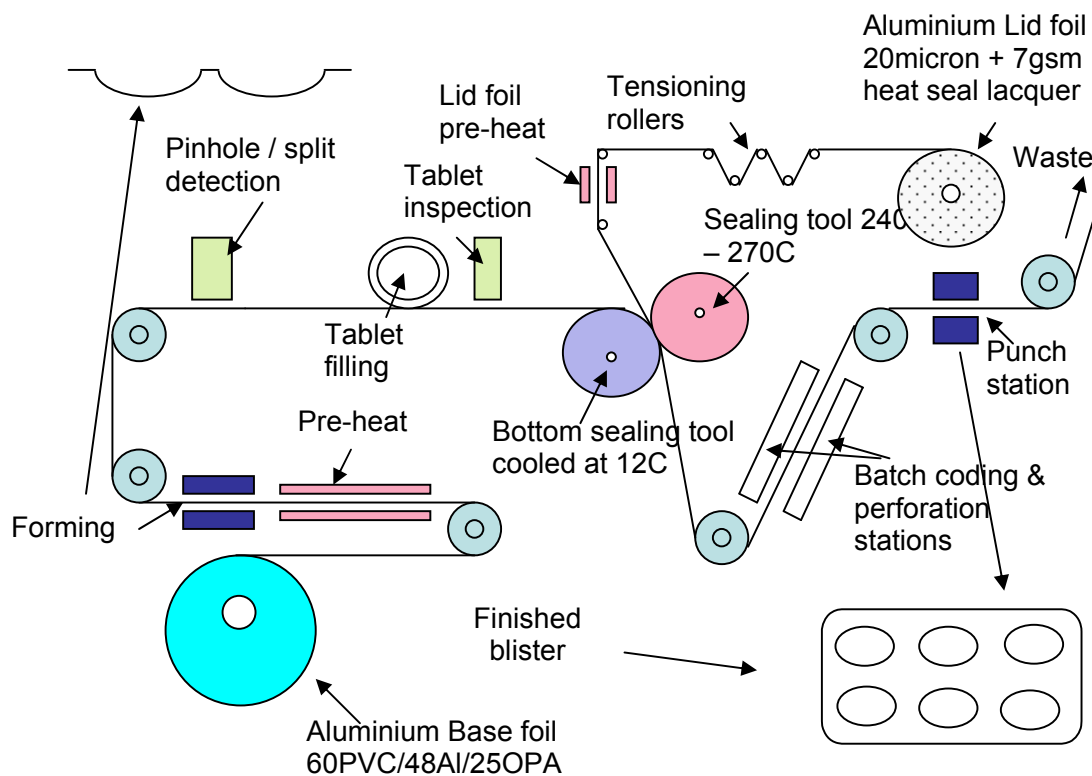
Chapter 4 Section 7

4.7 A study of the influence of Tool Geometry

4.7.1 Introduction

To secure the supply of Zyprexa blisters from Eli Lilly's Basingstoke manufacturing site, a new rotary IMA C80 blister machine was installed, Figure 40 details a typical rotary sealing blister machine.

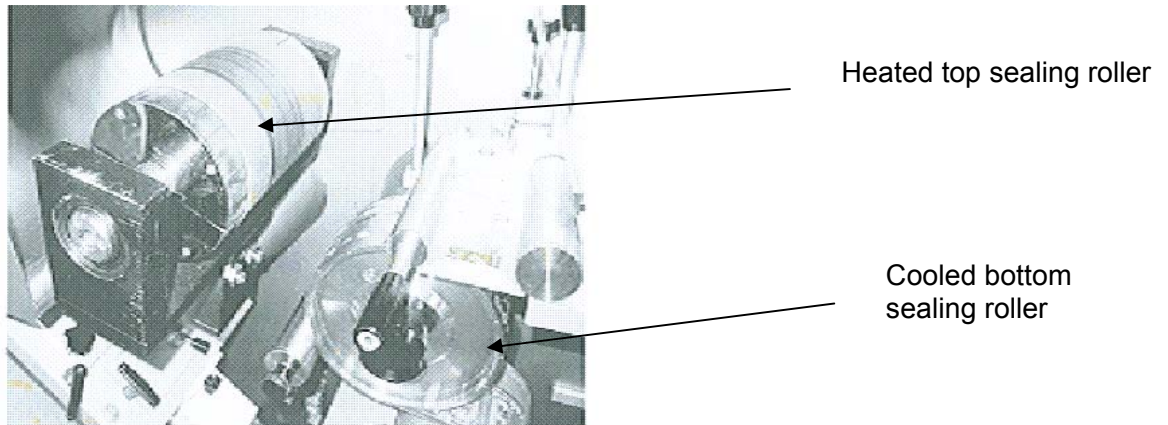
Figure 40 – Rotary Sealing Thermo-former²⁷



As part of the qualification process it was observed that there was ink residue on the top sealing wheel after a period of continuous running. On investigation it was evident that critical patient information was missing from the printed lidding material¹¹⁶. As previously discussed in **Chapter 2**, the rotary sealing process requires high temperatures and pressures to achieve a good quality seal²⁶. This

combination was the cause of the print adherence problems. Figure 41 details the rotary seal arrangement used on Band 24.

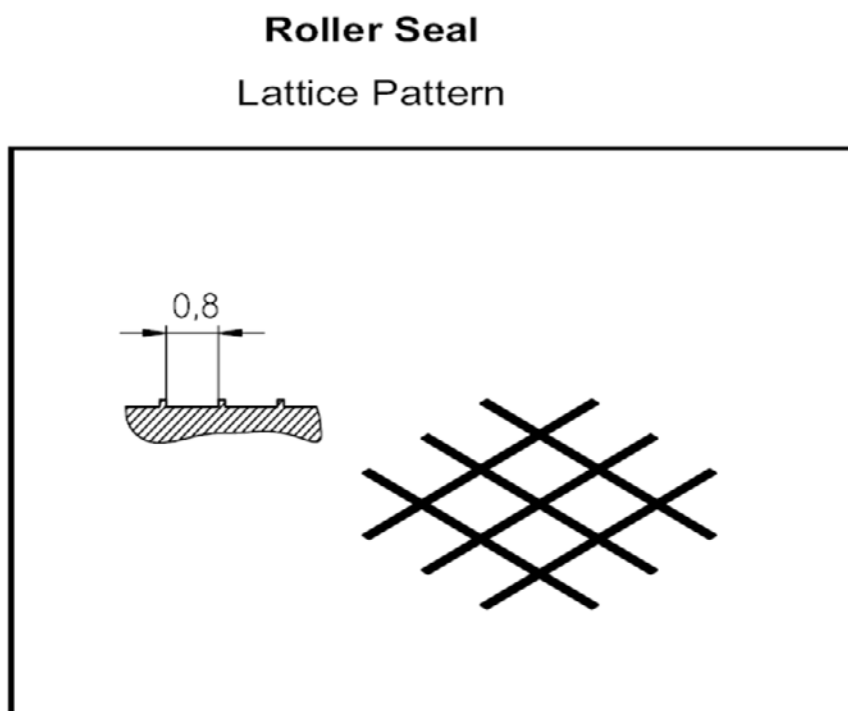
Figure 41 – Rotary Sealing Arrangement



For this reason an investigation was undertaken as part of my research studies to determine the factors influencing the offsetting of critical printed text and recommend a solution to resolve this problem.

The current sealing arrangement utilises a knurled top sealing roller detailed in Figure 42, and a plain bottom drive roller. The top sealing wheel is heated to 270°C, the pressure is 420KN and the line speed is 320 blisters per minute (bpm). Combined with the excessive temperature and pressure to seal the Zyprexa blisters it was causing offsetting of the ink from the lidding foil onto the top sealing roller¹¹⁶.

Figure 42 – Lattice Pattern – used on Band 24



Results of the Study to Assess Alternative Lidding Foils and Sealing Tool Patterns

The purpose of the study was to assess different types of blister lidding foils, un-lacquered, and top coated lacquered, also a foil with a modified ink formulation. The study also assessed various sealing pattern combinations that give the best print quality and seal integrity of finished blister strips. The lidding foils were manufactured by two vendors, Constantia and Alcan Cramlington. Each foil was loaded in turn on the blister machine and critical sealing parameters of temperature, speed and pressure was varied to identify the optimum parameters for print quality and seal integrity. Tables 56 – 61 document the results from the initial production line trials to assess the alternative sealing arrangements^{116,117}.

Table 56 - Experiment 1 – Current Sealing and Drive Roller with Alternative Lidding Foils.

Vendor / Foil	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Constantia / non-lacquered	200	100	420	Print quality acceptable but showing early signs of print fading.
Constantia / non-lacquered	200	250	420	Print quality acceptable but showing early signs of print fading.
Constantia / non-lacquered	240	100	420	Print quality deteriorating.
Constantia / non-lacquered	240	250	420	Print quality deteriorating.
Constantia / non-lacquered	280	100	420	Visual appearance of print very poor – not acceptable.
Constantia / non-lacquered	280	250	420	Visual appearance of print very poor – not acceptable.
Constantia / lacquered	200	100	420	Print quality acceptable but showing early signs of print fading.
Constantia / lacquered	200	250	420	Print quality acceptable but showing early signs of print fading.
Constantia / lacquered	240	100	420	Print quality deteriorating.
Constantia / lacquered	240	250	420	Print quality deteriorating.
Constantia / lacquered	280	100	420	Visual appearance of print very poor – not acceptable.
Constantia / lacquered	280	250	420	Visual appearance of print very poor – not acceptable.
Alcan Cramlington new formulation	200	100	420	Visual appearance of print poor – print easily scratched off from foil surface.
Alcan Cramlington new formulation	200	250	420	Visual appearance of print poor – print easily scratched off from foil
Alcan Cramlington new formulation	240	100	420	Visual appearance of print poor – print easily scratched off from foil
Alcan Cramlington new formulation	240	250	420	Visual appearance of print poor – print easily scratched off from foil
Alcan Cramlington new formulation	280	100	420	Visual appearance of print poor – print easily scratched off from foil
Alcan Cramlington new formulation	280	250	420	Visual appearance of print poor – print easily scratched off from foil
Results and conclusions				
– None of the foils performed better than the current foil from Alcan Cramlington.				
– No significant difference between lacquered and un-lacquered foil.				

**Table 57 - Experiment 2 – Current Sealing and new Crimped Drive Rollers
with Alternative Lidding Foils.**

Vendor / Foil	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Alcan Cramlington / non-lacquered	240	100	420	Improvement in visual appearance of print, but not to standard of platen sealing. Quality the same as with lacquered foil.
Alcan Cramlington / non-lacquered	240	320	420	Improvement in visual appearance of print, but not to standard of platen sealing. Quality the same as with lacquered foil.
Alcan Cramlington / non-lacquered	270	100	420	Poor print quality at higher temperatures. Quality the same as with lacquered foil.
Alcan Cramlington / non-lacquered	270	320	420	Poor print quality at higher temperatures. Quality the same as with lacquered foil.
Alcan Cramlington / lacquered	240	100	420	Improvement in visual appearance of print, but not to standard of platen sealing.
Alcan Cramlington / lacquered	240	320	420	Improvement in visual appearance of print, but not to standard of platen sealing.
Alcan Cramlington / lacquered	270	100	420	Poor print quality at higher temperatures.
Alcan Cramlington / lacquered	270	320	420	Poor print quality at higher temperatures.
Constantia / non-lacquered	240	100	420	Improvement in visual appearance of print, but not to standard of platen sealing. Quality the same as with lacquered foil.
Constantia / non-lacquered	240	320	420	Improvement in visual appearance of print, but not to standard of platen sealing. Quality the same as with lacquered foil.
Constantia / non-lacquered	270	100	420	Poor print quality at higher temperatures. Quality the same as with lacquered foil.
Constantia / non-lacquered	270	320	420	Poor print quality at higher temperatures. Quality the same as with lacquered foil.
Constantia / lacquered	240	100	420	Improvement in visual appearance of print, but not to standard of platen sealing.
Constantia / lacquered	240	320	420	Improvement in visual appearance of print, but not to standard of platen sealing.
Constantia / lacquered	270	100	420	Poor print quality at higher temperatures.
Constantia / lacquered	270	320	420	Poor print quality at higher temperatures.

Table 57 Continued - Experiment 2 – Current Sealing Roller and new Crimped Drive Rollers with Alternative Lidding Foils.

Vendor / Foil	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Alcan Cramlington / new ink / lacquer	240	100	420	Visual appearance of print poor – print easily scratched off from foil surface.
Alcan Cramlington / new ink / lacquer	240	320	420	Visual appearance of print poor – print easily scratched off from foil surface.
Alcan Cramlington / new ink / lacquer	270	100	420	Visual appearance of print poor – print easily scratched off from foil surface.
Alcan Cramlington / new ink / lacquer	270	320	420	Visual appearance of print poor – print easily scratched off from foil surface.
Results and Conclusions: <ul style="list-style-type: none"> - No visual improvements observed using lacquered foils. - Marginal print quality improvement observed at 240°C, but deteriorates at 270°C. - Alcan standard foil gives best performance. - Blister seal strength very good – will be tested at Mont-Saint Guibert (MSG). 				

Table 58 - Experiment 3 – Crimped Sealing Roller and Crimped Drive Roller with Constantia non-Lacquered Lidding Foil.

Vendor / Foil	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Constantia / non-lacquered	240	100	420	Slight visual improvement to print quality. Leakers found during leak test – crimp pattern piercing foil around the circumference of the blister pocket.
Constantia / non-lacquered	240	150	420	Slight visual improvement to print quality. Leakers found during leak test – crimp pattern piercing foil around the circumference of the blister pocket.
Constantia / non-lacquered	240	320	300	Slight visual improvement to print quality. Weak seal resulting in leakers.
Constantia / non-lacquered	255	100	300	Slight visual improvement to print quality. All blisters (12) passed leak test.
Constantia / non-lacquered	255	320	300	Slight visual improvement to print quality. Two blisters from 12 tested failed the leak test. Leakers were on outside pockets of blister strips, which corresponded to areas of incomplete crimp pattern on new sealing roller.
Constantia / non-lacquered	270	100	300	Slight visual improvement to print quality. One blisters from 12 tested failed the leak test. Leakers were on outside pockets of blister strips, which corresponded to areas of incomplete crimp pattern on new sealing roller.
Constantia / non-lacquered	270	320	300	Slight visual improvement to print quality. All blisters (12) passed the leak test.
Results and Conclusions: <ul style="list-style-type: none"> - Crimp from this sealing combination is too aggressive at 420KN pressure . - Crimp pattern on sealing roller was not fully formed. This was the probable cause of the leaking blisters on tests 5 & 6. - Slight visual improvement to print quality at lower sealing temperatures, however deterioration was observed as temperature increased. - Test only carried out on Constantia non-lacquered lidding foil. 				

**Table 59 - Experiment 4 – New Crimped Sealing Roller and Current (Plain)
Drive Roller with Constantia non-Lacquered Lidding Foil.**

Vendor / Foil	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Constantia / non-lacquered	240	100	420	Slight visual improvement to print quality. Leakers found during leak test – crimp pattern piercing foil around the circumference of the blister pocket. All 12 blisters leaked.
Constantia / non-lacquered	240	150	420	Slight visual improvement to print quality. All blisters (12) passed the leak test.
Constantia / non-lacquered	240	320	300	Slight visual improvement to print quality. All blisters (12) failed the leak test – weak seal.
Constantia / non-lacquered	255	100	300	Print quality deteriorating. All blisters (12) passed the leak test.
Constantia / non-lacquered	255	320	300	Print quality deteriorating. Majority of blisters tested (12) failed leak test – weak seal.
Constantia / non-lacquered	270	100	300	Print quality deteriorating. All blisters (12) passed the leak test.
Constantia / non-lacquered	270	320	300	Print quality deteriorating. All blisters (12) passed the leak test.
Results and Conclusions: <ul style="list-style-type: none"> - Crimp from this sealing combination is too aggressive at 420KN pressure . - Weak seal when sealing pressure is dropped to 300Kn. - Print quality deteriorates as sealing temperature is increased. - Tests were focused on seal integrity – only Constantia non-lacquered lidding foils were used. 				

Table 60 - Experiment 5 – New Plain Sealing Roller and new Crimped Drive Roller with Alcan non-Lacquered Lidding Foil.

Vendor / Foil	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Alcan Cramlington / non-lacquered	220	200	300	Print quality good – no break up. All blisters (12) passed leak test. 50 empty blisters sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	220	320	300	Print quality good – no break up. All blisters (12) passed leak test. 50 empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	220	200	400	Print quality good – no break up. All blisters (12) passed leak test. 50 empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	220	320	400	Print quality good – no break up. All blisters (12) passed leak test. 50 empty blisters sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	240	200	300	Print quality good – no break up. All blisters (12) passed leak test. 50 empty blisters sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	240	320	300	Print quality good – no break up. All blisters (12) passed leak test. 50 empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	240	200	400	Print quality good – no break up. All blisters (12) passed leak test. 50 empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	240	320	400	Print quality good – no break up. All blisters (12) passed leak test. 50 empty blisters sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	270	200	300	Print quality good – no break up. All blisters (12) passed leak test. 50 empty blisters sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	270	320	300	Print quality good – no break up. All blisters (12) passed leak test. 50 empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.

Table 60 Continued - Experiment 5 – New Plain Sealing Roller and New Crimped Drive Roller with Alcan Non-Lacquered Lidding Foil.

Vendor / Foil	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Alcan Cramlington / non-lacquered	270	200	400	Print quality good – no break up. All blisters (12) passed leak test. 50 empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	270	320	400	Print quality good – no break up. All blisters (12) passed leak test. 50 empty blisters sent to MSG for seal strength testing.
Results and Conclusions: <ul style="list-style-type: none"> - Print quality good at all temperatures / operational settings. Best quality observed at lower sealing temperatures. - Slight creasing of lidding foil observed around embossing area – cosmetic only. Can be eradicated by slitting lidding foil. - Sealing tool combination gave best print quality of finished blister. - Samples sent to MSG, Global Packaging and Technical Development (GPTD) group for seal integrity and WVTR testing. 				

Table 61 - Experiment 6 – Current Sealing Roller and new Crimped Drive Roller with Alcan non-Lacquered Lidding Foil.

Vendor / Foil	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Alcan Cramlington / non-lacquered	220	200	300	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty samples sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	220	320	300	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	220	200	400	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	220	320	400	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty samples sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	240	200	300	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty samples sent to MSG for seal strength testing.
Alcan Cramlington / non-lacquered	240	320	300	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.
Alcan Cramlington / non-lacquered	240	200	400	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty + 10 desiccant filled blisters sent to MSG for seal strength and MVTR testing.

Table 61 - Experiment 6 – Continued - Current Sealing Roller and new Crimped Drive Roller with Alcan non-Lacquered Lidding Foil.

Vendor / Foil	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Results / Comments
Alcan Cramlington / non-lacquered	240	320	400	Improvement in visual appearance – minimal break up. All blisters (12) passed leak test. 50 Empty samples sent to MSG for seal strength testing.
Observations: <ul style="list-style-type: none"> - Extension of experiment 2. Focusing on Alcan foil running at various temperature, speed and pressure settings. Note: Trials at 270°C carried out in experiment 2. - Seal appears strong, no leakers. - Print quality not as good as new plain sealing roller & new crimped drive roller (experiment 5), but seen as best alternative if plain top seal is not acceptable to the market. - Samples sent to MSG (GPTD) for seal integrity and WVTR testing. 				

Results Summary of the Sealing Trials using Combinations of Sealing Tool Arrangements and Alternative Lidding Foils

The results indicated that there was no improvement in print quality observed with any of the trial foils.

- The foils with heat-seal protective lacquer performed no better than foils without lacquer.
- Alcan foil with new ink / lacquer formulation gave the poorest print quality, and was easy to scratch off ink.
- Alcan non-lacquered (standard production foil) performed best.
- The plain top sealing roller / new crimped drive roller combination produced blisters with highest print quality, because the knurled sealing pattern that inherently can remove the printing surface was etched onto the bottom drive roller on the base foil side of the blister.
- The crimped sealing roller / new crimped drive roller combination produced a very good seal due to the alignment of the knurling patterns. However, due to the aggressive nature of this double crimp pattern the foil was being pierced around the circumference of the pocket.

1. Assuming positive test results it is recommended that the plain seal / new crimp drive roller combination is implemented.
2. Based on trial results continue to use the standard Alcan non-lacquered lidding foil.

Following the results from the tooling trials the blisters produced with the plain sealing roller and new crimped drive roller, reference experiment 5, Table 60, and current sealing roller and new crimped drive roller, reference experiment 2, Table 57, were sent to the GPTD, MSG for seal strength and WVTR testing.

GPTD (MSG) Qualification of new Sealing Tools on the IMA C80 Blister Sealing Machine

The objective of the current study is to investigate the new tooling arrangements on the IMA C80 blister sealing machine (Band 24). This was achieved by performing MVTR, burst pressure, and seal strength tests on blisters produced on Band 24 during the initial tooling combination trials^{116,117} documented in Tables 56 – 61. Furthermore, to compare these results against previous studies on blisters produced using platen sealing.

Blister Sealing Combinations and Test Criteria:

1. Current sealing roller and new crimped drive roller with Alcan Cramlington none lacquered foil.
2. New plain sealing roller and new crimped drive roller with Alcan Cramlington non-lacquered foil.

The blisters were produced from the initial tooling trials^{116,117} documented in Tables 56 – 61, the number of samples supplied to MSG for testing and the parameters that they were produced are detailed in Table 62. The tests were performed at MSG according to Table 63, and the equipment used is detailed in Table 64.

Materials

All blisters supplied to MSG for qualification have been produced using coldform base laminate and 20µm hard tempered non-lacquered lidding foil manufactured by Alcan Cramlington, see Figure 43.

Figure 43 – Double Foil (Formpack) Blister²⁴

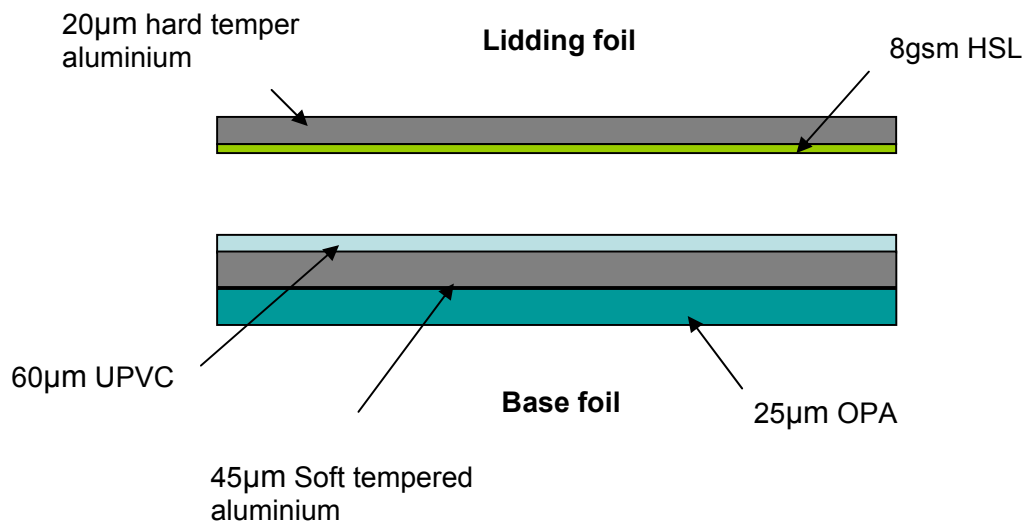


Table 62 - Blister Sealing Combinations and Sample Details

Exp	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Number of blisters supplied to MSG
1	Current sealing roller & new crimped drive roller.	220	200	300	50 Empty samples for seal strength testing.
2	Current sealing roller & new crimped drive roller.	220	320	300	50 Empty + 10 desiccant filled blisters for seal strength and MVTR testing.
3	Current sealing roller & new crimped drive roller.	220	200	400	50 Empty + 10 desiccant filled blisters for seal strength and MVTR testing.
4	Current sealing roller & new crimped drive roller.	220	320	400	50 Empty samples for seal strength testing.
5	Current sealing roller & new crimped drive roller.	240	200	300	50 Empty samples for seal strength testing.
6	Current sealing roller & new crimped drive roller.	240	320	300	50 Empty + 10 desiccant filled blisters for seal strength and MVTR testing.
7	Current sealing roller & new crimped drive roller.	240	200	400	50 Empty + 10 desiccant filled blisters for seal strength and MVTR testing.
8	Current sealing roller & new crimped drive roller.	240	320	400	50 Empty samples for seal strength testing.
9	New plain sealing roller & new crimped drive roller.	220	200	300	50 Empty samples for seal strength testing.
10	New plain sealing roller & new crimped drive roller.	220	320	300	50 Empty + 10 desiccant filled blisters for seal strength and MVTR
11	New plain sealing roller & new crimped drive roller.	220	200	400	50 Empty + 10 desiccant filled blisters for seal strength and MVTR
12	New plain sealing roller & new crimped drive roller.	220	320	400	50 Empty samples for seal strength testing.

Table 62 Continued - Blister Sealing Combinations and Sample Details

Exp	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Number of blisters supplied to MSG
13	New plain sealing roller & new crimped drive roller.	240	200	300	50 Empty samples for seal strength testing.
14	New plain sealing roller & new crimped drive roller.	240	320	300	50 Empty + 10 desiccant filled blisters for seal strength and MVTR.
15	New plain sealing roller & new crimped drive roller.	240	200	400	50 Empty + 10 desiccant filled blisters for seal strength and MVTR.
16	New plain sealing roller & new crimped drive roller.	240	320	400	50 Empty samples for seal strength testing.
17	New plain sealing roller & new crimped drive roller.	270	200	300	50 Empty samples for seal strength testing.
18	New plain sealing roller & new crimped drive roller.	270	320	300	50 Empty + 10 desiccant filled blisters for seal strength and MVTR.
19	New plain sealing roller & new crimped drive roller.	270	200	400	50 Empty + 10 desiccant filled blisters for seal strength and MVTR.
20	New plain sealing roller & new crimped drive roller.	270	320	400	50 Empty samples for seal strength testing.
21	Platen sealing blister tooling.	180	306	n/a	Blisters previously tested at GPTD, results will be used for comparison to rotary sealing.
22	Platen sealing blister tooling.	180	306	n/a	Blisters previously tested at GPTD, results will be used for comparison to rotary sealing.
23	Platen sealing blister tooling.	180	72	n/a	Blisters previously tested at GPTD, results will be used for comparison to rotary sealing.
24	Platen sealing blister tooling.	180	72	n/a	Blisters previously tested at GPTD, results will be used for comparison to rotary sealing.

Table 63 - Test Plan

To evaluate the blisters produced using the new sealing arrangement the following tests were performed detailed in Table 63.

Test	Experiments	Number of samples to be tested
Water Vapour Transmission Rate (mg/cavity/day)	2,3,6,7,10,11,14,15,18 19	10
Burst Strength (N/cm)	1,2,3,4,5,6,7,8,9,10,11,12,13, 14,15,16,17,18,19,20	10
Seal Strength (N/cm)	1,2,3,4,5,6,7,8,9,10,11,12,13, 14,15,16,17,18,19,20	10
Methylene Blue Dye blister leak test (Pass/Fail)	1,2,3,4,5,6,7,8,9,10,11,12,13, 14,15,16,17,18,19,20	10

Table 64 - Equipment

The equipment used to perform the tests in Table 63 are detailed in Table 64.

Equipment
Balance AT460
Environmental chamber (40°C/75%RH)
Lippke Skye 1520 SL burst tester
Zwick tensile equipment
Vacuum dry chamber

Test description**Water Vapour Transmission Rate**

The purpose of this test was to evaluate the moisture protection of the sealed blisters by weight gain. The test was performed using ICH 40°C/75%RH condition. Ten blisters were filled with desiccant pellets (test samples) and

another 10 are sealed empty (reference samples). All the blisters were weighed at 0, 1, 7, 14 and 38 days. The initial weights (day 0) were measured after three days pre-conditioning in the environmental chamber. Only 14 and 38 days results are reported.

Burst Pressure

The purpose of this test was to evaluate the sealing quality between the aluminium lidding foil and the base laminate, by increasing the internal pressure of the cavity and measuring the pressure when it bursts. The lidding foil was slightly punctured with a needle so that it was possible to inflate the cavity. The leak tightness between the cavity and the equipment was realised with a rubber spectrum. The individual values were above the minimum burst pressure of 800mbar, which assured an excellent seal between the lidding foil and base laminate.

Test conditions were as followed:

- Three blisters per experiment.
- Four randomly chosen cavities per blister were evaluated.
- Pressure speed increase 1000 Pa/sec.
- Results expressed in bar.

Seal Strength

The purpose of this test was to evaluate the seal strength between the aluminium lidding foil and the base laminate, and to qualify the force required to peel both materials apart. These values are an excellent measure for determining the quality of the sealing process. The test is realised on 10mm wide strips that were cut in the centre of a blister cavity in the longitudinal direction, randomly chosen on a blister card. Ten cavities per experiment were tested. At one end the aluminium lidding foil, and at the other end the base

laminate, were fixed in the jaws of the tensile equipment, which pulled it at a constant speed of 12.5mm/min.

Methylene Blue Dye Test

The purpose of this test was to evaluate the seal integrity of the blister cavity. Ten blisters per experiment were placed in a methylene blue dye solution for one minute at 10 inch of Hg (absolute pressure). The release of the vacuum to atmosphere pressure was done in one minute. Each cavity of each blister was opened and visually inspected for methylene blue dye ingress in the cavity.

Results and Discussions

Table 65 – WVTR - (Rotary Sealing)

Experiment	Seal arrangement combination	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	WVTR (mg/cavity/day)
2	Current sealing roller & new crimped drive roller.	220	320	300	0.002
3	Current sealing roller & new crimped drive roller.	220	200	400	0.002
6	Current sealing roller & new crimped drive roller.	240	320	300	0.002
7	Current sealing roller & new crimped drive roller.	240	200	400	0.002
10	New plain sealing roller & new crimped drive roller.	220	320	300	0.002
11	New plain sealing roller & new crimped drive roller.	220	200	400	0.002
14	New plain sealing roller & new crimped drive roller.	240	320	300	0.004
15	New plain sealing roller & new crimped drive roller.	240	200	400	0.002
18	New plain sealing roller & new crimped drive roller.	270	320	300	0.004
19	New plain sealing roller & new crimped drive roller.	270	200	400	0.004

Table 66 – WVTR - (Platen Sealing)

Experiment	Seal arrangement combination	Sealing Temperature (°C)	Line Speed (bpm)	Sealing Pressure (KN)	WVTR (mg/cavity/day)
21	Platen sealing blister tooling.	180	304	n/a	0.003
22	Platen sealing blister tooling.	180	304	n/a	0.006
23	Platen sealing blister tooling.	180	72	n/a	0.007
24	Platen sealing blister tooling.	180	72	n/a	0.004

Observations

WVTR results on IMA rotary sealed blisters were equivalent or better than results obtained from platen sealed blisters tested using cold form base laminate and 20µm hard tempered lidding foil.

Table 67 – Burst Pressure - (Rotary Sealing)

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Burst Pressure (bar)
1	Current sealing roller & new crimped drive roller.	220	200	300	0.9
2	Current sealing roller & new crimped drive roller.	220	320	300	0.9
3	Current sealing roller & new crimped drive roller.	220	200	400	0.9
4	Current sealing roller & new crimped drive roller.	220	320	400	1.0
5	Current sealing roller & new crimped drive roller.	240	200	300	1.1
6	Current sealing roller & new crimped drive roller.	240	320	300	1.1
7	Current sealing roller & new crimped drive roller.	240	200	400	1.1
8	Current sealing roller & new crimped drive roller.	240	320	400	1.1
9	New plain sealing roller & new crimped drive roller.	220	200	300	0.9
10	New plain sealing roller & new crimped drive roller.	220	320	300	0.9
11	New plain sealing roller & new crimped drive roller.	220	200	400	1.0
12	New plain sealing roller & new crimped drive roller.	220	320	400	1.0

Table 67 – Continued - Burst Pressure - (Rotary Sealing)

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Burst Pressure (bar)
13	New plain sealing roller & new crimped drive roller.	240	200	300	1.0
14	New plain sealing roller & new crimped drive roller.	240	320	300	1.1
15	New plain sealing roller & new crimped drive roller.	240	200	400	1.0
16	New plain sealing roller & new crimped drive roller.	240	320	400	1.1
17	New plain sealing roller & new crimped drive roller.	270	200	300	1.3
18	New plain sealing roller & new crimped drive roller.	270	320	300	1.4
19	New plain sealing roller & new crimped drive roller.	270	200	400	1.3
20	New plain sealing roller & new crimped drive roller.	270	320	400	1.4

Table 68 Burst Pressure (Platen Sealing)

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Burst Pressure (bar)
21	Platen sealing blister tooling.	180	306	n/a	1.4
22	Platen sealing blister tooling.	180	306	n/a	1.4
23	Platen sealing blister tooling.	180	72	n/a	1.7
24	Platen sealing blister tooling.	180	72	n/a	1.8

Observations from Burst Tests

The results obtained from Tables 67 - 68 show good sealing quality with average burst pressure above 1×10^5 Pa and all individual results above 8×10^4 Pa. Blisters obtained at a sealing temperature of 220°C show slightly lower results, therefore, it is recommended to work at a higher temperature using rotary sealing. The results also showed that platen sealing gives a higher burst resistance to rotary sealing.

Table 69 – Seal Strength - (Rotary Sealing)

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Seal Strength \pm STD Deviation (N/cm)
1	Current sealing roller & new crimped drive roller.	220	200	300	5.8 ± 0.4
2	Current sealing roller & new crimped drive roller.	220	320	300	5.7 ± 0.3
3	Current sealing roller & new crimped drive roller.	220	200	400	5.8 ± 0.3
4	Current sealing roller & new crimped drive roller.	220	320	400	5.7 ± 0.4
5	Current sealing roller & new crimped drive roller.	240	200	300	6.0 ± 0.5
6	Current sealing roller & new crimped drive roller.	240	320	300	6.4 ± 0.4
7	Current sealing roller & new crimped drive roller.	240	200	400	6.0 ± 0.5
8	Current sealing roller & new crimped drive roller.	240	320	400	6.4 ± 0.4
9	New plain sealing roller & new crimped drive roller.	220	200	300	5.8 ± 0.4
10	New plain sealing roller & new crimped drive roller.	220	320	300	5.7 ± 0.4
11	New plain sealing roller & new crimped drive roller.	220	200	400	5.8 ± 0.4
12	New plain sealing roller & new crimped drive roller.	220	320	400	5.7 ± 0.4

Table 69 – Continued - Seal Strength - (Rotary Sealing)

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Seal Strength ± STD Deviation (N/cm)
13	New plain sealing roller & new crimped drive roller.	240	200	300	6.0 ± 0.5
14	New plain sealing roller & new crimped drive roller.	240	320	300	6.4 ± 0.4
15	New plain sealing roller & new crimped drive roller.	240	200	400	6.0 ± 0.5
16	New plain sealing roller & new crimped drive roller.	240	320	400	6.4 ± 0.3
17	New plain sealing roller & new crimped drive roller.	270	200	300	6.3 ± 0.3
18	New plain sealing roller & new crimped drive roller.	270	320	300	6.4 ± 0.4
19	New plain sealing roller & new crimped drive roller.	270	200	400	6.3 ± 0.3
20	New plain sealing roller & new crimped drive roller.	270	320	400	6.4 ± 0.3

Table 70 - Seal Strength - (Platen Sealing)

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Seal Strength ± STD Deviation (N/cm)
21	Platen sealing blister tooling.	180	306	n/a	7.3 ± 0.4
22	Platen sealing blister tooling.	180	306	n/a	7.4 ± 0.5
23	Platen sealing blister tooling.	180	72	n/a	8.0 ± 0.5
24	Platen sealing blister tooling.	180	72	n/a	7.9 ± 0.4

Observations from the Seal Strength Testing

It was observed that blisters produced on Band 24 using the new sealing arrangements show seal strength values that can be considered as acceptable even if they are lower than the typical ≥ 6 N/cm. These lower values are due to

the rotary sealing used on Band 24 vs the >7N/cm reference value measured on blisters from platen sealing^{118,119}.

It can also be observed that for blisters sealed at 220, 240 and 260°C, the seal strength results obtained by cutting the samples in the longitudinal direction are lower than in the lateral direction. This is due to the reduced distance between the cavities.

Table 71 – Methylene Blue Dye Testing

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Leaking cavities
1	Current sealing roller & new crimped drive roller.	220	200	300	0
2	Current sealing roller & new crimped drive roller.	220	320	300	0
3	Current sealing roller & new crimped drive roller.	220	200	400	0
4	Current sealing roller & new crimped drive roller.	220	320	400	0
5	Current sealing roller & new crimped drive roller.	240	200	300	0
6	Current sealing roller & new crimped drive roller.	240	320	300	0
7	Current sealing roller & new crimped drive roller.	240	200	400	0
8	Current sealing roller & new crimped drive roller.	240	320	400	0
9	New plain sealing roller & new crimped drive roller.	220	200	300	0
10	New plain sealing roller & new crimped drive roller.	220	320	300	0
11	New plain sealing roller & new crimped drive roller.	220	200	400	0
12	New plain sealing roller & new crimped drive roller.	220	320	400	0

Table 71 – Continued – Methylene blue dye Testing

Experiment	Seal arrangement combination	Sealing Temp (°C)	Line Speed (bpm)	Sealing Pressure (KN)	Seal Strength ± STD Deviation (N/cm)
13	New plain sealing roller & new crimped drive roller.	240	200	300	0
14	New plain sealing roller & new crimped drive roller.	240	320	300	0
15	New plain sealing roller & new crimped drive roller.	240	200	400	0
16	New plain sealing roller & new crimped drive roller.	240	320	400	0
17	New plain sealing roller & new crimped drive roller.	270	200	300	0
18	New plain sealing roller & new crimped drive roller.	270	320	300	0
19	New plain sealing roller & new crimped drive roller.	270	200	400	0
20	New plain sealing roller & new crimped drive roller.	270	320	400	1

Observations from the Methylene Blue Dye Testing

The only leaking cavity was due to a pinhole in the lidding foil, and not attributed by the sealing process.

4.7.2 Conclusions and Recommendations from Study

It can be concluded from the rotary sealing study that the blisters produced using the new plain top seal roller with the crimped drive roller gave the best performance in terms of seal integrity and peel force. Furthermore, that the blisters produced using the platen sealing process gave a higher seal strength and the tightest seal in terms of moisture protection compared to rotary sealing. However, the rotary sealing process still gives adequate moisture protection and a seal strength of 6N/mm.

The recommendation therefore, is to change to the plain top seal roller and the crimped drive roller using standard non-lacquered lidding foil.

Furthermore, it can be deduced from the results that a sealing temperature target of $280 \pm 10^{\circ}\text{C}$ could be recommended to maintain a good seal.

Therefore, the best production conditions are:

- Sealing pressure – 420KN
- Sealing temperature - $280 \pm 10^{\circ}\text{C}$
- Production speed – 250bpm

Chapter 4 Section 8

4.8 A Study of Polymer Film Layer Thickness

4.8.1 Introduction

The current Aclar base laminate used at Brecon Pharmaceuticals to produce Japanese Zyprexa and JP Evista blisters is sourced from Techni-Flex. The material construction for Zyprexa consists of three layers, 191 μ m UPVC/51 μ m PE/51 μ m PCTFE. The material construction for Evista consists of 3 layers, 191 μ m UPVC/51 μ m PE/15 μ m PCTFE. Figures 44-45 detail the material construction.

Figure 44 – Material Construction (Japanese Zyprexa)

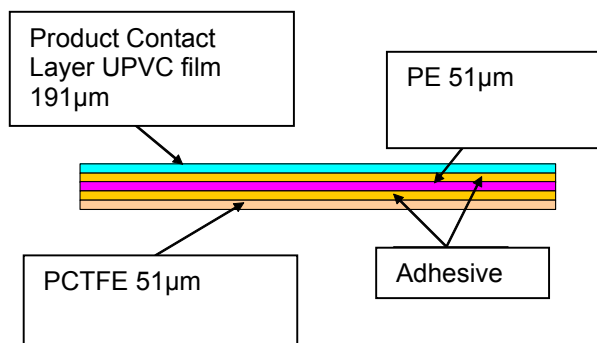
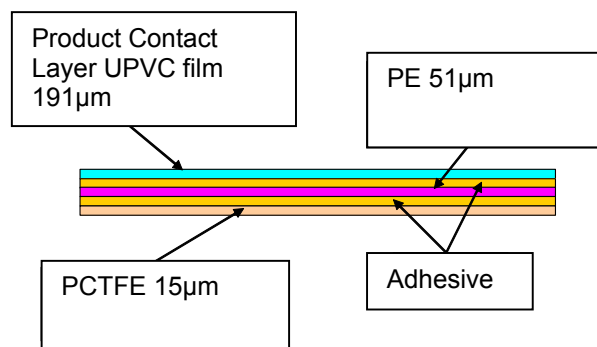


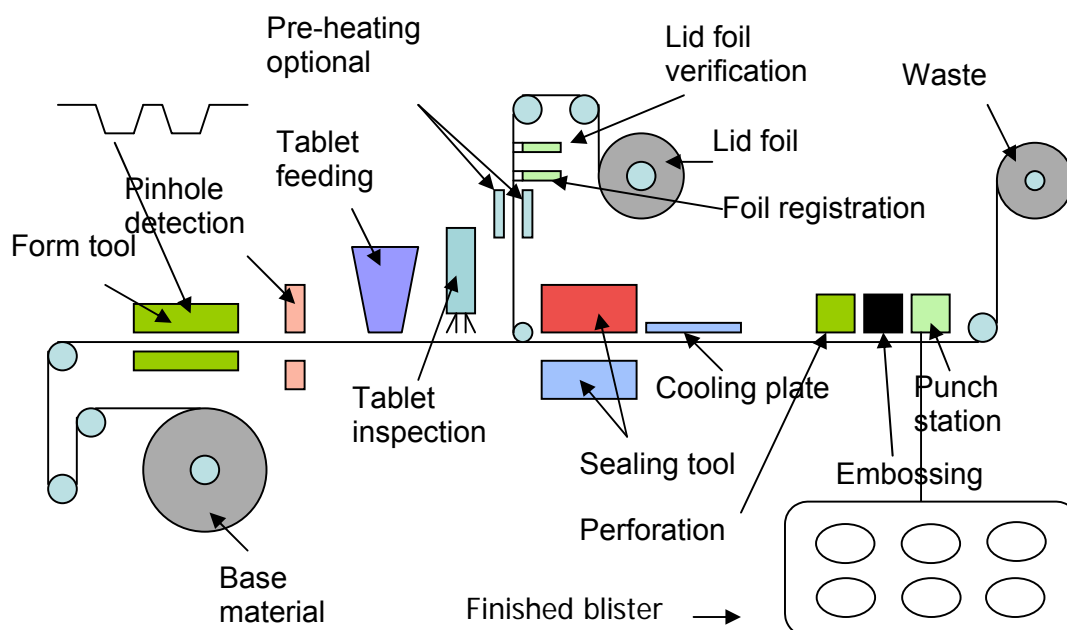
Figure 45 – Material Construction (Japanese Evista)



A new alternative blister base laminate to Aclar with identical material construction but with a different source of PCTFE laminate, trade name Vaposhield has been recommended for routine production use. Aclar PCTFE is currently manufactured by Honeywell. Vaposhield will be manufactured by a Japanese company called Daiken. Daiken can produce their PCTFE with the same chemical formulation as Aclar PCTFE^{120,121}. The rationale being to secure the source of supply if the Aclar material is ever discontinued, furthermore that the new material gives improved line performance^{120,121,122,123}.

A preliminary study was performed to confirm that both materials are equivalent in terms of seal integrity and material compliance, mechanical and physical properties and that Vaposhield can be used as an alternative source of supply to Aclar^{124,125,126}. An optimisation exercise was also performed on the NOACK 623 and NOACK 760 platen sealing thermoforming blister sealing machines to confirm Vaposhield is compatible with the production equipment¹²⁷. Figure 46 details the main components of the platen sealing blister machine.

Figure 46 – Platen Sealing Thermo-former²⁷



Compatibility Trials

Production compatibility trials were performed using both the existing Aclar base laminate and the new Vaposhield base laminate as a comparison on the NOACK 623 and NOACK 760 thermoformers. This was to ensure the new material functioned effectively and a good heat seal was achieved when using the current validated parameters. The critical machine parameters considered to control seal quality and moisture permeability are sealing temperature, line speed and pre-heat forming temperature. The purpose of this study was to confirm that the seal quality using the new material can be maintained whilst using the following sealing parameters in Table 72. The previously validated parameters are also shown in Table 73.

Table 72 – Thermoformer Sealing Parameters used During Trials

Thermoformer	Product	Sealing Temp (°C)	Line speed Cycles per Minute (CPM)	Blister forming temperature (°C)
NOACK 623	Evista	190 to 210	19 to 25	135
NOACK 760	Zyprexa	180 to 200	18 to 30	145

Table 73 – Validated Settings

Thermoformer	Product	Sealing Temp (°C)	Line speed (CPM)	Blister forming temperature (°C)
NOACK 623	Evista	190 to 210	19 to 25	130 to 140
NOACK 760	Zyprexa	180 to 200	18 to 30	140 to 150

Methylene blue dye tests were performed on blisters from each predetermined settings to demonstrate the quality of the seal achieved. Further to this samples were supplied for the following equivalence and performance testing.

Experimental Method and Acceptance Criteria

Table 74 – Trial Material Details

Product	Description	Lot ID	Supplier
Zyprexa	Aclar base material – VRG520 (current)	94310	Techni-Flex
Zyprexa	Lidding foil – FOG620 – material code FL0070TRIAL	A042925	Alcan Cramlington
Zyprexa	Vaposhield base material – VRG520 (new)	1014394	Techni-Flex
Evista	Aclar base material – VRG570 (current)	85736	Techni-Flex
Evista	Lidding foil – FOG730 – material code FL0062TRIAL	A042929	Alcan Cramlington
Evista	Vaposhield base material – VRG570 (new)	1014396	Techni-Flex

The sealing parameters under test were run at normal production conditions. Seal quality was examined using the methylene blue dye test; reference Tables 75-76 for results.

Rationale behind the following test matrix was to:

- Compare Aclar and Vaposhield at different settings.
- Define an operating window.
- Have a Vaposhield reel by reel comparison.
- Have Vaposhield WVTR data at USP test conditions, as this information is included in NDA dossier for Aclar.

Table 75 - Results of Compatibility Trials - NOACK 623 (JP Evista)

Test	Material	Sealing Temp (°C)	Line Speed (cpm)	Base Foil Forming Temp (°C)	Seal Integrity test (8 samples) Pass/Fail	Number of blisters supplied for Moisture Permeability Test	Number of blisters supplied for Burst/Seal & Delamination Tests
1	Vaposhield reel 1	190	25	135	Pass	10	50
2	Vaposhield reel 1	190	19	135	Pass	10	50
3	Vaposhield reel 1	210	25	135	Pass	10	50
4	Vaposhield reel 1	210	19	135	Pass	10	50
5	Aclar	190	25	135	Pass	10	50
6	Aclar	190	19	135	Pass	10	50
7	Aclar	210	25	135	Pass	10	50
8	Aclar	210	19	135	Pass	10	50
9	Vaposhield reel 1	200	22	135	Pass	n/a	100
10	Vaposhield reel 2	200	22	135	Pass	n/a	100
11	Vaposhield reel 3	200	22	135	Pass	n/a	100
12	Aclar	200	22	135	Pass	n/a	100
13	Vaposhield reel 1	200	22	130	Pass	n/a	100
14	Aclar	200	22	130	Pass	n/a	100
15	Vaposhield reel 1	200	22	140	Pass	n/a	100
16	Aclar	200	22	140	Pass	n/a	100
Note* 100 consecutively produced blisters were inspected from each experiment for cosmetic appearance and full pocket form, no defective samples were found.							

Table 76 - Results of Compatibility Trials- Continued — NOACK 760 (JP Zyprexa)

Test	Material	Sealing Temp (°C)	Line Speed (cpm)	Base Foil Forming Temp (°C)	Seal Integrity test (3 samples) Pass/Fail	Number of blisters supplied for Moisture Permeability Test	Number of blisters supplied for Burst/Seal & Delamination Tests
1	Vaposhield reel 1	180	30	145	Pass	10	50
2	Vaposhield reel 1	180	18	145	Pass	10	50
3	Vaposhield reel 1	200	30	145	Pass	10	50
4	Vaposhield reel 1	200	18	145	Pass	10	50
5	Aclar	180	30	145	Pass	10	50
6	Aclar	180	18	145	Pass	10	50
7	Aclar	200	30	145	Pass	10	50
8	Aclar	200	18	145	Pass	10	50
9	Vaposhield reel 1	190	24	145	Pass	24	100
10	Vaposhield reel 1	200	24	140	Pass	24	90
11	Vaposhield reel 1	200	24	150	Pass	23	100
Note* 100 consecutively produced blisters were inspected from each experiment for cosmetic appearance and full pocket form, no defective samples were found.							

The trials confirmed that the running characteristics of the new Vaposhield material were similar to that of the current Aclar base material. No alterations to the thermoformer settings were required to run the new material. Furthermore, a good quality seal was achieved using the current machine parameters used in routine production, as indicated by the methylene blue dye test.

Samples were tested for permeability, seal integrity, burst strength and delamination tests on both Japanese Zyprexa 10s blister format and Japanese Evista 14s blister format. A less expensive investigational material (250µ PVC/10µ PCTFE) was also tested to determine its barrier properties and equivalency to the standard structures (191µ PVC/51µ PE/ 15µ PCTFE and 191µ PVC/51µ PE/ 51µ PCTFE). Table 77 details the material descriptions and specification for both the current Aclar and Vaposhield base materials, and investigational material.

Table 77 – Material Description and Specifications

Material	Description	Supplier
Aclar base material – VRG570 (current)	191µ PVC/51µ PE/ 15µ PCTFE	Techniplex
Vaposhield base material – VRG570 (new)	191µ PVC/51µ PE/ 15µ PCTFE	Techniplex
Lidding foil – FOG730 – material code	20µ Aluminium with LA1723 Heat Seal	Alcan Cramlington
Aclar base material – VRG520 (current)	191µ PVC/51µ PE/ 51µ PCTFE	Techniplex
Vaposhield base material – VRG520 (new)	191µ PVC/51µ PE/ 51µ PCTFE	Techniplex
Vaposhield base material – VRG520 (new Investigational Material)	250µ PVC/10µ PCTFE	Techniplex
Lidding foil – FOG620 – material code FL0070TRIAL	20µ Aluminium with LA1723 Heat Seal Lacquer	Alcan Cramlington

Table 78 - Equipment

The equipment used to perform the tests are detailed in Table 78.

Equipment	Identification Number
Balance AT460	98061903
Mocon permatran 3/31	95110909-95110910
Lippke Skye 1520 SL burst tester	95062709
Zwick tensile equipment	95100305
Vacuum dry chamber	95061504
Environmental chamber (23°C/75%RH)	99120604
Environmental chamber (25°C/60%RH)	95122203
Environmental chamber (30°C/60%RH)	95082419
Environmental chamber (40°C/75%RH)	95122204

Test Description

WVTR Evaluation on Flat Sheets

The purpose of this test was to evaluate the moisture protection of the laminates in flat sheet format. Two samples of each film material were prepared and placed on both Mocon cells and modules. The test was performed on every blister material, except on the current Aclar base laminate.

WVTR Evaluation on Formed Blisters

The purpose of this test was to evaluate the moisture protection of the sealed blisters by weight gain. The test is performed using USP 23°C/75%RH and ICH 25°C/60%RH, 30°C/60%RH and 40°C/75%RH conditions. For each condition, four blisters from each material was produced and filled with desiccant pellets (test samples) and another four are sealed empty (reference). All the blisters were weighed at 0, 1, 7, 14 and 28 days. The initial weights (day 0) were measured after one day pre-conditioning in the environmental chamber. Only the final results (day 28) are reported.

Burst Pressure

The purpose of this test was to evaluate the sealing quality between the aluminium lidding foil and the base laminate, by increasing the internal pressure of the cavity and measuring the pressure when it bursts. The lidding foil was slightly punctured with a needle so that it is possible to inflate the cavity. The tightness of the seal between the cavity and the equipment was realised with a rubber spectrum. The individual values were above the minimum burst pressure of 8×10^4 Pa, which assured an excellent seal between the lidding foil and base laminate.

Test conditions were as followed:

- Three blisters per material.
- Three cavities per blister were evaluated.
- Pressure speed increase 10mbar/sec.
- Results expressed in bar.

Seal Strength

The purpose of this test was to evaluate the seal strength between the aluminium lidding foil and the base laminate, and to qualify the force required to peel both materials apart. These values are an excellent measure for determining the quality of the sealing process. The test was realised on 10mm wide strips that are cut in the centre of a blister cavity in the longitudinal direction, randomly chosen on a blister card. Five cavities per experiment were tested. At one end the aluminium lidding foil, and at the other end the base laminate, were fixed in the jaws of the tensile equipment, which pulled it at a constant speed of 12.5mm/min.

Tensile strength on Flat Sheet

The purpose of this test was to quantify the force needed to elongate a 5mm wide strip. Five samples of each blister film laminate was tested. Each end of the strip was fixed in the jaws of the tensile tester, which stretched it at a constant speed of 12.5mm/min.

Delamination on Flat Sheet

The purpose of this test was to evaluate and quantify the force needed to separate the PCTFE foil from the PVC-PE foil of the blister film laminate. For this, strips of 10mm wide were cut. Five samples of each blister material was tested. Each sample was cut on the width on the PVC side to delaminate the PVC-PE foil (one end of the strip) from the PCTFE foil (the other end of the strip). Each end of the strip was fixed in the jaws of the Zwick, which peeled it at a constant speed of 12.5mm/min.

Delamination on Formed Blisters

The purpose of this test is to evaluate and quantify the force needed to separate the PCTFE foil from the PVC-PE foil of the formed blister film laminate.

For this, strips of 5mm wide were cut. Five samples of each blister film laminate was tested. Each sample was cut in the width on the PVC side to delaminate the PVC-PE foil (one end of the strip) from the PCTFE foil (the other end of the strip). Each end of the strip was fixed in the jaws of the Zwick, which peeled at a constant speed of 12.5mm/min.

Results and Discussion

Table 79 - WVTR Evaluation on Flat Sheets

Material	WVTR Average (g/m ² / day)
Aclar base material – VRG570 (current)	0.3038
Vaposhield base material – VRG570 (new)	0.2956
Vaposhield base material – VRG520 (new)	0.0875
Vaposhield base material – VRG520 (new investigational material)	0.4158

Table 80 - WVTR on Formed Blisters (23°C/75%RH)

Material	Test Number	WVTR Average (g/m ² / day)
		Average
Aclar base material – VRG570 (current)	G0898	0.0515
Vaposhield base material – VRG570 (new)	G1027	0.0493
Vaposhield base material – VRG520 (new)	G1029	0.0128
Aclar base material – VRG520 (current)	G1017	0.0196
Vaposhield base material – VRG520 (new Investigational Material)	G1026	0.0612

Table 81 - WVTR on Formed Blisters (25°C/60%RH)

Material	Test Number	WVTR Average (g/m ² / day)
		Average
Aclar base material – VRG570 (current)	G0898	0.0470
Vaposhield base material – VRG570 (new)	G1027	0.0447
Vaposhield base material – VRG520 (new)	G1029	0.0133
Aclar base material – VRG520 (current)	G1017	0.0132
Vaposhield base material – VRG520 (new Investigational Material)	G1026	0.0586

Table 82 - WVTR on Formed Blisters (30°C/60%RH)

Material	Test Number	WVTR Average (g/m ² / day)
		Average
Aclar base material – VRG570 (current)	G0898	0.0850
Vaposhield base material – VRG570 (new)	G1027	0.0820
Vaposhield base material – VRG520 (new)	G1029	0.0257
Aclar base material – VRG520 (current)	G1017	0.0255
Vaposhield base material – VRG520 (new Investigational Material)	G1026	0.1076

Table 83 - WVTR on Formed Blisters (40°C/75%RH)

Material	Test Number	WVTR Average (g/m ² / day)
		Average
Aclar base material – VRG570 (current)	G0898	0.2667
Vaposhield base material – VRG570 (new)	G1027	0.2621
Vaposhield base material – VRG520 (new)	G1029	0.0868
Aclar base material – VRG520 (current)	G1017	0.0951
Vaposhield base material – VRG520 (new Investigational Material)	G1026	0.3380

Observations from the WVTR Evaluation

It can be seen that the results do not indicate any significant difference between Aclar and Vaposhield laminates. Therefore, it can be concluded that the barrier properties of Vaposhield and Aclar are equivalent. Furthermore, it can be seen that when the thickness of the PCTFE layer is 33% lower; comparing G1027 to G1026, the water permeability increases more or less by the same factor.

Table 84 - Burst Strength

Material	Test Number	Burst Pressure \pm s (mbar)
Aclar base material – VRG570 (current)	G0898	1319 \pm 67
Vaposhield base material – VRG570 (new)	G1027	1408 \pm 174
Vaposhield base material – VRG520 (new)	G1029	1410 \pm 101
Aclar base material – VRG520 (current)	G1017	1319 \pm 42
Vaposhield base material – VRG520 (new Investigational Material)	G1026	1546 \pm 149

Observations from the Burst Strength Testing

For all tested materials, the average burst test results are well above the 8×10^4 Pa limit set during the original study to introduce the Aclar base material. Furthermore, the results obtained on the Vaposhield and new investigational material show a higher burst strength compared to the results obtained on Aclar, therefore, it can be concluded that both materials are equivalent to, or better performing than Aclar in terms of the sealing quality of the formed blisters.

Table 85 - Seal Strength

Material	MSG Lot Number	Seal Strength \pm s (N/cm)
Aclar base material – VRG570 (current)	G0898	7.6 ± 0.33
Vaposhield base material – VRG570	G1027	7.22 ± 0.31
Vaposhield base material – VRG520	G1029	7.70 ± 0.45
Aclar base material – VRG520 (current)	G1017	7.60 ± 0.25
Vaposhield base material – VRG520 (new Investigational Material)	G1026	7.84 ± 0.31

The average seal strength results for all materials tested are well above 6N/cm, and do not indicate any significant difference. Therefore, it can be concluded that the Aclar, Vaposhield and the new investigational laminates are equivalent in terms of sealing quality.

Table 86 - Tensile Strength on Flat Sheet

Material	MSG Lot Number	Tensile Strength \pm s (N/cm)
Aclar base material – VRG570 (current)	G0898	113.99 ± 1.97
Vaposhield base material – VRG570	G1027	112.01 ± 6.34
Vaposhield base material – VRG520	G1029	124.02 ± 13.50
Aclar base material – VRG520 (current)	G1017	131.22 ± 7.29
Vaposhield base material – VRG520 (new Investigational Material)	G1026	141.72 ± 9.26

Observations from the Tensile Strength Testing

The results do not indicate any significant difference between the laminates.

Therefore, it can be concluded that the Aclar, Vaposhield and investigational laminates are equivalent in terms of resistance to elongation.

Table 87 - Delamination Strength on Flat Sheet

	MSG Lot Number	Delamination Force \pm s (N/cm)
Aclar base material – VRG570 (current)	G0898	1.57 \pm 0.17
Vaposhield base material – VRG570 (new)	G1027	4.76 \pm 0.16
Vaposhield base material – VRG520 (new)	G1029	4.06 \pm 0.29
Aclar base material – VRG520 (current)	G1017	3.99 \pm 0.22
Vaposhield base material – VRG520 (new Investigational Material)	G1026	Not possible PCTFE film too thin

Observations from the Delamination Strength Testing on Flat Sheet

For all tested materials, the average delamination force results are well above 1N/cm. In both cases the delamination force for Vaposhield laminates is higher or equal to those of the corresponding Aclar laminates. It can therefore, be concluded that the Aclar and the Vaposhield blister are equivalent in terms of adhesion between the PVC-PE and the PCTFE foils.

Table 88 - Delamination Strength on Formed Blisters

Material	MSG Lot Number	Delamination Force \pm s (N/cm)
Aclar base material – VRG570 (current)	G0898	2.6 \pm 0.07
Vaposhield base material – VRG570 (new)	G1027	2.52 \pm 0.34
Vaposhield base material – VRG520 (new)	G1029	4.06 \pm 0.29
Aclar base material – VRG520 (current)	G1017	4.38 \pm 0.96
Vaposhield base material – VRG520 (new Investigational Material)	G1026	Not possible PCTFE film too thin

Observations from the Delamination Strength Testing on Formed Blisters

For all tested materials, the average delamination force results were well above the 1 N/cm. It can therefore, be concluded that the Aclar and the Vaposhield laminates are equivalent in terms of adhesion between the Aluminium-PVC-PE and the PCTFE foils.

4.8.1 Conclusion from the Study

The study confirmed that both the current Aclar and new Vaposhield base laminates were equivalent in terms of seal strength, burst strength, delamination resistance and seal integrity and that Vaposhield can be used as an alternative source of supply to Aclar^{124,125,126}. The study also confirmed following an optimisation exercise performed on the NOACK 623 and NOACK 760 platen sealing thermoforming blister sealing machines that Vaposhield is compatible with the production equipment¹²⁷.

It can also be concluded that the new investigational material has a much higher water permeation rate, which is of a level expected of a material that is 33% lower in thickness compared with the standard structure with a 51 μ PCTFE layer. The new material also provides equivalent or improved barrier properties to tensile strength, burst strength and seal integrity. For these reasons the new investigational material can be considered for further evaluation.

Chapter 5

5.1 Conclusions

As we have seen the blister sealing is a very complex and highly specialised process, and that all though there has been many advancements both in equipment and materials, there are many areas to focus on to further enhance the runnability of the blister materials and improve the operational efficiency of the blister lines.

This study has identified the critical areas of the blister sealing process that must be considered when developing new materials and processes. Optimum tool design and blister layout, appropriate choice of materials and equipment all of which are essential components in achieving protection, containment and identification of the product throughout its shelf life. However, probably thee most important aspect that was identified was the function of the adhesive.

The adhesive function within the blister pack is critical to the dispensing process, it also guarantees the protection of the product throughout its shelf life, protects the material under stressed conditions, both when forming the blister and at extreme climatic conditions.

The study has also identified many problems associated with blister sealing, such as blister laminates that are prone to delamination between the plies if the forming parameters have not been fully optimised, pinholes and splits may also be experienced during forming if the material is being overstressed. Furthermore, high temperatures that are required for rotary sealing may cause warping of the sealing tools, degradation of the adhesive and at worst case ingress of moisture into the blister cavity. All of which may result in the required dose not being administered.

Another critical aspect that has been identified is material / product compatibility at the development stage of a product. The technologists must ensure the material does not react with the product over time. Furthermore, that the structure of the blister pack may require adjusting to protect the product from moisture, oxygen or light.

Good blister layout design must also be achieved during development, with the maximum seal area around the pocket. Consideration to the type of knurling pattern and tooling design is also essential at an earlier stage of the development, and the type of sealing equipment, such as rotary or platen sealing?.

It is also evident from my studies that the critical sealing parameters of temperature, pressure and dwell time must be optimised to ensure the heat seal lacquer on the lidding material is transferred to the contact layer. If these parameters are not correctly set it will result in leaking blisters.

As discussed the most critical part of the blister sealing process is the function of the heat seal adhesive on the lidding foil and the compatibility with its corresponding sealing surface. It was therefore, essential to understand the theories of adhesion, the types of adhesives that are commercially available and the important characteristics and properties of adhesives. This, with the knowledge I have gained during my studies on blister sealing will assist further research into developing new adhesives and structures to achieve a higher degree of protection and containment within the blister pack.

Chapter 6

6.1 Summary

The following critical parameters were identified as relevant to the blister sealing process.

6.1 Modeling of the Heated Platen Sealing Process

By using the conventional conductive heat transfer process as described in Section 4.1, combined with the knowledge of the platen heat sealing process, the heat transfer from the heated sealing plates to the drug product can be effectively modeled and deduced. The results of the study concluded that given typical sealing conditions the drug product was exposed to a maximum temperature of 36.88°C for a period of <2.5 seconds. This temperature has no detrimental effects on the majority of drug products. Previously to this study, the determination of heat transfer was not routinely performed when developing pharmaceutical primary contact blister materials. However, any future development studies will include the determination of the heat transfer through the lidding material from the heated sealing plate to the drug product to prove suitability of the blister materials based upon the model predicted.

6.2 Moisture Transmission Rate of Coldform Blisters

The results from Section 4.7 have confirmed that the decisive criterion for the imperviousness of the pack to water vapour is the tightness of the seal and provided that the material does not contain any pinholes or splits the atmospheric moisture can only penetrate through the seal, as previously discussed in **Chapter 2**. In the case of the aluminium / aluminium blister the slight increase in moisture is due to the cross diffusion through either the PVC or the seal through the unsealed areas (land areas) or the edge of the blister

into the cavity. Therefore, to further reduce the moisture permeation then the distance between the cavity and land area could be increased.

The process used to determine the permeability of moisture through the seal is by filling the blister pockets with a desiccant, usually calcium chloride and weighing the blisters over a period of time to calculate the weight gain in g/m^2 per day. Previous to this study any development studies to introduce new pharmaceutical blister materials relied on the consistency and efficiency of the desiccant studies giving satisfactory results. However, due to the calculations of total moisture permeation developed in this study any future studies will compare the physical results using desiccant filled blisters to the theoretical calculations derived from this study and as presented in Section 4.2 . This will also give a higher degree of confidence in the correct selection of blister materials.

6.3 Peel Testing of MDPI Blister Strips

The adhesive strength between the flexible laminates of blister strips is of considerable practical importance. Generally, it would be important to maximise the adhesive strength of a given structure. However, in the specified case of the MDPI flexible laminates it is a requirement to be able to peel both laminates apart within the inhaler to expose the blister pocket. For this reason the peel strength is critical to the function within the MDPI device. Therefore, it was imperative to determine the peel force and the adhesive fracture toughness of the adhesive within the lidding and base laminates when introducing any changes to the structure of the adhesive by performing seal strength testing. Furthermore, the theoretical calculations as derived in Section 4.3 will now be used to compare the physical peel test results with the theoretical values. This will increase the confidence level in the correct selection of the adhesive structure.

6.4 Importance of Tool and Sealing Parameter Comparability

It can be deduced from Section 4.4 that the new recessed land area change parts inserted in the sealing wheel have provided a larger operating sealing range in terms of higher temperatures and pressures without sticking in the non sealed land area of the blister strip. Although, at half speed using more elevated seal parameters, it led to partial sticking of the unsealed land area. This reaffirms the importance of comparability between the tooling design and the critical sealing parameters of temperature, pressure and time.

Section 4.5 also confirmed that blister pocket profiles should avoid square or near right angled corners or bases as this may make both release from the forming tool difficult and lead to thinning in those areas. Generally blister pockets should have an adequate clearance with the product and have an adequate radius at both the top (dome) and where the pocket emerges into the blister flange.

As previously mentioned the three most important functions in achieving a good seal are temperature, pressure and speed. However, consideration of the forming characteristics is also essential, because it is paramount to the overall sealing operation. If the critical parameters of the forming operation have not been fully understood then delamination of the layers can occur under stressed conditions. Furthermore, if either the temperature of the lower sealing plate has been heated up during production by continuous contact with the upper sealing plate or mis-registration occurs between forming and sealing (sealing on the edge of the cavities) it can cause delamination earlier in the cycle. This phenomenon has been observed on MDPI blisters after 12 months storage at 40°C / 75RH and documented in Section 4.5 and therefore, reaffirms the importance of good tool design and the requirement to fully optimise the sealing parameters.

It can also be deduced from Section 4.7 that the rotary process offers more control on dwell time and satisfactory control of heat, but due to the increased pressures and temperatures required to achieve a uniform hermetic seal, combined with a harsh sealing process and a positive knurling pattern, it has a major impact on the print quality of the finished blister. So by evaluating various types of tooling design, such as positive and negative knurling patterns, with plain and etched top sealing and drive rollers the results have proven that all these factors significantly affect blister peel force, moisture ingress and overall seal integrity of the sealed blister.

It can also be deduced in Section 4.7 that the blisters produced using a plain top seal roller with the crimped drive roller gave equivalent performance in terms of seal integrity and peel force to the standard knurled top seal roller. Furthermore, that the blisters produced using the platen sealing process give a higher seal strength and the tightest seal in terms of moisture protection. The results from Section 4.7 also proved that temperature, time and dwell have a major impact on seal integrity.

To guarantee an effective seal, consideration must also be given to the sealing jaw pattern, such as line, cross hatch, or pyramid design, also if the area or width of seal zone is too narrow, the seal may not be totally effective. The design of the blister layout and the pocket profile is also critical to the performance of the pack and the degree of protection it gives to the product.

All of the above reinforce the importance of the comparability between the tooling design and the critical sealing parameters. If the sealing parameters and the equipment have not fully optimised and / or fully understood then this may result in poor line performance, defective blister packs and most importantly effect the administered dose.

6.5 Importance of the Adhesive Function within Blister Packs

The importance of the adhesive function within the blister pack is critical to the dispensing process for example on the MDPI device, it also guarantees the protection of the product throughout its shelf-life and protects the material under stressed conditions, both when forming the blister and at extreme climatic conditions.

The adhesive must also stand up to high sealing temperatures and dwell times on the rotary sealing blister machine. The high dwell time may result in lower productivity and to compensate an increase in temperature may be considered, but this may result in damage of the seal tools, thermal damage to the adhesive and the outer side of material, off-setting of printing inks and reduced binding strength of individual layers within the blister structure.

However, the sealing temperature could be reduced by pre-heating the heat seal lacquer on the lidding material or the PVC layer on the base material, the softening point of the PVC being between 90 to 100°C. Such pre-heating can be done by installing a heating table with direct heat contact. However, due to the low softening point of the heat-seal lacquer the inner side can be heated with radiant heat at a minimum distance. The new heat-seal lacquer as investigated in Section 4.6 is capable of sealing between 200°C to 240°C on a rotary blister machine.

6.6 Importance of Consistent Material Quality

The trials in Section 4.8 confirmed that the running characteristics of the new Vaposhield material were similar to that of the current Aclar base material. No alterations to the thermoformer settings were required to run the new material. Furthermore, a good quality seal was achieved using the current machine parameters used in routine production. However, it can also be deduced that although the Vaposhield laminate is an acceptable alternative, the structure of PCTFE / PE / PVC is not without its problems, such as material shrinkage and

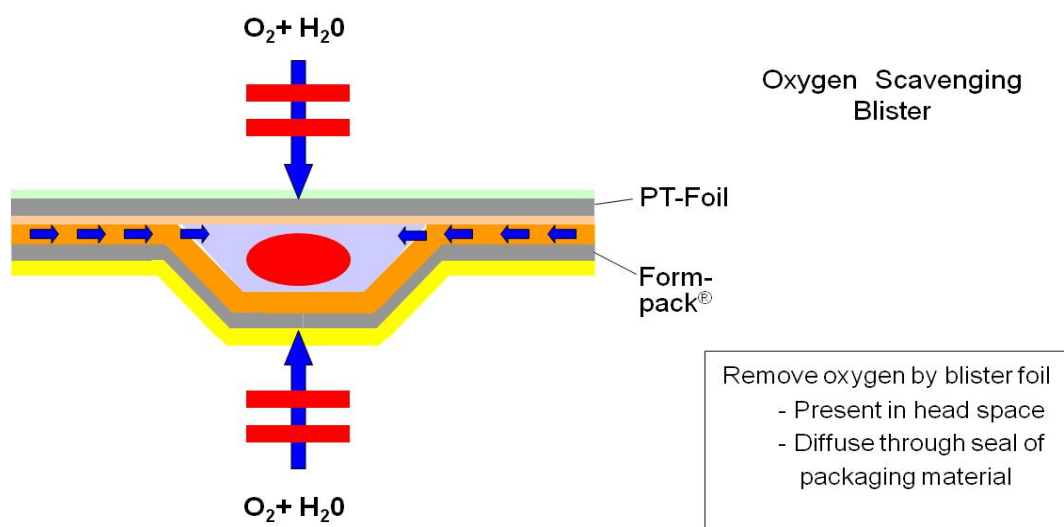
thinning of the blister cavity due to un-optimised sealing parameters. Therefore, if any containment of the blister pack is breached, it may result in product failure, with moisture and any extraneous contaminants migrating into the product causing instability of the drug and at worst case, the prescribed dose will not be administered. Therefore, a scientific approach to optimising and validating the sealing parameters and careful consideration of the requirements of the product is of the uppermost importance. For example the blister pack may require an additional barrier from moisture, oxygen or light to protect the drug product. In this case the clear Aclar film would not be acceptable. Therefore, a more suitable structure such as the aluminium / aluminium blister may be considered as this is the ultimate moisture barrier, it also protects the product from light. Furthermore, the conventional blister pack having a base laminate made from plastic film cannot in all cases adequately guarantee that the product retains its quality during the required shelf life.

Chapter 7

7.1 Future Work

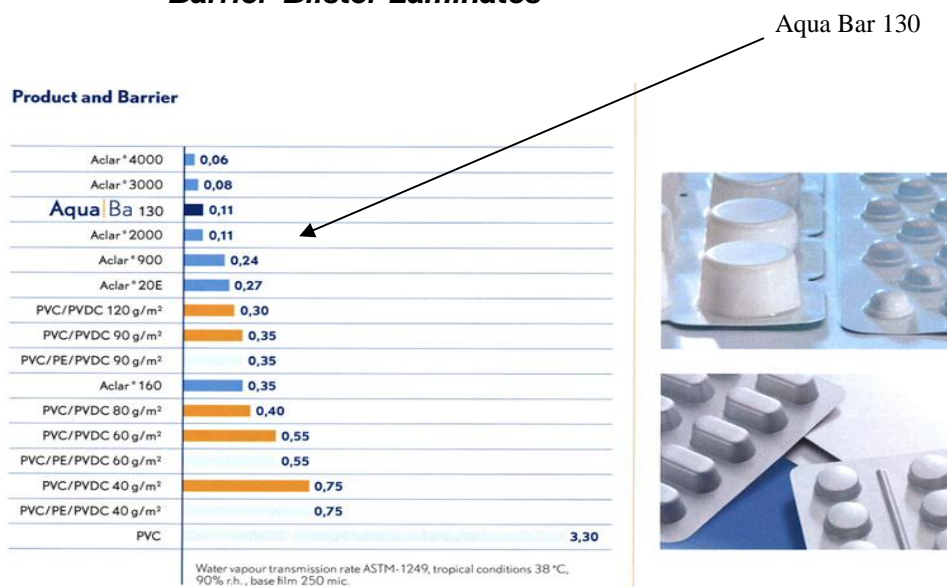
The detailed studies have been conducted alongside some major suppliers of blister packaging materials within the pharmaceutical industry. This has provided an in-depth understanding and knowledge of the current and new advanced barrier materials under development. Future Studies will evaluate these higher barrier films such as increased barrier to oxygen as required to guarantee the efficacy and shelf life of new drugs currently under development. The product starts to oxidise when exposed to oxygen, resulting in the required dose not being administered. As previously discussed the aluminium / aluminium blister is the ultimate barrier material, however, the oxygen sealed within the cavity must be evacuated. So by introducing an oxygen scavenging layer within the structure of the blister lidding foil as depicted in Figure 47, it will theoretically remove any oxygen within the cavity and stabilize the product throughout its shelf-life so the required dose can be administered throughout. Therefore, a study of scavenger layers could be of great interest.

Figure 47 - Oxygen Scavenging Blister



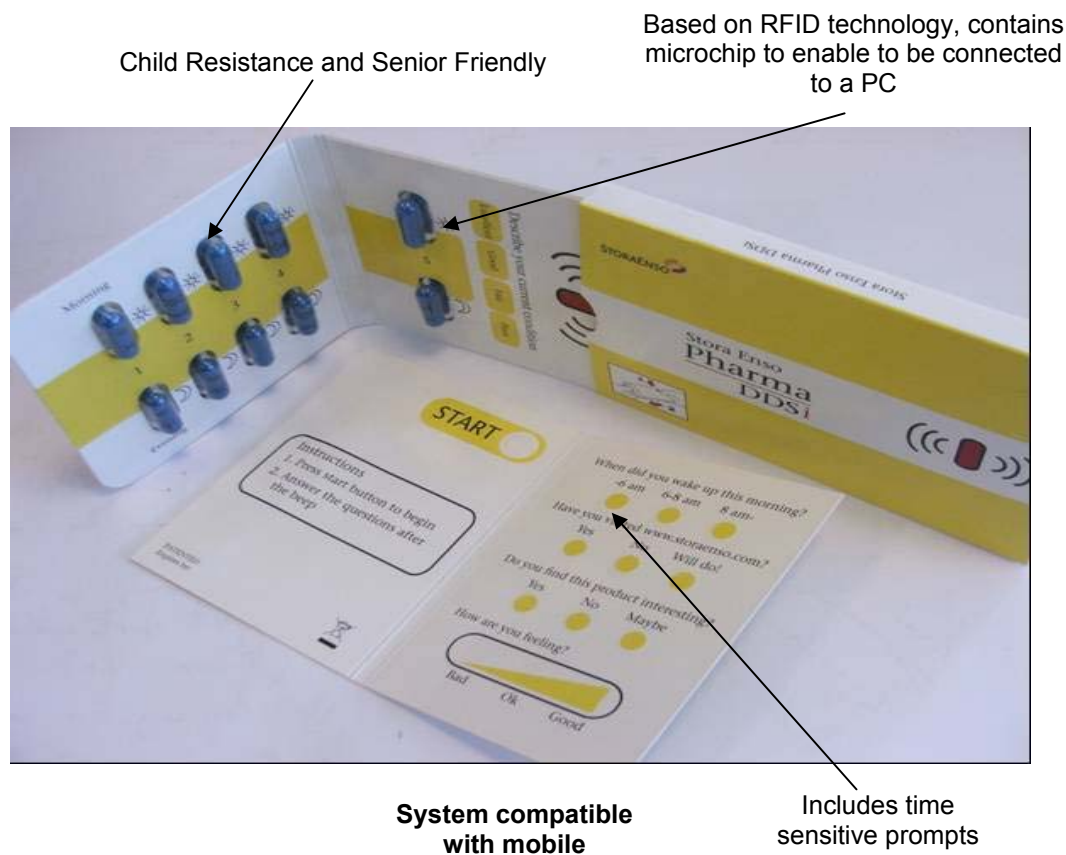
Further studies will also be focusing on less permeable duplex thermoformed laminates to moisture vapour, such as Aqua Bar 130, reference Figure 48. The primary objective being to reduce the material cost, by switching to from a triplex to a duplex structure, whilst retaining the barrier properties to moisture and gas.

Figure 48 – Moisture Vapour Transmission Rates of Thermoformed High Barrier Blister Laminates



Furthermore, recent enforced regulatory changes for child resistant packaging and tamper evidence have provided additional challenges for the pharmaceutical companies. Coupled with the ever increasing complexity in the treatment of a number of therapeutic areas and combination therapies, it is leading to increased patient non-compliance which costs the health authorities in the region of one billion pounds a year. The pharmaceutical companies have been tasked with developing compliance type blister packs. Figure 49 shows a compliance type blister pack that will be developed as part of my future studies into improved patient compliant blister packs.

Figure 49 – Compliance Blister Pack

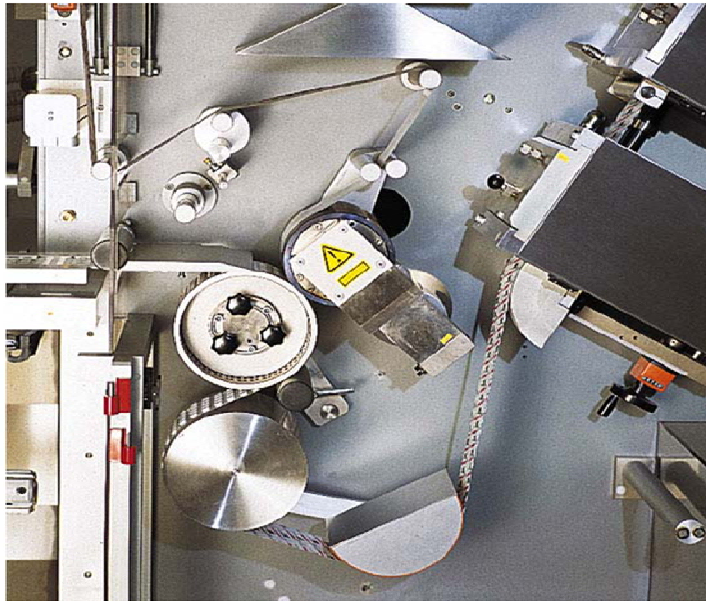


In addition to reducing the environmental impact and to ensure sustainability, I will be researching alternative PVC based blister laminates, such as PP, PET and structures such as PP/CoC/PP and OPA/AL/HDPE. I will also look at introducing materials from renewable and more environmental friendly sources such as Poly Lactic Acid (PLA), to guarantee security of supply and overall sustainability of our products.

8.0 Appendices and References

Appendix 1 – Roller and Platen Sealing

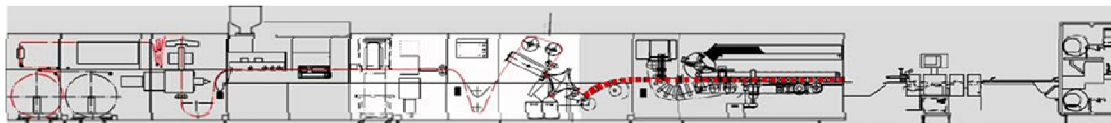
Roller or platen sealing



■ Roller sealing



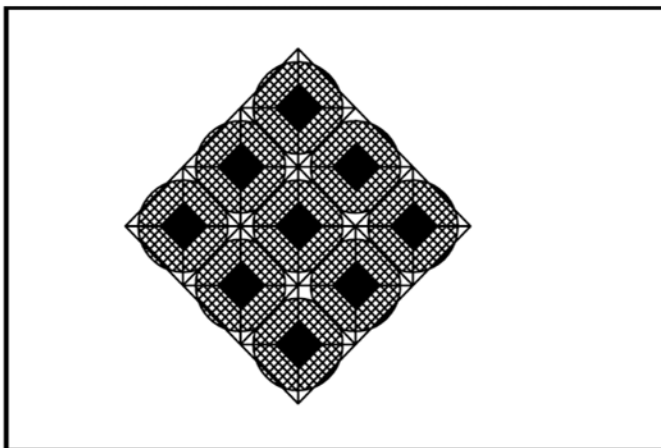
■ Platen sealing



Appendix 2 – Roller and Platen Sealing Patterns

Seal Pattern and - parameter

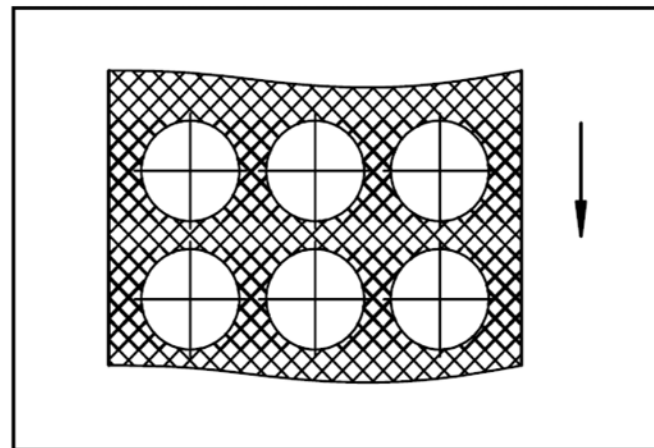
Platen Sealing



Parameter

- Even pressure over full area
- With PVC Blister – 120 – 150 N/cm²
- With Aluminium blister often higher
- Temperature – 160 - 180°C

Roller Sealing



Parameter

- Uneven pressure over length of seal line
- With PVC Blister – 60 – 100 N/cm²
- Temperature – 190 - 240°C

Appendix 3 – Roller and Platen Sealing Tooling

Tooling

Platensealing

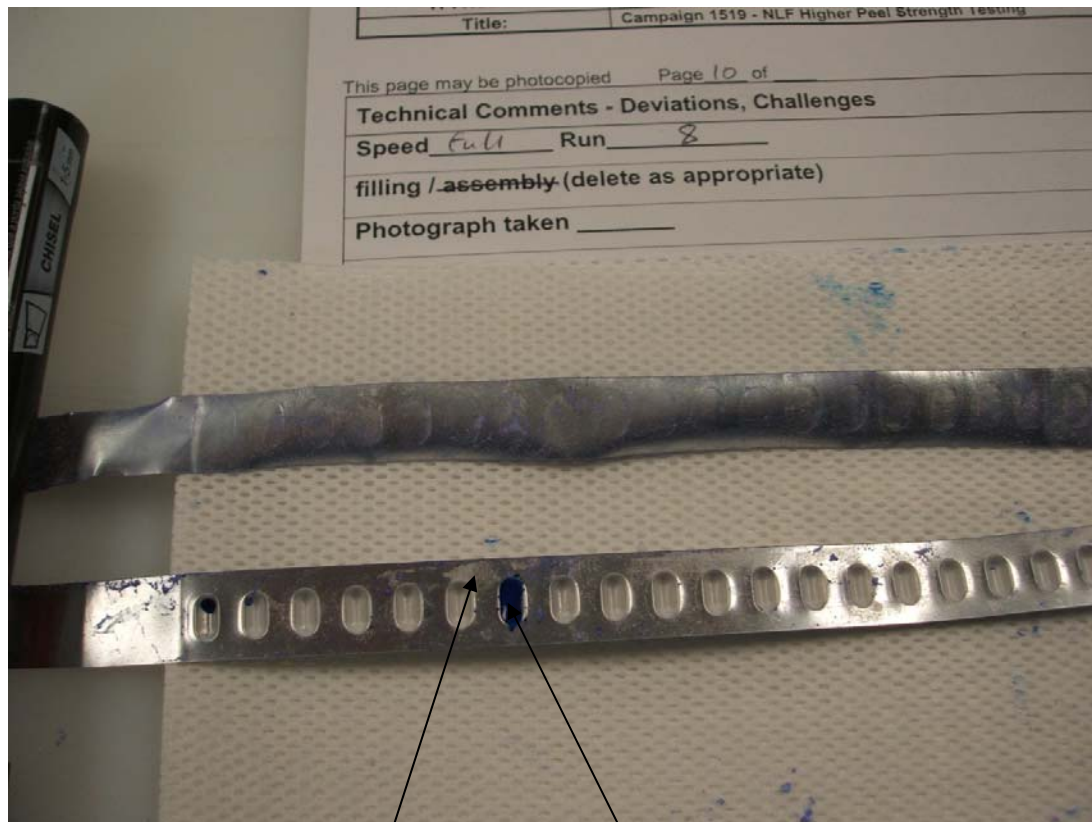


Rollersealing



Appendix 4 – Images

Lactose on Strip (Powder Spatter)

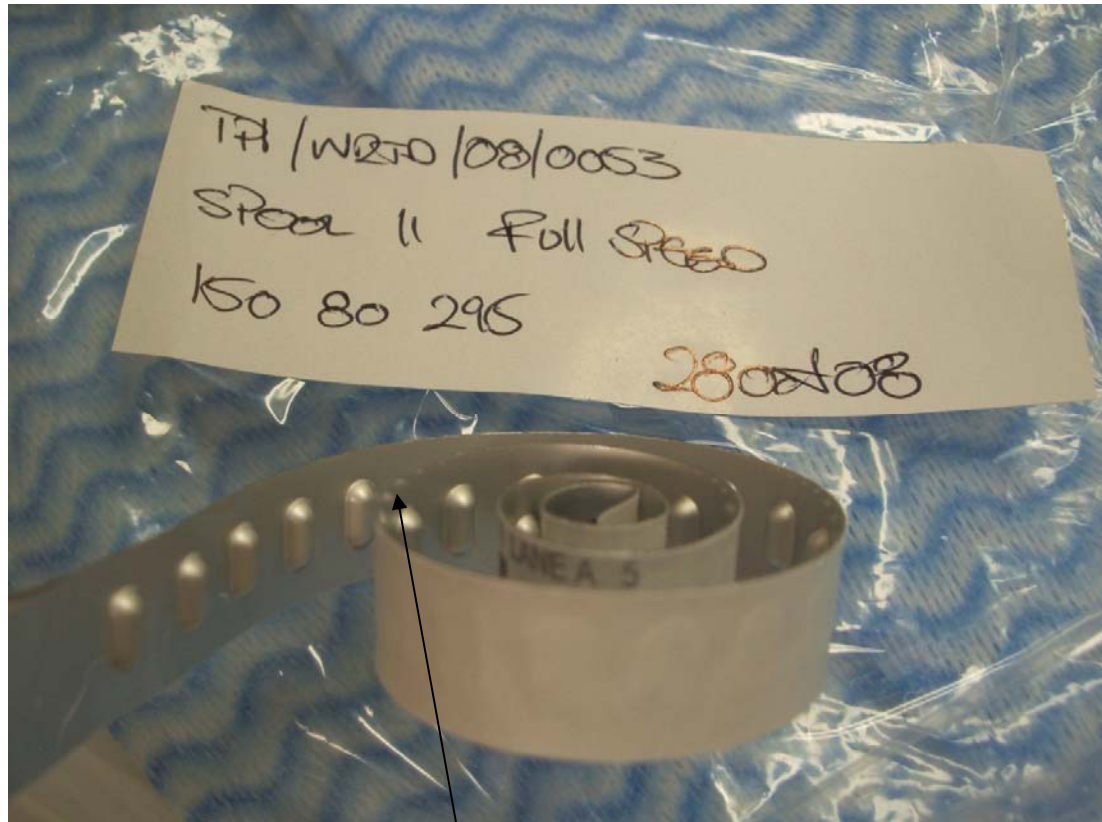


Powder Spatter

Leaking Blister

Appendix 5 – images

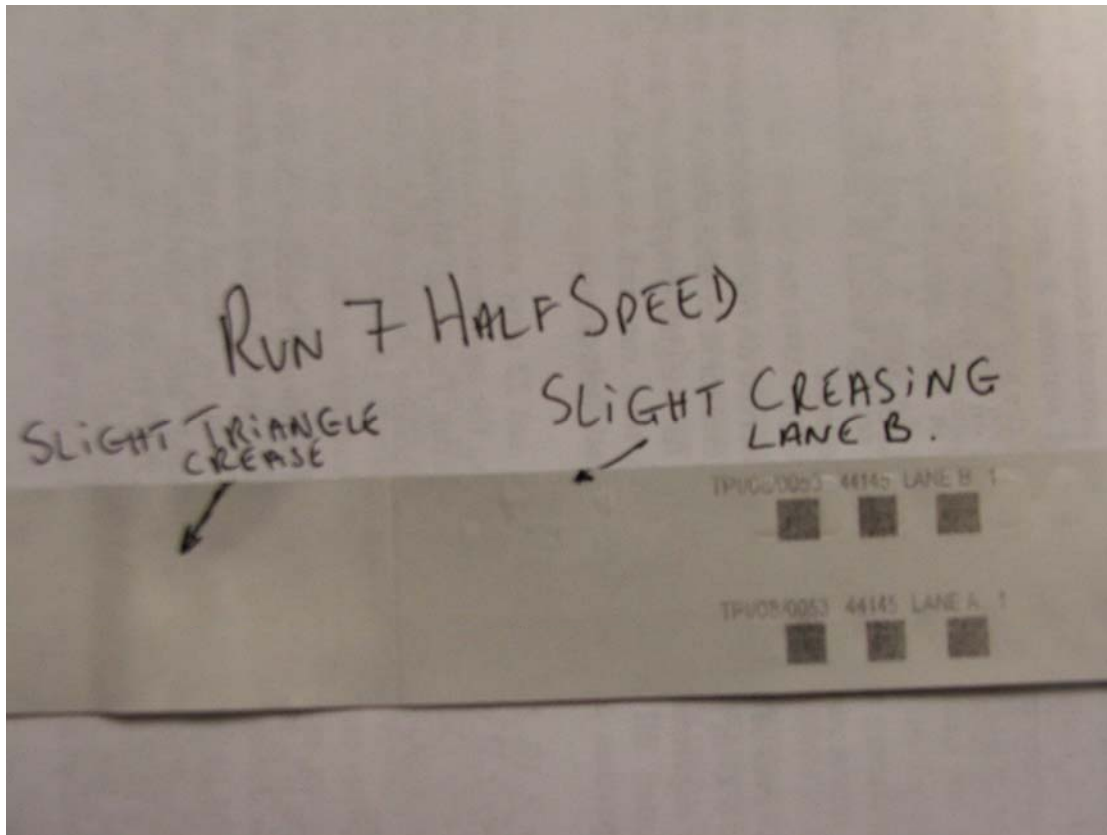
Strip Edge Quality



Feathering

Appendix 6 – images

Creasing on strip



Appendix 7 – SEM Pictures of the New Heat Seal Lacquer on Lid Foil

Project 1

28.06.2010 10:55:39

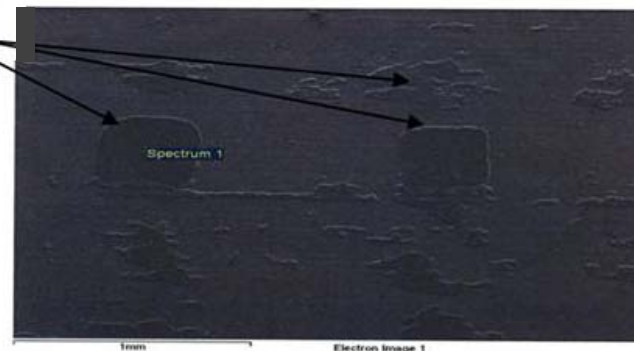
Spectrum processing :
No peaks omitted

Processing option : All elements analyzed (Normalised)
Number of iterations = 4

Standard :
C CaCO3 1-Jun-1999 12:00 AM
O SiO2 1-Jun-1999 12:00 AM
Cl KCl 1-Jun-1999 12:00 AM

Element	Weight%	Atomic%
C K	79.71	87.61
O K	10.67	8.80
Cl K	9.63	3.58
Totals	100.00	

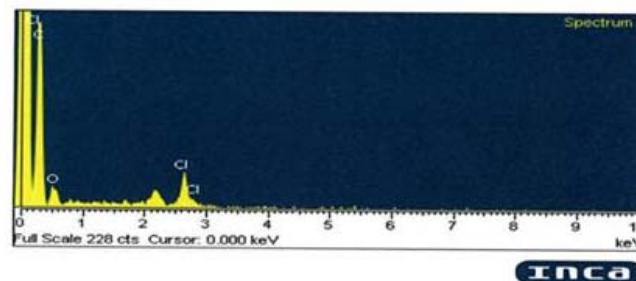
Heat Seal Lacquer
on Lidding Foil



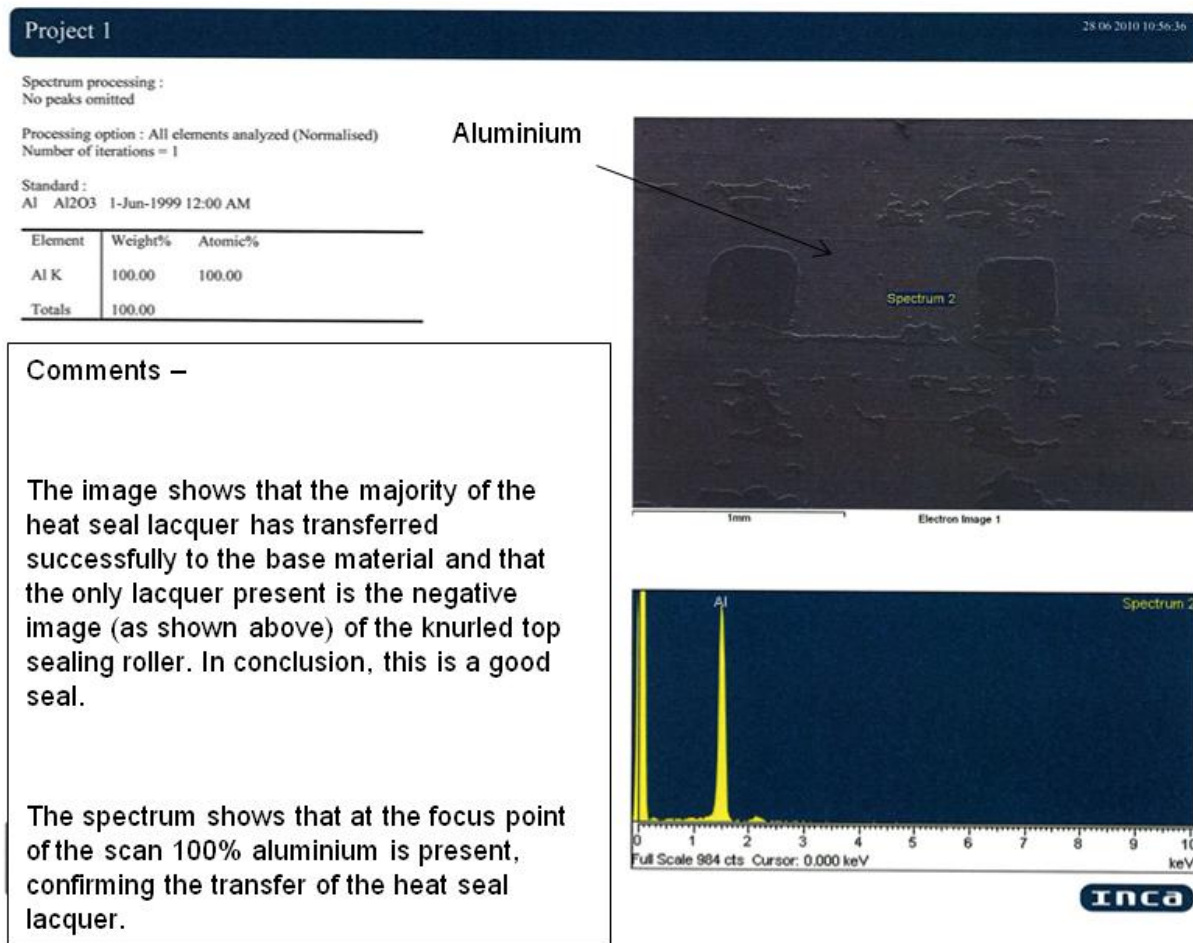
Comments –

The image shows that the majority of the heat seal lacquer has transferred successfully from the lidding foil to the base material and that the only lacquer present on the lidding foil is the negative image (as shown above) of the knurled top sealing roller. In conclusion, this is a good seal.

The spectrum shows that at the focus point of the scan as indicated above the main components of the heat seal lacquer are present.



Appendix 7 Continued – SEM Pictures of the New Heat Seal Lacquer of Lid Foil



Appendix 7 Continued – SEM Pictures of the New Heat Seal Lacquer on the Base Foil

Project 1

28.06.2010 11:22:10

Spectrum processing :
Peak possibly omitted : 2.109 keV

Processing option : All elements analyzed (Normalised)
Number of iterations = 4

Standard :
C CaCO₃ 1-Jun-1999 12:00 AM
O SiO₂ 1-Jun-1999 12:00 AM
Cl KCl 1-Jun-1999 12:00 AM

Element	Weight%	Atomic%
C K	74.26	82.67
O K	16.63	13.90
Cl K	9.11	3.43
Totals	100.00	

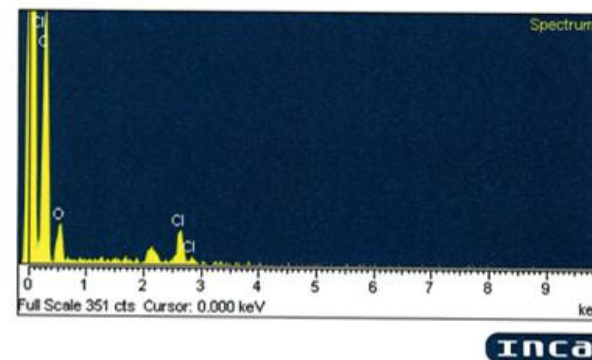
Heat Seal
Lacquer



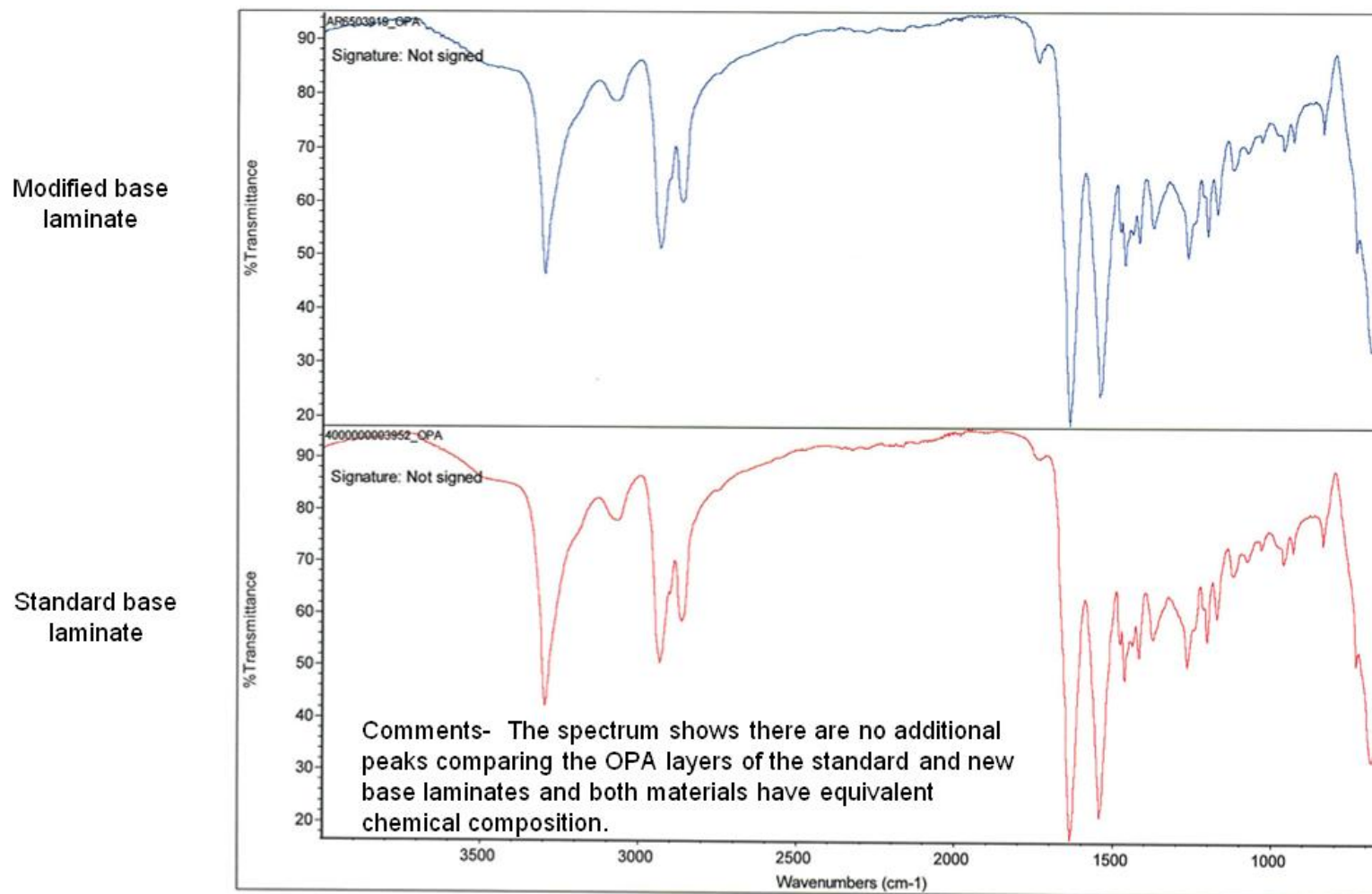
Comments –

The image shows that the majority of the heat seal lacquer has transferred successfully from the lidding foil to the base material. In conclusion, this is a good seal.

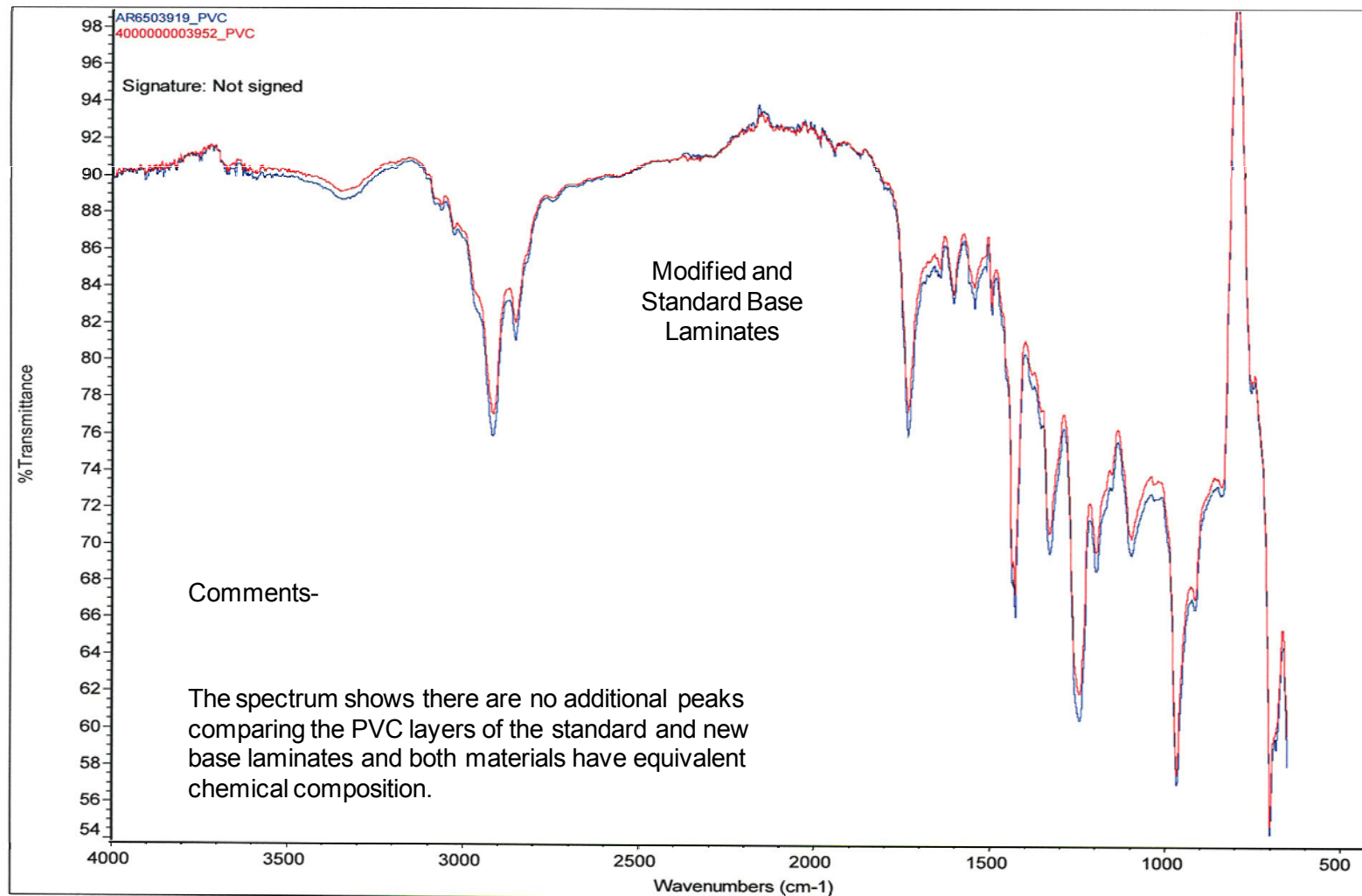
The spectrum shows that at the focus point of the scan the main components of the heat seal lacquer are present, confirming the transfer of the heat seal lacquer to the base material.



Appendix 8 – FTIR Spectrum of the Modified and Standard MDPI Base Laminate (Outside OPA Layer)



Appendix 8 Continued – FTIR Spectrum of the Modified MDPI Base Laminate (Inside PVC Layer)



Appendix 9 – Determination of the Melting Points of the PVC layer within the Standard and Modified MDPI Base Laminates using DSC

Modified Base
Laminate

Standard Base
Laminate

Comments-

The results of the DSC analysis confirms the PVC melting points of both the standard and modified MDPI base laminates of 84°C.

References

- (1) Technical Report – Packaging Material for the Packaging Industry, by E.Pasbrig, Lawson Mardon Singen / Neher. Sept 2002.
- (2) Pharmaceutical Packaging Technology by D.Dean, Roy Evans, I.H.Hall. Published 2000 by Taylor Francis. ISBN 0-7484-0440-6.
- (3) Quality Control of Packaging Materials in the Pharmaceutical Industry, by K.Hurburn, ISBN: 0 8247 82 43 7.
- (4) Plastics in Packaging by D.Dean. ISBN -13 9780902799288. Published by Pira International.
- (5) Packaging of Pharmaceuticals, Packages & Closures, by D.A Dean, the Institute of Packaging ISBN No. 0 9507567 6 8.
- (6) Practical Packaging Series, Packaging for Protection, by K.Waterhouse, the Institute of Packaging, ISBN No. 0 946467 01 3.
- (7) Alcan Packaging University – The Future of Packaging, Technical training Material, by Alcan Pharmaceutical Packaging, 6th March 2008.
- (8) Technical Report – Designed Barrier – How Tight is a Blister, by E.Pasbrig, Lawson Mardon Singen / Neher. Sept 2002.
- (9) Presentation on the Thermo-forming of Pentapharm® Aclar® Laminates – July 30th 2008, by Uhlmann, Klockner Pentaplast and Honeywell.
- (10) Alcan Technical Report on the Sealing of Cold-Form Base Laminates, 29/09/2002.
- (11) Medicines Control Agency, Consultation Letter MLX 291, Dated 26th Nov 2002.
- (12) Optimisation on Child Resistant Packaging, Europe & International by D.Pethick GSK R&D Harlow, Feb 2006.
- (13) German Child Resistant Guidelines DIN Standard 55559 – in-Pharma Technologists.com News Headlines 5th April 2004.
- (14) World report on Child Injury Prevention by Ed-Margie Peden et al. World Health Organisation, 2008..
- (15) Healthcare Compliance & Packaging Council (HCPC) Europe, July / Aug 2005 Newsletter, Issue No. 1.

- (16) Child Safe Packaging Group – www.childsafepackaginggroup.com.
– Article dated 11/10/1999.
- (17) Congress of the US Congressional Budget Office – A CBO Study Oct 2006 – R&D in the Pharmaceutical Industry.
- (18) The Centre of Professional Achievement – Packaging of Pharmaceuticals Course, Course Director, D.A Dean, Volume II, Nov 1998, 23-25 Nov, Amsterdam.
- (19) www.zeusinc.com/UserFiles/zeusinc/Documents/Zeus_Low_Temp.pdf.
- (20) Eli Lilly & Co. Global Packaging Technology, Packaging Technical & Development Training Program, Moint-Saint Guibert (MSG) Belgium, 10th Sept 2001.
- (21) Department of Medicines Policy and Standards, Health Technology and Pharmaceuticals, World Health Organisation. Presentation by Dr Dave Elder and Dr Simon Mills, GSK. Cape Town, South Africa. 16-21st April 2007.
- (22) Presentation by Honeywell Speciality Films in conjunction with RM Consulting – understanding how Innovative Packaging Solutions can create your competitive advantage for the 21st Century.
- (23) Break through solution for Non Compliance Packaging OtCM™ Assisting Therapy Compliance. Certificate Number SCS- 002622. WWW.fsc.org. 1996 Forest Stewardship Council.
- (24) Double Foil Blister (Formpack) Sealing report by E.Pasbrig, A.L Packaging, 1998.
- (25) Technical Report – Information Regarding Formpack, by E.Pasbrig, Lawson Mardon Singen / Neher. Sept 2002.
- (26) Solutions for the Perfect Blister Pack Quality with Rotary sealing Technology, Technical Memorandum by P.Van Geert 28/02/2005.
- (27) MSc in Packaging Technology Dissertation by K.Allen 2002. Loughborough and Brunel Universities.
- (28) Multilayer Flexible Packaging, Technology and Applications for Food, Personal care, and OTC Pharmaceutical Industries. Publisher: William Andrew ISBN-10-0815520212.

- (29) Practical Packaging Series, Laminates & Lamination, by J.Briston, the Institute of Packaging, ISBN No. 0 946467 00 5.
- (30) Blister Thermoforming Choices, Pharmaceutical Intelligence Journal, issue Sept 2006.
- (31) Alcan Packaging Company Presentation by Karl Mesmer, Alcan Sales Director – A Company Overview – 20th May, 2005.
- (32) Fundamentals of Packaging Technology, by W.Soroka, Reviewed UK Edition, A.Emblem & H.Emblem. ISBN-1930268289. Institute of Packaging Professionals.
- (33) Technical Presentation by S.Schmid, Teich AG, Oct 2003 on Pharmaceutical Blister Packs. AW Flexible Packaging Healthcare on Coldform Laminating, 2001.
- (34) Presentation by Alcan Packaging – Aluminium Foil Printing & Slitting Process Technical Presentation, by Steve Williams, Alcan Cramlington Sales Director, at Eli Lilly & Co. Oct 2001.
- (35) Optical Tool geometry by E.Pasbrig Alcan Packaging, Impact Exerted by STREC Software. 2002.
- (36) Interchangeability of PVC Films and Aluminium Foils, Pharmaceutical Technology Journal, Nov 1997 Issue.
- (37) Properties of Polymers, D.W.Van Krevelen, (Third Edition) Chapter 22 – Chemical Degradation. Published by Elsevier Science. ISBN10-044482877X.
- (38) Plastics in Packaging Conversion Processes, J.Briston, the Institute of Packaging, ISBN No. 0 9507567 04 1.
- (39) Plastics Additives – Gacgter / Muller (4th Edition). Publisher Hanser Gordner, June 1997. ISBN-10-0195208552.
- (40) Plastics Materials, J.A Brydson. A Butterworth-Heinemann Title; 7 edition (26 Oct 1999). ISBN-10: 0750641320.
- (41) Technical Presentation by Industria Macchine Automatiche (IMA) on Sealing Technology. Nov 2002, Eli Lilly & Co, Basingstoke Hants.

- (42) The Centre of Professional Achievement – Packaging of Pharmaceuticals Course, Course Director, D.A Dean, Volume I, Nov 1998, 23-25 Nov, Amsterdam.
- (43) Pharmaceutical Packaging Handbook by Edward j Bower, Bausch and Lomb. Rochester, New York, USA. ISBN-9781587161513. Published by Informa, March 2009.
- (44) Whiley Encyclopedia of Packaging Technology 2nd Edition, by A.Brody & K.Mars, 1997, ISBN 0471063975.
- (45) Packaging Design Workbook. The Art and Science of Successful Packaging. Author John Silva. Published by Rockport Publishers. ISBN-10-1592537081.
- (46) Practical Packaging Series Laminates and Lamination, by J.Briston, ISBN No. 0 / 946467 00/5.
- (47) The Effects of Packaging on the Stability of a Moisture Sensitive Compound, by J.Allinson, R.Dansereau & A.Sukr 12/03/2001.
- (48) Technical memorandum 04/08/2005 – Confirmation of Coldform Blisters, Oxygen and WVTR Permeation Rates, by T.Schwarz, Alcan Packaging Singen.
- (49) Technical Memorandum on the Tension in Formpack Laminate After Forming (Outside) by P.Classens Alcan Packaging Singen, July 2001.
- (50) Technical Memorandum – Delamination Under Stressed Conditions (High Temperature & Humidity 40°C, 75% RH), by P.Classens Alcan Packaging Singen, 22/05/2001.
- (51) Technical Company Presentation by GP Solutions, 22 Jan 2010 for GlaxoSmithKline, R&D Harlow.
- (52) Technical Company Presentation by Baltimore Innovations on Desiccated Base Films for GlaxoSmithKline, R&D Harlow. Aug 2009. WWW.baltimoreinnovations.co.uk
- (53) Technical Company Presentation by Alcan Packaging on Desiccated Base Films for GlaxoSmithKline, R&D Harlow. June 2010. WWW.Amcor.com

- (54) Packaging of Pharmaceuticals and Healthcare Products by H. Lockhart & F.A Paine, 1996, ISBN 0751401676.
- (55) Package Evaluation – Function of the Package, Diploma in Packaging Course, London City Polytechnic, Moorgate, London.
- (56) Adhesion Science - RSC Paperbacks by J.Comyn -.ISBN 200330345, 1997 series, J. Publishers.
- (57) The Attainment of Controlled Adhesion by Incorporation of Low Level Additives in a PDMS Based Adhesive – Doctoral Thesis by U.Ana 2005.
- (58) Adhesion and Adhesives - Science and Technology by A.J. Kinloch. Kluwer Academic Publishers, (Aug 1987) ISBN 041227440X.
- (59) Adhesives Bonding: Science, Technology and Applications. R.D Adams, CRC Press 2005. ISBN-9780849325847.
- (60) MTS Project 3 Environmental Durability of Adhesive Bonds. Report number 11, Locus of Failure of Bonded Joints. D.M Brewis, G.W Critchlow, I.Mathieson and K.Ebtehaj, Dec 1996.
- (61) Paper by D.E Pacham. The Mechanical Theory of Adhesion. School of Material Science, University of Bath. <http://people.bath.ac.uk>
- (62) Adhesives for Packaging 29th April 2004, Society of Chemical Industry 15 Belgrave Square, London.
- (63) International Journal of Adhesion & Adhesives Volume 23, Issue 2, 2003. A review of some basics of adhesion over the past four decades.
- (64) International Journal of Adhesives Volume 22 – 2002. Lactic Acid Based Polymers as Hot Melt Adhesives for Packaging Applications. M.Viljanma, A.Sodergard, P.Tormala, Tampere University of Technology, Institute of Bio Materials.
- (65) Heat Sealing Technology and Engineering for Packaging Principles and Applications. Author Kazuo Hishinuma. Translated by Hiroaki Miyagawa. Published by DE Strech Publications Inc 2009. ISBN 1932078851 & 9781932078855.
- (66) Surface Energy and Wetting, By Zisman and Colleagues. WWW.adhesives.org. structural design / surface energy and wetting.

- (67) A Protocol for the Determination of Adhesive Fracture Toughness of Flexible Laminates by Peel Testing Mandrel Peel Method. An ESIS Protocol – June 2005. L.F Kaweshita, D.R Moore, J.G Williams.
- (68) A Protocol for the Determination of Adhesive Fracture Toughness of Flexible Laminates by Peel Testing Fixed Arm and T-Peel Methods. An ESIS Protocol – Feb 2006. D.R Moore, J.G Williams.
- (69) SEM and X-Ray Microanalysis, 3rd Edition by Joseph I Goldstein, Dale E Newbury, Patrick Echlin, David C Joy, Charles E Lyman, Eric Lifshin, Linda Swagger and Joseph R Michael. Publisher Springer 2003. ISBN 10-9780306472923.
- (70) Fondeur.F. and Koenig J.L, 1993. Journal of Adhesion, vol.43: 236-271.
- (71) Msc in Packaging Technology, Assessment M2/3 on Thermal Analysis by K.Allen, Reg No, 9648202.
- (72) Msc in Packaging Technology, Assessment M2/4 on SEM, XFR, EPMA, XPS & Auger by K.Allen, Reg No, 9648202.
- (73) Induction to the Principles of Heat Transfer – efunda engineering fundamentals Website - <http://www.efunda.com> - 22/06/2007.
- (74) Definition of Heat – Wikipedia Free Encyclopedia Website – http://en_Wikipedia.org/Wiki/Heat - 22/06/2007.
- (75) 1 D Conduction Theory in Heat Transfer – efunda engineering fundamentals Website - <http://www.efunda.com> - 22/06/2007.
- (76) General Conduction Theory in Heat Transfer – efunda engineering fundamentals Website - <http://www.efunda.com> - 22/06/2007.
- (77) Forced Convection Theory in Heat Transfer – efunda engineering fundamentals Website - <http://www.efunda.com> - 22/06/2007.
- (78) Heat Equations - Wikipedia Free Encyclopedia - http://en_Wikipedia.org/Wiki/Heat-Equations - 22/06/2007.
- (79) Platen Heat sealing of Discuss Product, Application to Rotary Sealing, CTS – Process Engineering 2002.
- (80) Describing Heat Flow, Technical Memorandum dated Jan 2006, by Packaging Technology, GSK, GMA Ware, to Model the Heat Flow of the MDPI Rotary Sealing Process.

- (81) Single use Medical Packaging, by T.I. Overthrow Consultancy Services, at Brunel University 17th May 1995.
- (82) Encyclopedia of Packaging Technology, 3rd Edition, Published by Willey. Edited by Kit L Yam. ISBN 978-0-470-08704-6.
- (83) International Conference on Harmonisation (ICH) Steering Committee, 1994, 1998).
- (84) Pentaparm Quality Films for Pharmaceutical Packaging, Report by Klockner Pentaplast & Aerni Leuch AG. Edition 04/05.
- (85) Eli Lilly & Co. Drug Development process by P.Van Geert 08/02/1999.
- (86) Tekniflex ECO Price & Barrier Performance Comparison by Tekchni Films – Technical Presentation 2004.
- {87) USP Chapter 671 Containers for Performance Testing, Presentation by A.DeStephano, General Chapters. IPC-USP 7th Annual Scientific Meeting, Feb 6-7 2008. Hyderabad International Conference Centre, Hyderabad India.
- (88) USP Chapter 671 Containers for Performance Testing, Revision Bulletin Official Dated 2007.
- (89) Formpack with Desiccant, Technical presentation on Moisture Ingress, Oct 2009.
- (90) Alcan Packaging Singen Technical Presentation on the Determination of Lacquer Weight on Laminating Machine LKM23, 6th October 2009.
- (91) Technical presentation – Basis for using MVTR Per Unit Product in the Evaluation of Moisture Barrier Equivalence of Primary Packages for Solid Oral Dosage Forms, by PQRI Container / Closure Working Group, Sept 2004.
- (92) A discussion of net water gain for WVTR determination. S.Yoon Eli Lilly, D.Sparks Eli Lilly, S.Selke Michigan State University. Pharmacopeial Forum Vol. 35(2) Mar-Apr 2009.
- (93) Technical Presentation on Blister Packaging Films & Properties, by Klockner Pentaplast, Uhlmann & Honeywell, 30th July 2009.

- (94) Improvement Program Plan & FMEA with Alcan Packaging – MDPI Lidding & Base Foil Laminates, Presentation by E.Tossitti and M.Huttlestone, 30th Nov 06.
- (95) Technical presentation on the Development of Non Tearing Lidding Foil for MDPI, by P.Classens, Alcan Packaging Singen, 07/03/2006.
- (96) Technical presentation on the New Lidding Foil Status 23rd April 2008 by R Walker, GSK R&D, Ware.
- (97) Technical Presentation on the Alternative Lidding Foil for MDPI, by A.Borzak, GSK, GMS Ware, May 2006.
- (98) Technical Presentation on the Alternative Lidding Foil for MDPI, by R.Walker, GSK, GMS Ware, April 2006.
- (99) Close Up, Uhlmann Customers Journal, issue 1 2005.
- (100) Tekni-Films Thermoforming Packaging Troubleshooting Guide Part II – Production Variables 14/05/2007.
- (101) Problems and Solutions in Thermoforming, Technical Presentation by EVC Rigid Films, Gmbh, Pharmaceutical Division. WWW.evc-films.com.
- (102) Technical Presentation by Alcan Packaging Singen, Oct 2005 on the New Improved Formpack Base Laminate.
- (103) Report – Comparison Delamination of Formpack Laminates, by Alcan Packaging Singen, 26th May 2004.
- (104) Report – Presentation of Laminate Materials for Coldform Blisters with Increased Stability by Alcan Packaging Singen, July 2006.
- (105) Technical Development Report 26th May 2004, on the Development of Quality Advanced by Alcan Packaging Singen.
- (106) Technical Development Report 4th June 2004, on the Development of Quality Advanced by Alcan Packaging Singen.
- (107) Report on the Study by Research and Development, report number HD2005/00115/00 on the Evaluation of an Alternative Adhesive and Primer System in Alcan Packaging Singen Coldform Laminate, by A.Smith GSK, R&D Harlow June 2003.
- (108) Quality Advanced 2 Technical data Sheet, provided by Alcan Packaging Singen May 2009.

- (109) Confirmation of Compliance Certificate for Formpack Base Laminate, 21st Jan 2004.
- (110) EMEA – Guidelines on Plastic Immediate Packaging Materials by D.Ingles, Medical / Pharmaceuticals, Rapra Pharma.
WWW.raprapharma.co.uk.
- (111) NDA / MAA Submission Guide – Regulatory Submission Guidance 26/06/2009.
- (112) European Medicines Agency Inspections, CPMP/QWP/4359/03 – EMEA/CVMP/205/04 – Guideline on Plastic Immediate Packaging Materials.
- (113) 01/2008:30111 Corrected 6.0 – 3.1.11 Materials Based on Non-Plasticised Poly (Vinyl Chloride) for Containers for Dry Dosage Forms for Oral Administration.
- (114) Technical Report by GlaxoSmithKline, Global Manufacturing and Supply, reference WSPT/09/004. Approval of an Alternative Heat Seal Lacquer for MDPI Filled Strips, Aug 2009.
- (115) Alcan Technical Report TELV/Sto/04.10.2007 on the Qualification of the New Heat Seal Lacquer.
- (116) Technical Trial Technical Memorandum Dated 12 – 19 Dev 2003. Band 24 Trials by K.Allen & B.Scott.
- (117) Line Trial Protocol PK/2003/07, Production Trial of New Rotary Blister Sealing Tooling Combinations by K.Allen, Jan 2003.
- (118) Eli Lilly & Co. Global Packaging Technology & Development Test Report 02-132, IMA C80 Blistering Machine, Qualification for Basingstoke March 19th 2003.
- (119) Eli Lilly & Co. Global Packaging Technology & Development Test Report 04-77, WVTR and Sealing Quality of 7s Zyprexa Blisters, Impact of the Installation of a New Plain Top Sealing Roller on Basingstoke Band 24.
- (120) Development Report to Qualify the new Vaposhield Base Laminate, by Techniplex Dated 24/07/2002.
- (121) Development Report to Qualify the new Vaposhield Base Laminate, by Techniplex Dated 11/10/2002.

- (122) Vaposhield Qualification Line Trial Protocol PK/2003/060, Japanese Evista on the Noack 623 Blister Machine, by K.Allen & B.Scott.
- (123) Technical Memorandum – Approval of an Alternative Alcar Base Laminate (Vaposhield) Manufactured by Tecniplex, for use at Brecon Pharmaceuticals, Dated Sept 2003.
- (124) Eli Lilly & Co. Global Packaging Technology & Development Test Report 02-54 – Vaposhield base laminate Qualification, Dated 7th Aug 2002.
- (125) Eli Lilly & Co. Global Packaging Technology & Development Test Report 04-12 – Vaposhield base laminate Qualification, dated 7th Aug 2004.
- (126) Eli Lilly & Co. Global Packaging Technology & Development Test Report 03-126 – Vaposhield base laminate Qualification, dated 7th Aug 2003.
- (127) Vaposhield Qualification Line Trial Protocol PK/2003/061, Japanese Zyprexa on the Noack 760 Blister Machine, by K.Allen & B.Scott.