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Glucose diffusion in tissue engineering membranes and scaffolds

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Glucose diffusion in tissue engineering membranes and scaffolds

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Abstract: Tissue engineering has evolved into an exciting area of research due to its potential in regenerative medicine. The shortage of organ donors as well as incompatibility between patient and donor pose an alarming concern. This has resulted in an interest in regenerative therapy where the importance of understanding the transport properties of critical nutrients such as glucose in numerous tissue engineering membranes and scaffolds is crucial. This is due to its dependency on successful tissue growth as a measure of potential cure for health issues that cannot be healed using traditional medical treatments. In this regard, the diffusion of glucose in membranes and scaffolds that act as templates to support cell growth must be well grasped. Keeping this in mind, this review paper aims to discuss the glucose diffusivity of these materials. The paper reviews four interconnected issues, namely, (i) the glucose diffusion in tissue engineering materials, (ii) porosity and tortuosity of these materials, (iii) the relationship between microstructure of the material and diffusion, and (iv) estimation of glucose diffusivities in liquids, which determine the effective diffusivities in the porous membranes or scaffolds. It is anticipated that the review paper would help improve the understanding of the transport properties of glucose in membranes and scaffolds used in tissue engineering applications.

Keywords: diffusion; glucose; membrane; scaffold; tissue engineering.

1 Introduction

Organ shortage and failures due to accidental and illness incidences have been a concern in almost every part of the world. Organ transplantation has been a common practice

in clinical settings and has been reported to be successful as early as the 1960s (Couch et al. 1966). Although it has been perceived to be successful, it also has its limitations, e.g. long patient waiting time and death of organ donors (Liu et al. 2013, Guo and Ma 2014). To overcome these limitations, engineers, biologists, chemists, and material experts have come together to create the tissue engineering (TE) approach as an alternative to organ transplantation, which provides a cost-effective treatment, resulting in improved health care and quality of lives of the patients. TE is therefore defined as a multidisciplinary field that helps to repair, replace, and restore the original functions of damaged tissues (Langer and Vacanti 1993, Liu et al. 2013). A simple illustration of TE principles is shown in Figure 1. As the figure shows, TE approach aims to mimic the *in vivo* environment to help in cell proliferation and differentiation into tissues and consequently tissue regeneration (Tabata 2014). In brief, living cells are harvested from a patient's body of relative excess followed by expansion of these cells *in vitro*. The cells are then loaded on tissue engineered scaffolds, which act as a template for cell growth in a process known as cell seeding. The cells are grown with the supply of nutrients (e.g. glucose and oxygen) and monitored for its physiologically relevant standards for bone TE (BTE) in terms of cell-cell and cell-matrix interactions as well as possessing the nanostructural and chemical extracellular matrices (ECMs) (Zhu et al. 2015) as found in the native ECM of the body. Surgical implantations into the host body are carried out, and finally, the functionality of the regenerated tissue is observed *in vivo*.

Due to its numerous successes, TE has become the leading choice in the field of regenerative medicine (Khaled et al. 2011). The main goal of TE is to produce an alternative that can overcome the limitations of traditional treatments and possess a good potential to eventually form an “artificial” organ that resembles the original organ in terms of function and ability. Furthermore, it is envisaged that a TE approach presents a permanent cure without the need for follow-up therapies (Langer and Vacanti 1993, Patrick et al. 1998). For example, BTE, which has been reported since the early 1980s (Amini et al. 2012), has become a substitute for bone grafting.

TE researchers have shown the possibility of growing artificial tissues both *in vitro* and *in vivo*, e.g. bone,

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Figure 1: Basic principles of TE (Vindigni et al. 2011; reproduced with permission of InTech publisher under CC BY-NC-SA 3.0 license. Available from <http://dx.doi.org/10.5772/24899>).

cartilage, tendon, and blood vessel tissues (L'Heureux et al. 2007, Schulz et al. 2008, Abousleiman et al. 2009, Grayson et al. 2010, Kimelman-Bleich et al. 2011, Omae et al. 2012). However, it is proven difficult to grow tissues *in vitro* than *in vivo* due to the absence of a natural capillary network that supplies nutrients (e.g. glucose) and removes waste products (e.g. lactic acid) as well as the inaccessibility of a controlled environment during cell cultivation (Li et al. 2014). Hence, the idea of growing artificial tissues in bioreactors has been introduced.

Bioreactors are defined as a growth kit that helps to monitor and control necessary conditions for cell growth (e.g. pH, pressure, temperature, nutrient supply, and removal of waste product) as well as synchronising both biological and biochemical processes involved in cell culture (Gardel et al. 2014). There have been several reported studies that show the development of these bioreactors to grow 3D tissues, such as spinner flasks (Page et al. 2013), rotating vessels (Nishi et al. 2013, Chao and Das 2015), and flow perfusion systems (Baptista et al. 2013). Although these bioreactors satisfy tissue engineers to the extent of improved tissue growth, they may still not be able to sustain the cell culture environments (Li et al. 2014). One of the reasons is due to the limited nutrient diffusion in the scaffold and membrane in the bioreactor.

An example of a bioreactor where the issues with limited mass transfer has largely been overcome is hollow

fibre membrane bioreactors (HFMBs) (Abdullah et al. 2006, Das and Jones 2006, Ye et al. 2006, Das 2007, De Napoli et al. 2011, Mohebbi-Kalhari et al. 2012). The presence of a network of hollow fibre membranes in the bioreactor allows nutrients (e.g. glucose) to diffuse into the scaffolding matrix and membrane and remove waste products produced by the cells (e.g. lactic acid) (Ye et al. 2006). This therefore allows a nutrient circulation system identical to that in the natural tissue to be generated, consequently creating better mass transfer behaviour and allowing high nutrient concentration to be maintained in HFMBs (Abdullah and Das 2007, Pearson et al. 2013, De Napoli et al. 2014, Misener et al. 2014).

Mass transfer behaviour in TE bioreactors is generally governed by one or more than one of the following processes, namely, convection, diffusion, and reaction. Convection refers to the coupled mass transport due to fluid flow (i.e. advection) and diffusive transport, while diffusion refers to the transport of molecules due to concentration gradient alone. Reaction is illustrated by the formation of a new product (for e.g. C) as a result of a chemical or metabolic reaction. An example of a bioreactor that involves all three processes is the HFMBs. Figure 2 shows a schematic drawing that reveals the three main sections, mainly, the extracapillary space (ECS), which can be referred as scaffold; membrane; and lumen. In the figure, R_1 refers to the fibre lumen radius, while R_2 illustrates R_1 and the thickness of the membrane wall. R_3 represents R_2 and the ECS thickness, while L refers to the fibre length. As for A_1 , A_2 , and A_3 , they refer to the lumen, membrane wall, and half of the ECS, respectively.

Figure 2: Schematic diagram showing a single hollow fibre.

According to Ye et al. (2006), Das (2007), and Abdullah et al. (2009), the transport of a solute in the fibre lumen region is governed by advection and diffusion, but the advective process dominates the diffusive process. In the membrane region, solute transport is governed by diffusion only. In the ECS, the solute transport is governed by reaction and diffusion processes; however, reaction process dominates the diffusive transport.

A surge of interest has been observed in trying to understand the mass transfer behaviour in TE bioreactors (Khaled and Vafai 2003, Khanafer and Vafai 2006, Wang et al. 2009, Podichetty et al. 2014). In the last two decades, the use of membranes and scaffolds as a synthetic ECM for TE studies has also gained popularity, which is evidenced from the increasing number of publications (Figure 3A and B). The TE discipline has grown remarkably and the significance of understanding the importance of TE applications is demonstrated by the fact that the number of patients waiting for transplants is almost doubled to those who actually received the transplants, as shown in Figure

4 (Regional data, United Network for Organ Sharing). This trend continues, where only 27,036 people received transplants, while 77,917 people were on the waiting list, from January 2014 to November 2014.

To combat this challenge, numerous studies have been conducted to enhance the understanding of the field of regenerative medicine; more specifically, in the field of TE and research has already indicated the necessity of a bioreactor system, which is essential for a controlled environment during cell cultivation (Li et al. 2014).

One of the key features of most TE bioreactors is the use of membrane and scaffold, which acts as a support for cells to grow into new tissues before being implanted into the host tissue. One of the important criteria of this support system is the highly porous structure for ease of nutrient diffusion, particularly glucose, to produce a 3D structure of new tissues (Deans et al. 2012, Florkczyk et al. 2013, Guan et al. 2013). Table 1 shows some typical examples of morphological structures of membrane/scaffold materials that can have an effect on the nutrient diffusion for cell growth. These will be discussed later in the paper. Please note that the materials presented in Table 1 might not be necessarily used in TE applications. The objective here is to show the variation of morphological structure of various kinds of membranes/scaffolds, which can affect the solute diffusivity.

Since solute diffusion is dependent on the material morphology, there is not a particular membrane structure for better glucose diffusion; however, based from extensive literature studies, hollow fibre membranes seem to illustrate a promising indication for enhanced glucose

Figure 3: (A) Overview of the number of papers published with regard to TE membranes and scaffolds during the last 18 years (key words: membranes and scaffolds for TE; search engine: www.scopus.com). (B) Overview of the number of papers published with regard to glucose transport in TE materials during the last 18 years (key words: glucose transport in TE membranes and scaffolds, tissue bioreactors; search engine: www.scopus.com).

Figure 4: Overview of the number of patients on the waiting list, received transplants, and the donor statistics from 2000 to 2014 (data collected from www.unos.org).

Table 1: Some examples of membranes showing different morphological structures.

Membrane type	Schematic of cross-section	References
Poly(trimethylene terephthalate) (PTT) nanofiber membrane		Li et al. (2013), Xue et al. (2010)
Thin film composite (TFC) membrane		Han (2013)
PSf membrane		Crock et al. (2013), Zhao et al. (2011)
Poly(vinylidene fluoride) (PVDF) hollow fibre membrane		Sukitpaneenit and Chung (2009), Zhang et al. (2013a,b), Liu et al. (2009)
PVDF membrane		Lin et al. (2002), Li et al. (2012)
Polyethersulfone (PES) membrane		Madaeni and Bakhtiari (2012), Rahimpour et al. (2012), Daraei et al. (2013)
Poly(amide-imide) (PAI) hollow fibre membrane		Setiawan et al. (2011), Zhang et al. (2011)
Ceramic asymmetric membrane		Kim and der Bruggen (2010), DeFriend et al. (2003), Tsuru et al. (2001)
Cellulose acetate blend membrane		Han et al. (2013), Mohammadi and Saljoughi (2009)

Different morphological structures of these materials affect the glucose diffusivity through the materials.

delivery into the cells (Abdullah and Das 2007, Bettahalli et al. 2011a,b, Diban and Stamatialis 2014, Wung et al. 2014). Hollow fibre membranes have a large surface area-to-volume ratio, therefore allowing a relatively high flow rate of culture medium containing glucose to be maintained. The basic building blocks of any membrane material are usually non-periodic and display heterogeneity in nature as they vary within the same material, or from one material to another, which defines the non-linear and non-monotonic relationship between membrane material and glucose transport. If the membrane/scaffold material is less tortuous and more porous, the glucose diffusion is smoother than one in a more tortuous structure, which would limit the glucose diffusion. However, there is a possibility that the glucose diffusion may be enhanced especially in hydrophilic materials, but the results of Suhaimi et al. (2015b) indicated no difference between hydrophobic and hydrophilic materials with regard to diffusivity data. In this work, they investigated the glucose diffusion in both hydrophobic and hydrophilic materials, and their results showed that instead of a difference in diffusivity data due to hydrophobic and hydrophilic nature, the difference in the morphological structure of the materials was deduced as the primary factor for different diffusivity data presented in their work.

In a TE process, the supporting template for cell growth plays a crucial role in cell attachment, differentiation, and proliferation (Guo and Ma 2014). Researchers have identified several important characteristics which scaffolds must have, e.g. (1) biocompatibility and biodegradability, (2) high porosity and connectivity of pores for diffusion, (3) appropriate surface chemistry and surface topography for cellular interaction, (4) good mechanical properties for regeneration, and (5) low/no adverse response (Hutmacher 2001, Yang et al. 2001, Holzwarth and Ma 2011). Due to the importance in TE processes, several different materials have been investigated to develop potential scaffolds, such as ceramics (e.g. hydroxyapatite and tricalcium phosphate) and polymers (Sachlos and Czernuszka 2003, Guo and Ma 2014). For example, polymers have been reported to have a greater potential as scaffolds for TE purposes due to its processing flexibility and biodegradability (Nair and Laurencin 2007). Synthetic polymers such as aliphatic polyester (e.g. polyglycolic acid, polylactic acid [PLLA], and polycaprolactone [PCL]), polyanhydrides, polyphosphazenes (e.g. alanine and phenylalanine alkyl ester), polyurethanes (PUs) and poly(glycerol sebacate), and natural polymers such as collagen are some of the most commonly used polymers as scaffolds for TE (Freed and Vunjak-Novakovic 1998, Agrawal and Ray 2001, Hutmacher 2001, Sachlos and Czernuszka 2003, Nichol

et al. 2013, Guo and Ma 2014, Suhaimi et al. 2015b). Melt moulding, solution casting, phase separation, solvent-casting particulate-leaching, emulsion freeze drying, fibre meshes/fibre bonding, freeze drying, and gas foaming are some conventional scaffold fabrication techniques cited in the literature (Sachlos and Czernuszka 2003).

Meneghello et al. (2009) fabricated poly(lactic-co-glycolic acid)/polyvinyl alcohol (PVA) blended hollow fibre membranes, where the results demonstrated that 5% (w/w) addition of PVA helped to better transport the cell culture medium (CCM) and its constituents. Bettahalli et al. (2011a,b) developed polylactic acid (PLLA) hollow fibre membranes to test the delivery capability of these membranes to diffuse nutrients to the cells. Results showed that the transport of nutrients was high at a rate of 1963 l/(m² h bar). In the same year, De Napoli et al. (2011) investigated cell growth in layers of medical microporous polypropylene hollow fibre membranes, and the results showed cells formed thick multilayer among the membranes. More recently, Bettahalli et al. (2014) developed a multilayer scaffold by rolling PLLA electrospun sheets with a multibore hollow fibre membrane, and the results showed that the concept illustrated a good potential for developing complex and thicker tissues. Diban et al. (2014) developed a biodegradable poly(ϵ -caprolactone) scaffold, and results indicated good cell attachment, proliferation, and penetration into the scaffold. Permeance tests also indicated high water permeabilities, which is a positive indication of nutrient delivery into the cells.

Earlier, Ellis and Chaudhuri (2007) developed a HFMB based on poly(lactide-co-glycolide) (PLGA) sheets. Their results showed that varying the air gap and spinning temperature significantly changed the morphology of the hollow fibre membrane scaffold, allowing larger macrovoids and thicker skin formed. This is one step forward in addressing the size limitations in tissue engineered constructs for clinical practice. Chaudhuri et al. (2008) fabricated honeycomb-structured poly(DL-lactide) and poly[(DL-lactide)-co-glycolide] films using water droplet templating method. Osteoblast cells were able to attach and proliferate on these films, suggesting the potential of its application as TE scaffold. In the same year, Ellis and Chaudhuri (2008) studied the combination of three different lactide:glycolide ratios, and results showed that any ratio was able to support bone regeneration *in vitro*. Freed et al. (1993) and Galban and Locke (1999) considered the diffusion of nutrients such as glucose and oxygen in porous scaffolds, and both indicated that restriction diffusion of nutrients did limit cell growth, although it may not be the only limiting factor.

Since by definition a porous medium consists of a network of open spaces, in which a network of pores and fibres for membranes and scaffolds exists, the molecular diffusion is interrupted by the tortuous channels, and the combination of both porosity and tortuosity characterizes the morphological structure of the porous media (Figure 5). A relationship that takes into account the mass transport by diffusion, porosity, as well as the tortuosity, is summarized in Eq. (1):

$$D_e = D \frac{\varepsilon}{\tau}, \quad (1)$$

where D_e is the effective diffusion coefficient of the solute in membranes or/and scaffolds, D is the self-diffusion coefficient of the solute in the liquid that fills the pores, and ε and τ are the porosity and tortuosity of the material, respectively, with the assumption that the average pore diameter, d , is much greater than the mean free path of the solute diffusing in the given liquid.

Keeping these aspects in mind, the present review aims to give an overview of the diffusion of glucose in membranes and gels/scaffolds for TE applications as well as the self-diffusion of glucose in liquid. In effect, the review is divided into sections that represent the four terms in Eq. (1). Firstly, the paper will discuss the measurements of diffusion of glucose in membranes/scaffolds using various methods available. Secondly, it will deal with the techniques available to measure porosity and tortuosity of the porous media. Thirdly, the review will cover the effects of microstructure on the diffusion process. Lastly, the different methods available for the estimation of glucose self-diffusion in liquids will be reviewed briefly, given that their understanding is also required to quantify the effective diffusion of glucose in the membranes/scaffolds.

Figure 5: A representation of liquid diffusional pathway in porous media.

The field of TE holds a promising future in such a way that there are some health conditions that cannot be cured just by prescribing some medicines and drugs, such as liver failure and spinal cord failure (Langer 2009). When this happens, apart from organ transplants, which induce immunological responses to name a few, TE is the only hope that remains. It is greatly hoped that the present review will help in understanding the diffusion of nutrient and its effects on the membrane and scaffold microstructure, specifically, and in the field of TE, generally.

2 Measurements of glucose concentration or diffusivity

Numerous glucose diffusion studies have been reported for a vast number of applications ranging from TE (Hannoun and Stephanopoulos 1986, Weng et al. 2005, Rong et al. 2006, Papenburg et al. 2007, Wang et al. 2009, Jin et al. 2010, Podichetty et al. 2014), diabetes management (Maier et al. 1994, Wang and Musameh 2003, Boss et al. 2012), modern laser medicine (Chance et al. 1995, Liu et al. 1996, Tuchin et al. 1997, Wang 2000, Vargas et al. 2001, Yao et al. 2002, Bashkatov et al. 2003), pharmaceuticals (Andersson et al. 1997), chemical engineering, filtration (Yaroshchuk et al. 2011, Adams et al. 2013), oil and fat industry (Miyagi et al. 2012), and water desalination (Lonsdale et al. 1965, Sherwood et al. 1967). A review of these studies suggests that a number of different techniques could be applied to measure glucose concentration or diffusivity as discussed below.

2.1 Needle enzyme electrodes

A number of papers have been reported on the use of needle enzyme electrode to observe glucose diffusion. For example, Rong et al. (2006) presented an interesting work to measure directly the transient glucose concentration at the centre of a specially compressed and rolled collagen gel using needle enzyme electrodes. They first stabilised and calibrated the needle electrodes. Glucose was then oxidised by glucose oxidase enzyme solution to hydrogen peroxide, which was further oxidised to form an amperometric current. The current was read by an AUTOLAB PGSTAT10 potentiostat instrument. They also proposed a computational model to fit the simulated concentration profile to the experimental results. The glucose diffusion coefficient was estimated to be $1.3 \times 10^{-10} \text{ m}^2/\text{s}$ (Table 2) in the chosen gel,

Table 2: Examples of measured glucose diffusivity values for typical TE membranes and scaffolds.

Scaffold/membrane	Temperature (°C)	Porosity (%)	Methodology	Effective diffusivity ($10^{-10} \text{ m}^2/\text{s}$)	References
PLLA scaffold					
Ethanol	23	84.3±2.1	Diffusion cell – samples were analysed using an ultraviolet spectrophotometer at $\lambda=450 \text{ nm}$	0.15±0.5	Papenburg et al. (2007)
	23	82.6±0.7		0.33±0.1	
	4	75.2±1.6		1.04±4.5	
Isopropanol	23	86.0±0.8		0.26±0.2	
	23	86.0±1.2		0.64±1.7	
	4	83.0±2.6		0.86±1.5	
Inverted colloidal crystal (ICC) scaffold	25	NA	Computer simulation	3	Shanbhag et al. (2005)
Hydroxypropyl chitosan/gelatin/chondroitin sulfate (HPCTS/GEL/CS) scaffold	37	NA	Diffusion cell – samples were reacted with dinitrosalicylic (DNS) acid at 540 nm	1.16±0.11	Wang et al. (2009)
Poly(ϵ -caprolactone) (PCL) scaffold	37	80	Diffusion cell	1.78±0.50	Suhaimi et al. (2015b)
PLLA scaffold		80		1.39±0.28	
Collagen scaffold		72		37.1±2.78	
Polyvinylidene fluoride membrane	37	69	Diffusion cell	0.768±2.78	Suhaimi et al. (2015b)
Cellulose nitrate membrane		64		0.891±0.80	
Nanoporous polyethylene membrane	37	28.9±0.7	Diffusion cell – samples were analysed using a refractometer at 589.3 nm	0.18	Boss et al. (2012)
Asymmetric alumina membrane				1.39	
PSf membrane	20	NA	Diffusion was analysed based on a solution-diffusion model using a six cross-flow cell unit	0.07933	Adams et al. (2013)
PSf 5% β -cyclodextrin PU (β -CDPU) membrane				0.029	
PSf 8% β -CDPU membrane				0.183	
PSf 10% β -CDPU membrane				0.172	
Collagen scaffold	NA	NA	Needle enzyme electrodes	1.33	Rong et al. (2006)
Dextran-tyramine scaffold	NA	NA	Diffusion cell	3.2	Jin et al. (2010)
0.5% Agarose scaffold	25	NA	Refractive index	6.26	Weng et al. (2005)
1.5% Agarose scaffold				5.73	
N-isopropylacrylamide scaffold	10	NA	Diffusion cell connected to a computer	2.7±0.13	Andersson et al. (1997)
	20			3.74±0.20	
	30			4.65±0.57	

and the authors concluded that potential errors sourced from noise, baseline, and zero time determination were able to be kept as minimum as possible and consequently resulted in higher accuracy. Wang and Musameh (2003) conducted a study on needle enzyme electrodes to observe the potential of this technique for continuous monitoring of glucose, and results demonstrated positive response for future use. Fang et al. (2014) fabricated a glucose electrode coated with PLGA biodegradable membrane to test the long-term stability of the electrode in bovine serum at 37°C. The condition was to mimic the *in vivo* environment, and their results showed that 80% of its sensitivity was retained after 44 days inside the serum. They concluded that glucose sensors exhibited a good potential for real-time measurements of glucose concentrations inside the body. Glucose biosensors have been developed for over 50 years, with the aim of continuous measuring of glucose level. An error of <20% for glucose concentrations ranging between 1.65 and 22 mmol/l should be followed as recommended by the U.S. Food and Drug Administration (Yoo and Lee 2010). Needle enzyme electrode is seen as a good and reliable biosensor for measuring glucose concentration both *in vitro* and *in vivo*.

2.2 Diffusion cell

Diffusion cell technique has been used regularly used since Hannoun and Stephanopoulos (1986) measured both ethanol and glucose diffusivities in calcium alginate membranes, both seeded and not seeded with cells. More recently, Jin et al. (2010) studied the diffusion of glucose in different molecular weights of dextran-tyramine hydrogels to determine the ability of these hydrogels as injectable scaffolds for TE applications. They used a diffusion cell consisted of two chambers with identical volumes. Both chambers were filled with glucose solution and distilled water, respectively. The diffusion cell was subjected to a 37°C water bath. The concentration of glucose in both chambers were analysed using an ultraviolet spectrophotometer at a wavelength of 450 nm. Jin et al. (2010) also employed an enzyme-based system to help measure the glucose concentration. As what can be expected of diffusion work in similar cases, the glucose concentration in the glucose-solution-filled chamber decreased, while that of the distilled-water-filled chamber increased accordingly before reaching a plateau after 3 days. They also concluded that different molecular weights and degree of substitution of TA groups work well with glucose diffusion, where in all cases, over 70% of glucose diffused was observed.

Papenburg et al. (2007), in an attempt to observe the glucose diffusion in their own fabricated PLLA micropatterned sheets, also employed a diffusion cell. The glucose diffusion coefficient was measured to be $0.8\text{--}0.1\times 10^{-10}\text{ m}^2/\text{s}$ (Table 2). Boss et al. (2012) used the diffusion cell to measure the glucose diffusion coefficient across nanoporous alumina membrane, and results showed a value of $1.35 (\pm 0.31)\times 10^{-10}\text{ m}^2/\text{s}$ (Table 2). More recently, Suhaimi et al. (2015b) adopted the diffusion cell method to determine the glucose diffusion coefficient in typical TE membranes and scaffolds (Figure 6) saturated with water and cell CCM. Their results demonstrated reduced glucose diffusivities in materials saturated with CCM (e.g. from $1.20\pm 0.38\times 10^{-10}\text{ m}^2/\text{s}$ to $0.728\pm 3.37\times 10^{-10}\text{ m}^2/\text{s}$ for polyvinylidene fluoride membrane). Diffusion cell method is valid under the assumption of steady-state systems, which make use of Fick's first law to measure the glucose diffusivity.

2.3 Refractive index method

A group of researchers (Weng et al. 2005) attempted to further understand the glucose behaviour in agarose gel, which has a significant effect in molecular diffusion research in general and TE in particular. For this particular work, they adopted a refractive index method as a means to measure the glucose diffusion coefficient in the agarose gel. The gel was contained inside a triangular cell, where it was later immersed into the glucose solution. When this happened, the change of light was captured by a charge-coupled device (CCD) camera and post processed with specific software. The source of light came from a He-Ne laser. This method presents some advantages over others due to its capability to measure concentration *in situ* without interrupting the process as well as the simple post processing work thereafter. As such, the method has been used since in the early 1990s up until recently (Maier et al. 1994, Chance et al. 1995, Liu et al. 1996, Tuchin et al. 1997, Wang 2000, Vargas et al. 2001, Yao et al. 2002, Bashkatov et al. 2003, Zhang et al. 2013a,b, Trichet et al. 2014, Ullah et al. 2014, Pleitez et al. 2015).

In general, when light passes through a prism, some, if not all, will be refracted back in what is known as refractive angle. This refractive angle resembles refractive index of the prism. Weng et al. (2005) indicated in their work the success of monitoring glucose transport in the agarose gel as well as determining the diffusion coefficients using the method. They deduced $5.73\times 10^{-10}\text{ m}^2/\text{s}$ (Table 2) as the diffusivity in 1.5% agarose gel at 25°C. This figure is comparable to the value of Andersson and Oste (1994), whose work

Figure 6: SEM micrographs showing the surface morphology of (A) polyvinylidene fluoride (PVDF) membrane, (B) cellulose nitrate membrane, (C) poly(caprolactone) scaffold, (D) poly(L-lactide) scaffold, and (E) collagen scaffold (Suhaimi et al. 2015b).

monitored the glucose diffusion in 1.2%–3.6% agarose gel at 25°C using a steady-state diaphragm cell. The obtained diffusion coefficients were around $4.25\text{--}6.15 \times 10^{-10} \text{ m}^2/\text{s}$, which is close to what Weng et al. (2005) obtained. Another pertinent work by Li et al. (1996) can be taken as a comparison, where they observed the glucose diffusion in 0.197% agarose gel at 37°C. The comparison indicated that the obtained glucose diffusivity was at least 50% more

than what Weng et al. (2005) obtained. They also compared the diffusivities of glucose in 0.5% and 1.5% agarose gel, and as expected, 0.5% agarose gel showed a slightly higher diffusion coefficient of $6.26 \times 10^{-10} \text{ m}^2/\text{s}$ due to lower polymer content, resulting in higher glucose mobility.

In 2006, Liang et al. (2006) attempted to improve the *in situ* refractive index method with temperature-controlled capability. They used protein instead of glucose to

measure the diffusion coefficient in agarose gel. Results proved that this improved method was reliable in measuring the protein diffusion at different temperatures. There seems to be no recent study reported on the use of refractive index method to monitor the glucose diffusion in TE materials. However, this method has been used recently to measure glucose level in tissue sample, and one such study is reported by Ullah et al. (2014), where they used the refractive index method to measure the glucose level in mouse blood. The aim of their study was to further understand the use of laser applications to determine blood glucose levels without incision. Their results showed a positive indication for future applications. This technique is suitable for materials such as transparent gel-like scaffolds since it involves light transmission from and to the solute molecules in the gel to capture the speed.

2.4 Dispersion model method

Apart from the polymer content of a gel matrix, the working temperature of the diffusion process also has an impact on the diffusing solute molecules. Andersson et al. (1997) conducted a temperature-dependent study on the effect of glucose diffusion at 10°C, 20°C, and 30°C in a swelling *N*-isopropylacrylamide gel using a dispersion model method. They noted in their report that due to dispersion and time delay during the actual experiment, the concentration recorded by the detector was different to the *in situ* concentration in the diffusion cell. For these reasons, they fitted the experimental concentration profiles into a mathematical model that corrected both the dispersion and time delay factors. The calculated diffusion coefficients of glucose at 10°C, 20°C, and 30°C are summarized in Table 3. They concluded that the glucose diffusivity agreed with Wilke-Chang temperature correlation (Wilke and Chang 1955), suggesting that the change in diffusivity was mostly due to the change in temperature, not due to the degree of gel swelling. On the other hand, Podichetty et al. (2014) reported that the use of dispersion model coupled with residence time distribution analysis to observe the distribution of glucose in PCL scaffold

and chitosan-gelatin scaffold. Their results showed that the surface properties of scaffolds had an effect on the glucose distribution and concluded that the combined approach gave useful insights to designing bioreactors for tissue regeneration. Since this method combines both experimental and modelling approaches, the mathematical model is validated by experimental measurements. The method is valid for small molecule in diluted and uncharged gel systems.

2.5 Six cross-flow cell unit method

A number of studies of glucose transport through different types of membranes have been carried out, but no or little work has been reported on the glucose diffusion in polymeric/cyclodextrin mixed-matrix membranes. Thus, Adams et al. (2013) presented a noble work on the transport of glucose through polysulfone (PSf)/ β -cyclodextrin PU mixed-matrix membranes of three different PSf concentrations. The surface morphology of the mixed-matrix membranes showed uniformly sized circular voids of a smooth structure (Figure 7).

Before conducting the investigation, the membranes were subjected to a pressure of 3.10 MPa for a period of 2 h, and, specifically for diffusion experiments, they were conditioned to a pH of 6.89 and a temperature of 20°C. The diffusion coefficients of glucose were calculated based on Fick's diffusion law assuming the concentration difference was the sole driving force. The corresponding diffusion coefficients are shown in Table 4. The authors concluded that mixed-matrix membranes performed well in diffusing glucose due to its increased hydrophilicity as well as its crystal structure. This method, which applies solution-diffusion system, is typically applicable for non-porous membranes in which the difference between solubility and diffusivity leads to separation of permeates. Table 2 summarises the different methodologies used for measurements of glucose diffusion in various membranes and scaffolds as well as the corresponding effective diffusion coefficients values from these studies.

Table 3: Effective diffusivities of glucose in swelling *N*-isopropylacrylamide gel (Andersson et al. 1997).

Temperature (°C)	Effective diffusivity (m ² /s)
10	$2.70 (\pm 0.13) \times 10^{-10}$
20	$3.74 (\pm 0.20) \times 10^{-10}$
30	$4.65 (\pm 0.57) \times 10^{-10}$

3 Porosity and tortuosity of TE membranes and scaffolds

Besides the interactions between the diffusing solute and the porous network in membranes and scaffolds, the amount of void spaces (porosity) and the tortuous path length (tortuosity), which increases the distance a

Figure 7: SEM micrographs showing surface morphology of (A) PSf membrane, (B) PSf 5% β -cyclodextrin PU (CDPU) membrane, (C) PSf 8% β -CDPU membrane, and (D) PSf 10% β -CDPU membrane (Adams et al. 2013; reproduced with permission of Elsevier).

Table 4: Glucose diffusivities in mixed-matrix membranes (Adams et al. 2013).

Membrane type	Effective diffusivity (m^2/s)
PSf	0.0793×10^{-10}
PSf 5% β -cyclodextrin PU (β -CDPU)	0.0290×10^{-10}
PSf 8% β -CDPU	0.1833×10^{-10}
PSf 10% β -CDPU	0.1717×10^{-10}

molecule has to traverse through the pore network, also have significant effects on the mass transport.

Porosity can be determined using either indirect or direct techniques. Examples of indirect techniques include liquid permeability (Palacio et al. 1999), permporometry (Mey-Marom and Katz 1986), air-liquid porometry (Hernandez et al. 1996), liquid-liquid porometry (Bechhold et al. 1931), scanning electron microscopy (SEM) (Riedel and Spohr 1980), transmission electron microscopy (TEM) (Nakao 1994), atomic force microscopy (AFM) (Binnig et al. 1986), field emission SEM (FESEM) (Dietz et al. 1992), thermoporometry (Brun et al. 1977), and gas adsorption-desorption

(Dollimore and Heal 1964, Gregg and Sing 1982). On the other hand, pycnometric methods, mercury intrusion, and apparent density estimation are some examples of direct techniques for measuring porosity (Palacio et al. 1999).

Comparisons between using direct and indirect techniques will be highlighted here. While the pycnometric method appears to be easy and simple, it can lead to hydration problem, which will have a significant effect on the porosity determination. Instead of wetting the porous material with water, mercury as the wetting agent has been proven to be more precise (Liabastre and Orr 1978). However, only certain pore sizes are able to work well with Hg-porosimetry due to a considerable amount of pressures needed to infuse mercury into very fine pores. Apparent density estimation is also another simple and easy method to comprehend, yet it tends to overestimate porosities, which may be due to hydration and the presence of contaminants as well as non-pure materials, whose densities are unaccountable for in the calculation of porosity. A common setback of using these direct techniques is the ability to detect non-active pores or dead-end pores in the porous materials.

Microscopic methods such as SEM, TEM, AFM, and FESEM present surface and cross-section micrographs of the porous material, and these images can be uploaded onto a computer and analysed using special software that enable surface porosity to be determined easily. However, the bulk porosity requires the cross section images to be captured at certain angles, which will eventually distort the overall structure. The air-liquid and liquid-liquid porometry techniques require two steps: the first one is to produce a flow graph against pressure or the resulting pore diameter, which can be deduced using Washburn equation (Washburn 1921). This step requires a suitable air and liquid to be pressurised in order to diffuse into the pores, while the second step involves integrating the cross-section area of the pore diameter, which results to porosity determination.

Palacio et al. (1999) reported the outcome using a gas penetration method in view of experimental and nominal porosities, and they acknowledged the difference between these two. This may be due to a lack of information from the manufactures on the techniques used to obtain the nominal values; therefore, comparisons of using the same method to confirm the porosity values are not possible. The nominal values are merely a representative for the same batches of the same membrane material and therefore cannot be truly justified. This method is preferred if all voids are to be investigated and also benefits from minimising structure distortion as only minimal pressures are required.

Tortuosity is defined by the increased distance that the diffusing solution has to travel due to pore bending and curves. Porosity, diffusion coefficient, and tortuosity are correlated (Van Cappellen and Gaillard 1996), and the latter can be determined experimentally, theoretically, and empirically. Shen and Chen (2007) reviewed two experimental methods: one is the work of Sweerts et al. (1991) aimed at determining the ratio of diffusivity in free media to the diffusivity in a porous material of known porosity, while the other one is the work of McDuff and Ellis (1979) aimed at determining diffusivities of marine sediments. They linked tortuosity to a formation factor obtained via electrical resistivity measurements. The former is time consuming while the latter needs electrical resistivity probes.

Theoretical methods of correlating porosity and tortuosity are generally based on the assumption of an idealised porous medium with the absence of adjustable parameters. Examples of such models can be seen in the works of Bhatia (1985), Dykhuizen and Casey (1989), and Petersen (1958). In contrast to the theoretical method, the empirical method encompasses adjustable parameters

Table 5: Porosity-tortuosity relations for idealised porous materials.

Relation	References
$\tau = 1 - 0.41 \ln \varepsilon$	Comiti and Renaud (1989)
$\tau = 1 - 0.49 \ln \varepsilon$	Mauret and Renaud (1997); Barrande et al. (2007)
$\tau = 1/\varepsilon^{0.33}$	Bear (1972); Dullien (1975)
$\tau = 1 + 0.8(1 - \varepsilon)$	Koponen et al. (1996)
$\tau^2 = 1 - \ln(\varepsilon^2)$	Boudreau (1996)
$\tau = \frac{\varepsilon}{1 - (1 - \varepsilon)^{1/3}}$	Beeckman (1990)

that differ in values in traditional literatures. The first reported work involving the empirical method is the work of Archie (1942). Some examples of the relationship between porosity and tortuosity for idealised porous material can be found in Table 5.

Suhaimi et al. (2015b) determined both porosity and tortuosity values for TE membranes and scaffolds experimentally. All materials were saturated with both water and CCM at temperatures of 27°C and 37°C. Porosity was evaluated using a pycnometric method, while tortuosity was derived from the determination of the ratio of diffusivity in free media to the effective diffusivity in the porous network (i.e. TE membranes and scaffolds). The corresponding porosity and tortuosity values are shown in Table 6. They concluded that tortuosities varied with temperature as what has been reported previously (Gao et al. 2014, Sadighi et al. 2013, Sharma and Chellam 2005).

4 Microstructure and diffusion

The relationship between nutrient diffusion (i.e. glucose in this paper) and membrane/scaffold morphology or tissue morphology is crucial for better understanding the transport behaviour of the nutrients. In addition, it will help to further improve the computational modelling work with regard to nutrient supply to the cells. An example of the relationship between solute diffusivity and tissue morphology is shown in the work of Shi et al. (2013). Temporomandibular joint (TMJ) disc, a fibrocartilaginous tissue, was taken as their tissue sample and five regions, namely, anterior, medial, intermediate, lateral, and posterior in three orthogonal orientations: medial-lateral, anterior-posterior, and superior-inferior were subjected to fluorescein diffusion. The diffusion process was analysed by a fluorescence recovery after photobleaching (FRAP) technique. All the tissue samples were examined using SEM for the purpose of observing the tissue morphology, that is, the collagen fibre structure (Figure 8).

Table 6: Porosity and tortuosity values in TE membranes and scaffolds (Suhaimi et al. 2015b).

Material	Porosity (%)	Tortuosity (dimensionless)			
		Water at 27°C	Water at 37°C	CCM at 27°C	CCM at 37°C
Polyvinylidene fluoride membrane	69	4.0	3.5	5.4	5.6
Cellulose nitrate membrane (CN)	64	2.4	3.1	4.8	4.4
PLLA scaffold	80	2.7	3.0	3.3	3.5
Poly(caprolactone) scaffold (PCL)	80	1.6	1.9	2.8	2.8

Shi et al. (2013) stated that the collagen fibre orientation may influence the fluorescein (a molecule that is similar to glucose in terms of molecular weight) diffusion based on the inhomogeneous and anisotropic diffusion style of the fluorescein in the TMJ tissue. Furthermore, both the anisotropic diffusion and collagen fibre orientation showed same degrees of similarity and trends in all five regions investigated. They demonstrated that the fluorescein diffusion was dependent on the composition of the region.

Another similar example can be seen in the work of Travascio et al. (2009), where they observed the diffusion of fluorescein in human annulus fibrosus (AF) via the FRAP technique. The diffusion process spanned across three regions namely inner AF (IAF), middle AF (MAF) and outer AF (OAF) in two directions, axial and radial, respectively. They concluded that their findings in a similar fashion to Shi et al. (2013), stating that a relationship between solute diffusivity in the human AF and the morphological structure and content of the tissue existed. This hypothesis was drawn based on the similar trend of both diffusivity values and water content, whereby higher water content as well as higher diffusivity value were determined in the IAF region compared to the OAF region. The morphological structure of the tissue samples was analysed using SEM (Figure 9).

An additional example that verified the relationship between transport property and morphological structure of the porous material is illustrated in the work of Li et al. (2007). They fabricated sulfonated poly(ether ether ketone ketone)s (SPEKK) membranes (Table 7) and observed the morphologies using TEM and AFM (Figure 10).

5 Glucose diffusivities in liquids

Attempts to deduce liquid diffusivities have been ongoing, dating back over many decades ago, and by far, the most frequently used method is a diaphragm cell method (DCM). The DCM has been used as early as some

60 years ago up until now (Mills 1957, Wendt and Shamim 1970, Choy et al. 1973, Tham et al. 1973, Turhan et al. 1995, Breer et al. 2014, Buzier et al. 2014) due to its precise and accurate measurements. Other methods have surfaced recently, such as Taylor dispersion method using a long capillary tube (Ribeiro et al. 2006 and 2014), static and dynamic light scattering (Soraruf et al. 2014), open-end capillary method (OECM) (Ouerfelli et al. 2014), and total internal reflection fluorescence microscopy (TIRF) (Uehara et al. 2014).

Generally, the DCM consists of two half-glass compartments with stirrers attached to both and a diaphragm in the middle to separate the content of the compartments. The diaphragm differs in every experiment, ranging from track-etched membrane, porous disk, dialysis paper, and to glass sinter membrane depending on the molecular size of the diffusing solutes. Both compartments are filled with the diffusing solution and distilled water, respectively. Samples are withdrawn from both compartments at allocated time intervals for measurement of concentration. The whole experimental set-up is conditioned to a working temperature.

The corresponding diffusion coefficient by the DCM method is given by

$$D = \frac{1}{\beta t} \ln \left(\frac{C_{\text{lower}}^0 - C_{\text{upper}}^0}{C_{\text{lower}}^0 - C_{\text{upper}}^0} \right), \quad (2)$$

where β is the cell calibration constant, which must be determined before the start of the diffusion experiment. The diaphragm cell is calibrated by performing a diffusion experiment of solute of known diffusivity at the same experimental conditions.

The Taylor dispersion method is typically used to investigate mutual diffusion coefficients of aqueous solutions. It involves a long capillary tube where it houses a number of ports for inlet point. The diffusing solution is injected into the ports and a metering pump is used to keep the flow consistent. The concentration of the dispersed injected sample is analysed by a differential refractometer

Figure 8: SEM micrographs showing the anterior-posterior–medial-lateral orientation of the collagen fibre in all five regions of the TMJ disc (Shi et al. 2013; reproduced with permission of Elsevier).

and the equivalent diffusion coefficient is calculated via the dispersion equation which followed the Gaussian concentration profile:

$$D = \frac{R^2}{48\bar{t}} \left[\frac{(1+4K^2)^{1/2} + 3}{(1+4K^2)^{1/2} + 2K^2 - 1} \right] \{1 + (1-\delta_a)^{1/2}\}, \quad (3)$$

where R and $\bar{t}$ are capillary tube radius and mean residence time, respectively, while K and δ_a are defined as follows:

$$K = \sigma / \bar{t}, \quad \bar{t} = L / \bar{u}, \quad \delta_a = (768)^2 \Theta \zeta_0$$

$$\text{and } \zeta_0 = \frac{2\sigma^2 - \bar{t}^2 + (\bar{t}^4 + 4\bar{t}^2\sigma^2)^{1/2}}{8\bar{t}^2 - 4\sigma^2}, \quad (4)$$

where σ , L , $\bar{u}$, and Θ are variance, capillary tube length, mean flow velocity, and a constant of 2.17014×10^{-5} , respectively.

Ouerfelli et al. (2014), in their report, presented the OECM for the purpose of investigating the diffusion of trivalent lanthanide and actinide ions in aqueous electrolyte solutions. They attached radioactive tracer to these solutions and deduced the diffusivity by the following equation:

$$D = 0.4053 \frac{l^2}{t} \ln \left(\frac{0.8106}{\Gamma} \right), \quad (5)$$

where l , t , and Γ are capillary length, diffusion time, and ratio of final average activity to total activity in the

Figure 9: SEM micrographs showing the axial sections of (A) IAF, (B) MAF, (C) OAF and the radial sections of (D) IAF, (E) MAF, and (F) OAF (Travascio et al. 2009; reproduced with permission of John Wiley and Sons).

Table 7: Fabrication details of SPEKK membranes (Li et al. 2007).

Membrane	Sulfonated degree (D _s)
SPEKK-1	0.78
SPEKK-2	0.97
SPEKK-3	1.23

capillary tube at initial time ($\Gamma=A(t)/A(0)$), respectively. Eq. (5) is valid only for concentrations up to 0.114 mol/l. Uehara et al. (2014) reported the diffusion of single-stranded DNA molecules (ssDNAs) in aqueous solutions by the TIRF technique (Figure 11).

The corresponding diffusion coefficients were evaluated based on their mean square displacements:

$$D=\lim_{t\rightarrow\infty}\frac{1}{2n_{\text{dim}}t}\langle r(t)-r(0)|^2\rangle, \tag{6}$$

where $r(t)$, n_{dim} , and $\langle \rangle$ are the ssDNA molecules' vector position at time t , dimension of $r(t)$, and ensemble average, respectively.

More recently, Suhaimi et al. (2015a) measured glucose diffusivity in both CCM and water (as reference fluid) using the DCM principle, and they concluded that the glucose diffusion coefficients in CCM were significantly

reduced than the ones in water. This was attributed to the higher dynamic viscosity of CCM compared to water as well as the multi-component interactions present in CCM, although the latter is believed not to be as significant as the former. While many authors assumed the diffusivity in cell culture media to be equal to that in water (Li 1982, Abdullah and Das 2007, Clark et al. 2011, Van Winkle et al. 2012), Suhaimi et al. (2015a) highlighted the significant differences between the diffusivities in both media. Table 8 summarises some examples of diffusing solutes and the corresponding diffusivity values that have been reviewed in this section.

6 Concluding remarks

Various different techniques have been used and applied to determine the effective diffusion coefficient of small solutes (e.g. glucose) in the porous material such as needle enzyme electrodes, refractive index method, dispersion model method, six cross-flow cell unit method, and diffusion cell. The suitability of each technique depends on the materials' properties to be investigated as well as the validity of each method. For example, the refractive index method is suitable only for transparent materials as light needs to transmit across the transparent gel to capture

Figure 10: TEM micrographs of (A1) SPEKK-1, (A2) SPEKK-2, and (A3) SPEKK-3 and AFM micrographs of (B1) SPEKK-1, (B2) SPEKK-2, and (B3) SPEKK-3 (Li et al. 2007; reproduced with permission of Elsevier).

Figure 11: The TIRF technique consisted of (A) optical system, (B) sealing sample solution, and (C) penetration of light (Uehara et al. 2014; reproduced with permission of the Institution of Engineering & Technology).

its speed of which refractive indexes are translated into concentration measurements. Needle enzyme electrodes, refractive index method, and dispersion model method are shown to require indirect and complicated methods for

the concentration measurements of the diffusant across the materials. On the other hand, six cross-flow cell unit and diffusion cell methods are simple and easy to use. We recommend diffusion cell as a way to investigate glucose diffusion in TE materials as it has been widely used and accepted. Moreover, this method works under the assumption of steady-state systems, which is usually the case for glucose diffusion across TE materials, as compared to six cross-flow cell unit, which involves the use of non-porous membranes. For some methods, there is only one or two studies reviewed for the particular method. As the aim of this review paper is to analyse and study methods that have been developed and used over the years in diffusivity measurements, it is still worth mentioning that even though there seems to be fewer studies reported using the methods, they can also be a potential technique for diffusivity determination.

There have been a number of equations developed and produced by various authors based on the methods studied. As such, the equations are used in different applications. For example, DCM will use Eq. (2), while the Taylor dispersion method will employ Eqs. (3) and (4). As the aim of the review paper is not to discuss which

Table 8: Typical diffusing solutes and their respective diffusivities.

Diffusing solute	Temperature (°C)	Methodology	Diffusivity ($10^{-10} \text{ m}^2/\text{s}$)	References
Chloride ion	25	DCM	20.33	Mills (1957)
Water-magnesium chloride-sodium chloride	25	DCM	0.3	Wendt and Shamim (1970)
Sodium ion	25	DCM	7.4	Choy et al. (1973)
Sodium chloride	25	DCM	14.6	Turhan et al. (1995)
Potassium chloride			18.7	
Glucose			6.6	
L-tryptophan	20		6.52	
Lysozyme			1.09	
Bovine serum albumin (BSA)			6.44	
Aqueous lactose	25	Taylor dispersion method using a long capillary tube	5.68 ± 0.035	Ribeiro et al. (2006)
Aqueous sucrose			5.25 ± 0.009	
Aqueous glucose			6.78 ± 0.020	
Aqueous fructose			6.89 ± 0.030	
Aspartic acid	25	Taylor dispersion method using a long capillary tube	8.20 ± 0.010	Ribeiro et al. (2014)
Monosodium salt			9.35 ± 0.007	
Single stranded DNA (ssDNA) molecule	NA	TIRF	2.73	Uehara et al. (2014)
Aqueous glucose in water	37	NA	9	Buchwald (2011)
Aqueous glucose in cell culture media (CCM)	37	Stokes-Einstein equation	5.926	Provin et al. (2008)
Glucose in water	27	DCM	6.98 ± 0.60	Suhaimi et al. (2015a)
	37		9.58 ± 0.13	
Glucose in CCM	27		5.67 ± 0.74	
	37		6.16 ± 1.25	

equation is the most appropriate one, as the equation used for estimating the liquid diffusivity depends on the method used, we will therefore not state it in this review paper. However, due to its simple, precise, and accurate measurements, DCM has been widely used, and hence, Eq. (2). In addition, with reference to Table 8, DCM seems to be the most frequently used method in determining the liquid diffusivity in free medium. The range of concentration used for DCM is also larger than other methods (Table 8); therefore, we can conclude that DCM is more applicable in wider applications.

Apart from pore size, porosity and tortuosity also affect the diffusion of a molecule through the porous material. Both direct and indirect approaches have been discussed with regard to their respective advantages and disadvantages, and we conclude that there is no general procedure to determine both porosity and tortuosity of the porous media. For example, while pycnometric method seems to be straightforward, it can result in hydration of the samples. Mercury has been proposed as a better wetting agent instead of water for pycnometric technique; however, it is only valid for certain pore sizes. Hence, we

conclude that the most appropriate method depends on the materials to be characterized. Sufficient studies have proven that there exists a relationship between the property of transport of solute and morphological structure, and these findings are crucial in better and improved understanding of the nutritional supply to extracellular matrix and cells for TE applications. Despite a number of literature works, the general relationship between membrane morphology and solute diffusion is not fully understood yet as the building blocks of the material varies within the same material, and from one material to another. The temperature and fluid that saturates it may also affect the microstructure, and this, in turn, affects the diffusion.

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