Preparation of nanoliposomes and nanocrystals using microfluidic strategies - poster

Preparation of nanoliposomes and nanocrystals using microfluidic strategies

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1. Introduction

- Nanocrystals (NC) and nanoparticles (NP) are used in pharmaceutical industries as it offers improved performance of active ingredients, stability, controlled-delivery, increased comfort and reduction in overall drug content. It is also used in other industries such as food, cosmetics and other nanotechnology applications.
- Microfluidic devices (MFD) offers better control of different parameters such as size of NP, particle size distribution, reaction conditions, reduced residence time, etc.
- Encapsulated drug NP in liposomes are helpful in targeted delivery for cases of drugs with poor water solubility.
- Liposomes are spherical vesicles, organised in one or several concentric phospholipidic bilayers with aqueous core inside.
- Poor water-soluble drugs such as Hydrocortisone (HC) and Rapamycin (Rap) pose problems, such as the exact amount of the active ingredient to be delivered to the cells in most need of these drugs in the body, as such, encapsulated drugs using liposomes are already being used in some cancer therapies (Myocet, Duanoxome, Doxi, Paclitaxel, Docetaxel, Etoposide, Hydroxytamoxifen, Doxorubicin, etc.)
- The aim is to produce drug NP in microfluidic and membrane devices, and encapsulate in such a way that they could be delivered and released to the appropriate site in the human body.

2. Experimental set up

Experiments were carried out in fabricated glass capillary microfluidic devices, to synthesise hydrocortisone nanosuspensions and modified ethanol injection method to produce liposomes. Figures 1 and 2 is the schematic diagram of the microfluidic device and the synthesis of the hydrocortisone nanoparticles in the device respectively, while Figure 3 is the schematic diagram of the modified ethanol injection method.

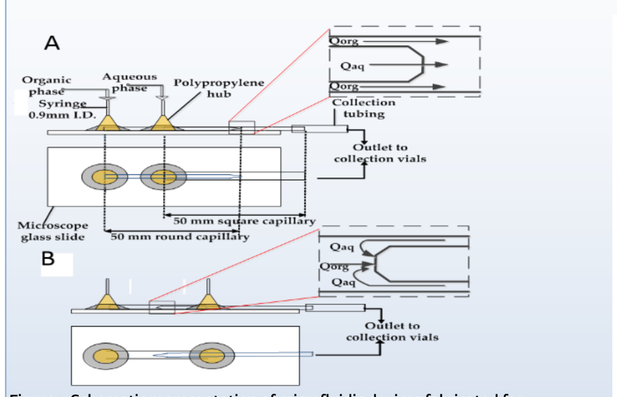


Figure 1 Schematic representation of microfluidic devices fabricated for experiments (A) Co-flow microfluidic device (B) Counter-current microfluidic device

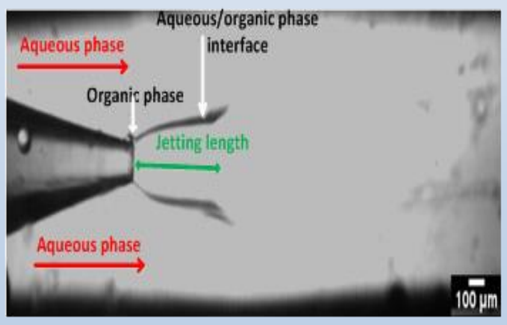


Figure 2 Nanosuspensions are formed at the inner capillary of the MFD.

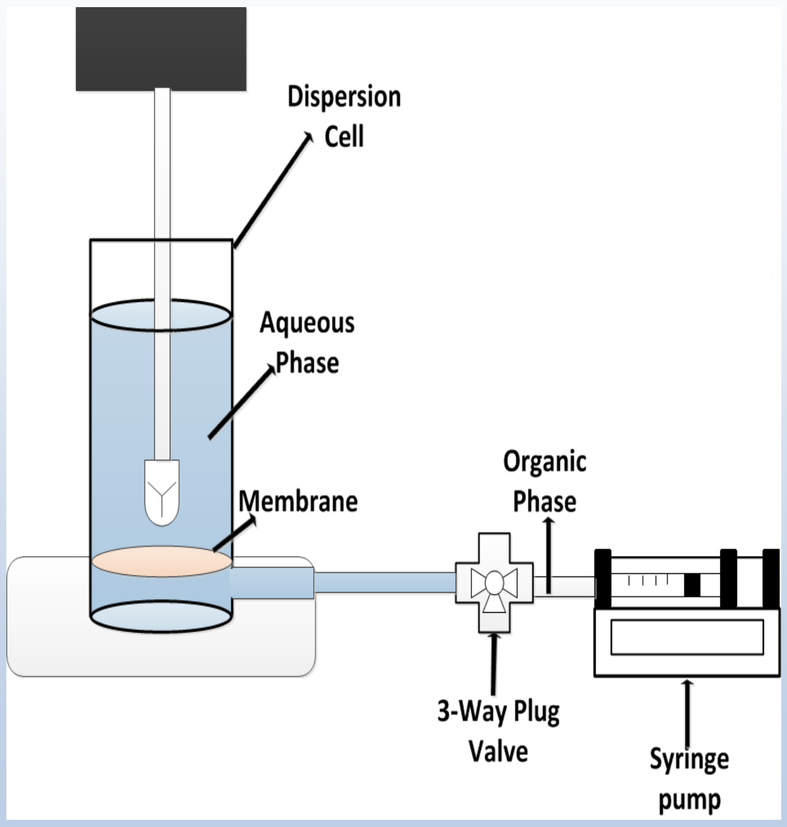


Figure 3 Schematic diagram of experimental set up for production of nanoliposomes using modified ethanol injection method

3. Nanocrystals formation

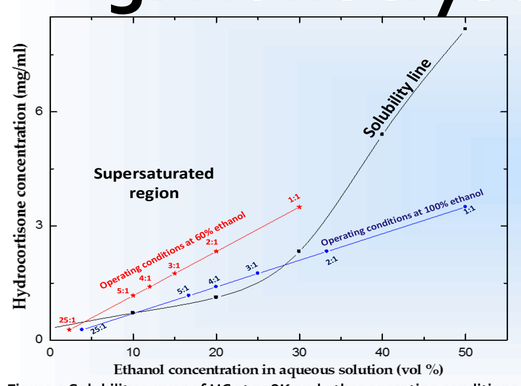


Figure 4 Solubility curves of HC at 298K and other operating conditions of the organic and aqueous phases of ratios 1:1 to 25:1

HC is completely soluble in 100% ethanol, but the solubility in pure water at 298 K is only 0.31 mg/mL, which means that the HC solubility in ethanol-water mixture shows large swings from nearly zero for pure water to infinity for pure ethanol. For crystallisation of HC to occur in the collection capillary, the operating line must be above the solubility line, e.g., in the supersaturated region of Figure 4.

The yield of nanocrystals would be rather low if 100% ethanol is used as solvent. In order to obtain a reasonable yield of drug nanocrystals, HC was dissolved in a 60/40 mixture of ethanol and water, rather than in pure ethanol.

4. Nanocrystal characterisation

XRPD profiles of processed and unprocessed HC were analysed. Peaks observed in Figure 7 corresponds to the profiles of the pure unprocessed and processed samples of HC as compared to the ICDD database for HC. This peak reduced for the processed drug which indicates the encapsulation of the drug in the polymer and stabilisers.

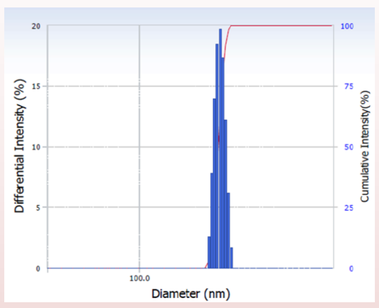


Figure 5 Size distribution of nanocrystals produced

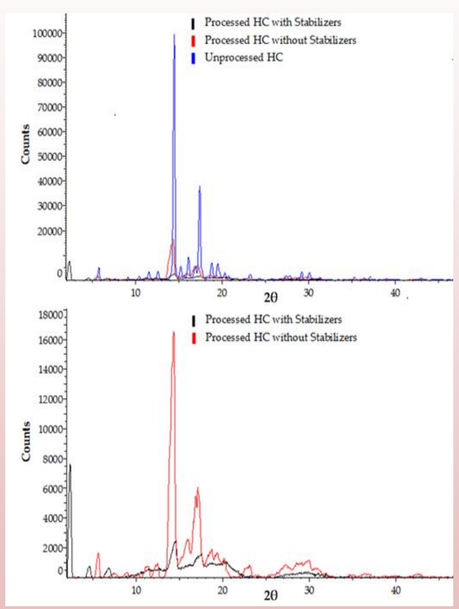


Figure 7 XRPD profiles of the unprocessed sample and processed HC with and without the stabilisers

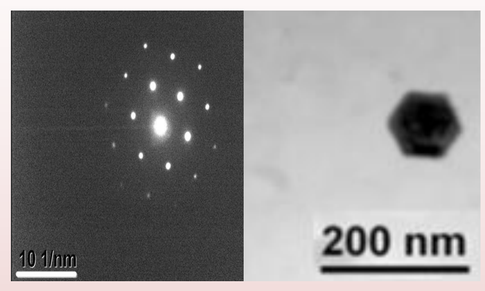


Figure 8 TEM images of HC nanocrystal produced

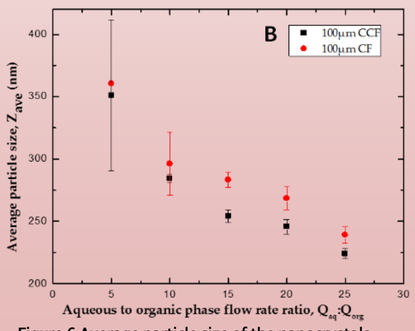


Figure 6 Average particle size of the nanocrystals produced in different geometries of the MFD

The counter-current MFD produced smaller sized nanocrystals due to the micromixing occurring in the smaller round capillary. The concentration of the HC used in the samples was 7mg/ml while the concentration of the stabilisers hydroxypropyl methyl cellulose (HPMC) was 0.2g/ml; Polyvinyl pyrrolidone (PVP) was 0.2g/ml and Sodium dodecyl sulfate (SDS) was 0.05g/ml

5. Nanoliposome characterisation

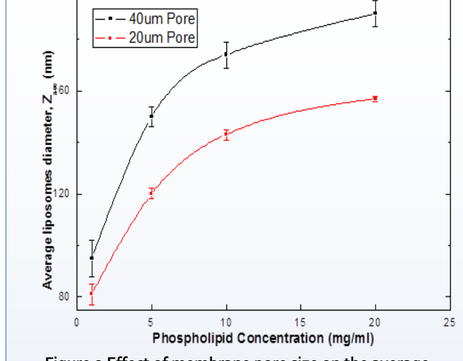


Figure 9 Effect of membrane pore size on the average diameter of nanoliposomes produced

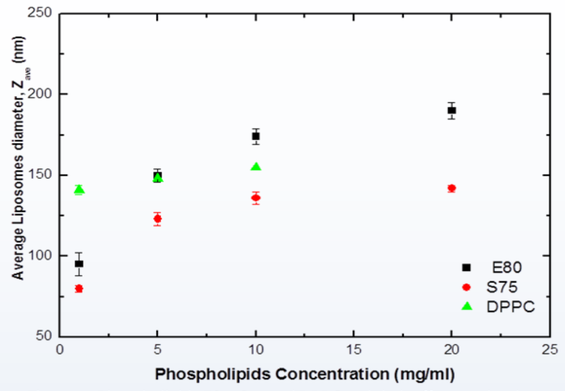


Figure 10 Phospholipids E80, S75 and DPPC and their effect on the size of nanoliposomes produced.

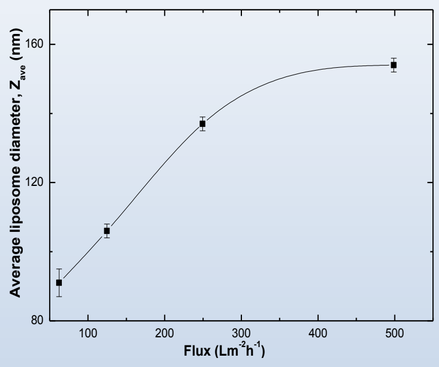
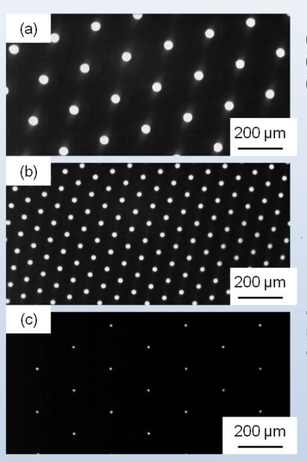


Figure 11 Changes in flux as it affects diameter of nanoliposomes produced



(a) L = 200 µm d_p = 40 µm
(b) L = 80 µm d_p = 20 µm
(c) L = 200 µm d_p = 10 µm

Maximum surface shear:

$$\tau_{max} = \frac{0.825\eta_{aq}\omega r_{trans}}{\sqrt{\eta_{aq} I(\rho_{aq}\omega)}}$$

Figure 12 Pore spacing and diameter of the pores of the nickel membranes used in the production of the nanoliposomes.

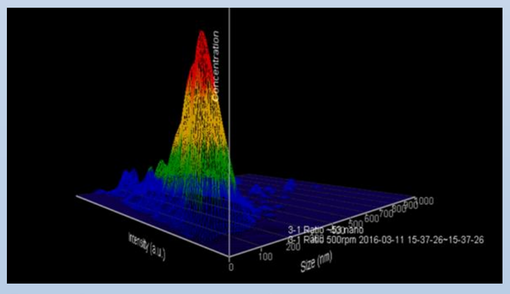


Figure 13 Particle size distribution of the nanoliposomes

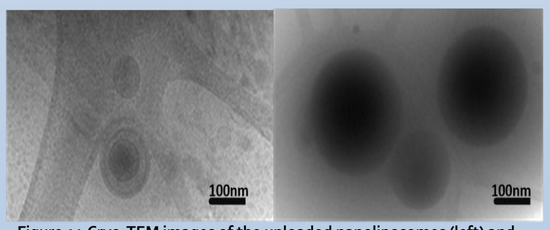


Figure 14 Cryo-TEM images of the unloaded nanoliposomes (left) and nanoliposomes encapsulating rapamycin (right).

Conclusion

- Nozzle diameter of MFD affect the size of nanocrystals produced.
- Concentration of phospholipids , flux, membrane pore size and rotational speed of paddle all affect the size of nanoliposomes produced, and therefore size of drug nanoparticles can be modified based on these parameters.

Future Work

- Synthesis of nanoparticles using 3D-printed MFD.
- Encapsulation of various drug nanoparticles produced and study of the release rates of encapsulated drugs.
- Synthesis of liposomes using continuous phase systems.

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