POSTER 52

CMAC
FUTURE MANUFACTURING RESEARCH HUB

Towards Controlling Crystallization Using Liposomes: Manipulation of Liposome Size Through Microfluidics

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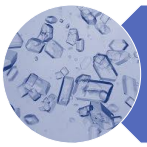
Background

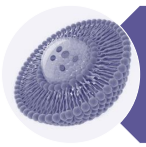
Crystallization plays an important role in defining the physico-chemical characteristics of pharmaceuticals. The ubiquity of crystal nucleation reactions - as well as the strong influence on product quality - emphasises the importance of understanding and controlling the process. Within this project, we are investigating the use of liposomes to control crystallization. Due to their nano-scale size and ability to facilitate well-controlled process conditions, liposomes present an excellent vehicle for crystallization studies. It has been shown that nanocrystalline precipitates of drugs such as doxorubicin, topotecan and idarubicin can be encapsulated inside liposomes for drug delivery purposes; however, the formation of these nano-crystals has never been extensively studied. In order to control the particle size of liposomes and to establish transmembrane gradients, we have used microfluidics.

Aims

Characterise liposomes of varying size and composition on their suitability as crystallisation vehicles



Closely study nucleation behaviour within liposomes, eventually relating the rate of nucleation to process conditions and liposome characterisation



Control the crystallisation of a loaded pharmaceutical compound in drug delivering liposomes

Results

Fig. 1A

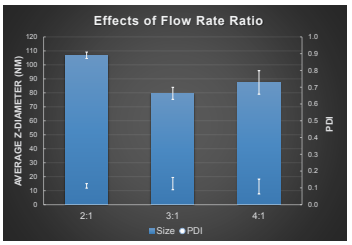


Fig. 1B

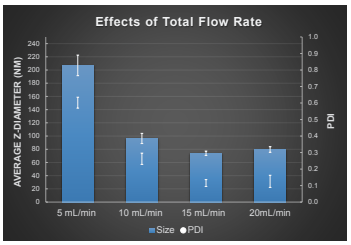


Fig. 1C

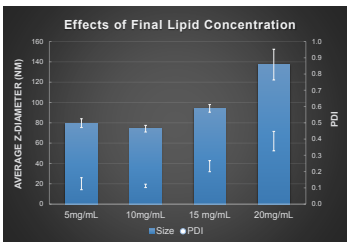
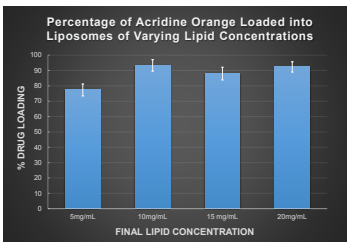


Fig. 1D

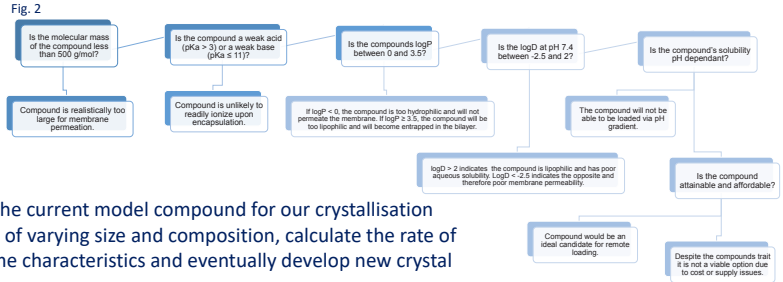


The size of liposomes can be easily manipulated by adjusting microfluidic parameters such as flow rate ratio and total flow rate (Fig. 1A, 1B). The final lipid concentration was also tested and at concentrations of 5 mg/mL and 10 mg/mL liposomes of consistent size (≈ 75 nm) and polydispersity index (< 0.2) were produced (Fig. 1C). For drug loading, encapsulation efficiency was typically high (>85%), with particle size having no notable impact (Fig. 1D). We can conclude that liposomes produced via microfluidics offer in-process size control and high reproducibility, therefore providing an ideal format for studying crystal nucleation behaviour.

Ongoing Research

Before analyzing crystal nucleation within liposomes, we must first identify suitable model compounds to use. We developed a decision tree to aid model compound selection by predicting a compounds encapsulation probability (Fig. 2).

Fig. 2



Using the decision tree, we have selected aceclofenac as the current model compound for our crystallisation studies. We will encapsulate aceclofenac inside liposomes of varying size and composition, calculate the rate of nucleation as a function of process conditions and liposome characteristics and eventually develop new crystal nucleation theories.