

## MONODISPERSE NIOSOMES NANOPARTICLES FORMULATION BY MICROFLUIDIC MIXING

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Niosomes nanoparticles are self-assembling vesicular nano-carriers obtained by hydrating a mixture of non-ionic surfactant and cholesterol or amphiphilic molecules. Niosomes can be unilamellar or multilamellar and are suitable as carriers of both hydrophilic and lipophilic drugs. Furthermore, niosomal vesicles are non-toxic, more stable than liposomes and thus result in lower production costs. One of the methods used for liposome production is through microfluidic mixing, which depends on the rapid mixing of the lipids in solvent with the aqueous phase in microchannels. Using microfluidic systems, a tight control of the mixing rates and ratios between the aqueous and solvent streams can be achieved, with lower liquid volumes required, which facilitates process development by reducing time and development costs. Here we used the microfluidic mixing for the production of niosomes. The particles produced were compared to the particles generated by the thin film hydration (TFH) method followed by extrusion and the particles from both methods were investigated for their physicochemical characteristics, stability, morphology and cytotoxicity.

### Materials and Methods:

Monopalmitin was obtained from Larodan Fine Chemicals Sweden, cholesterol and dicetyl phosphate (DCP) were obtained from Sigma–Aldrich Company Ltd., UK.

#### Formulation using microfluidics

Formulations were prepared on a NanoAssemblr™ (Precision NanoSystems Inc., Vancouver, Canada). Monopalmitin, cholesterol and DCP were dissolved in ethanol at a molar ratios of 50:40:10. Niosomes were manufactured by injecting the lipids and aqueous buffer into separate chamber inlets of the micromixer. The flow rate ratio (FRR; ratio between solvent and aqueous stream) as well as the total flow rate (TFR) of both streams were controlled by syringe pumps.

#### Formulation using TFH method

Monopalmitin, cholesterol and DCP were dissolved in chloroform at a molar ratios of 50:40:10 in a round bottom flask. The chloroform was then evaporated using a rotary evaporator and the lipid film was then hydrated with PBS to form multilamellar niosomes which were then passed through Avanti-polar miniextruder.

The particles generated from both methods were characterised by dynamic light scattering (DLS),  $\zeta$ -potential, and atomic force microscopy (AFM). Cytotoxicity assays were also performed on A2780 ovarian cancer cells and A375 melanoma cells

**Results:** Using microfluidics, monodisperse niosomes were prepared in one step with an average size of  $120 \pm 10$  nm determined by DLS and confirmed by AFM were shown to be spherical in shape. The size of the niosomes was controlled by monitoring the FRR and TFR in both the lipid and aqueous phases. In contrast, niosomes prepared with TFH method were too polydisperse and required a further size reduction step after preparation by extrusion or probe sonication which is time consuming and limited to the bench scale. A stability study was performed for the particles generated by both methods at four different temperatures (4, 25, 37 and 50°C) for 4 weeks and the vesicles were shown to be stable in terms of size and poly disparity index (PDI). Cytotoxicity studies showed that the IC<sub>50</sub> was around 625  $\mu\text{g/ml}$ .

**Conclusions:** Stable, charged niosomes, with controlled size can be manufactured by microfluidisation, which has the potential to be scaled up for pharmaceutical production.