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Investigation of the Preparation of Monodispersed Liposome Suspensions Using Microsieve Membranes

A. Laouni¹, 2, C. Charcosset2, R. G. Holdich¹, G.T. Vladisavljevic¹

¹Department of Chemical Engineering, Loughborough University, United Kingdom
²Laboratoire d’Automatique et de Génie des Procédés, Université Claude Bernard Lyon 1, France

Background

- Liposomes are spherical nanovesicles composed of one or several concentric phospholipidic bilayers with an internal aqueous phase
- Due to their biocompatibility and biodegradability, they have been extensively studied as drug carriers for efficacy enhancement and toxicity reduction
- Several techniques have been reported for liposomes preparation: thin film hydration, reversed phase evaporation, solvent injection...
- So far, only polymeric hollow fibre and tubular glass membranes have been used in the preparation of liposomes

Aims of the study

- Develop and optimise a novel strategy for the preparation of liposomes, based on dispersion of organic phase through microsieve membrane in a stirred cell. The use of microsieve membranes with uniformly sized pores and constant pore spacing allows a uniform dispersion of organic phase over the membrane surface, which makes easier to extrapolate the results for an industrial production.
- Investigate the reproducibility of the process
- Study the stability of the liposomal suspensions
- Apply this new process to the encapsulation of vitamin E

Optimisation of the process parameters and formulation factors

- Phospholipid concentration
- Aqueous to organic phase volume ratio
- Rotation speed
- Transmembrane flux
- Stabilizer
- Phospholipid type

Liposomes preparation using a stirred cell

The ethanolic phase (containing the required amounts of phospholipid and stabilizer) was permeated thorough the pores of the microsieve membrane into the aqueous phase, using a peristaltic pump. Then, the liposomal suspension was allowed to stand for 15 min under mechanical stirring and finally ethanol was removed by rotary evaporation.

What happens at the interface between the 2 phases?

When reproducing the process in a single pore (using a microfluidic channel device), microscopic observation showed: (A) Dripping mode: droplets were attached to the pore surface, however once detached we couldn’t see them suspended in the continuous phase since ethanol is miscible in water. (B) Jetting mode: when the flow rate was increased, jets ended in multi-concentric waves were observed. (C) Spontaneous liposomes formation occurred immediately when both phases were in contact and liposome aggregates were observed.

The optimum experimental conditions were:

1. Phospholipids concentration = 20 mg/ml
2. Aqueous to organic phase volume ratio = 4.5
3. Agitation speed = 600 rpm
4. Transmembrane flux = 142 L/m²/h
5. Stabilizer: cholesterol 5 mg/ml
6. Both Lipid E80 and POPC could be used:

Effect of the membrane pore size

When the membrane pore size decreased, the liposomes mean size decreased as well. A linear relationship was obtained which confirms the possibility of controlling the preparation characteristics by tuning the membrane parameters.

Vitamin E was successfully encapsulated within liposomes. The encapsulation efficiency was 99.87% for a drug to lipid ratio of 25%. The final concentration was 1.15 mg of vitamin E per ml of liposomes suspension.

Drug loading test

A new process was developed for liposomes preparation using microsieve membranes
This new technique led to the formation of narrow distributed liposomes
Vitamin E was successfully encapsulated with a high entrapment efficiency
The process was reproducible and the preparations showed very good stability
The use of microsieve membranes for liposomes preparation is simple, fast, reliable and present a potential for production at a large scale

Conclusion

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