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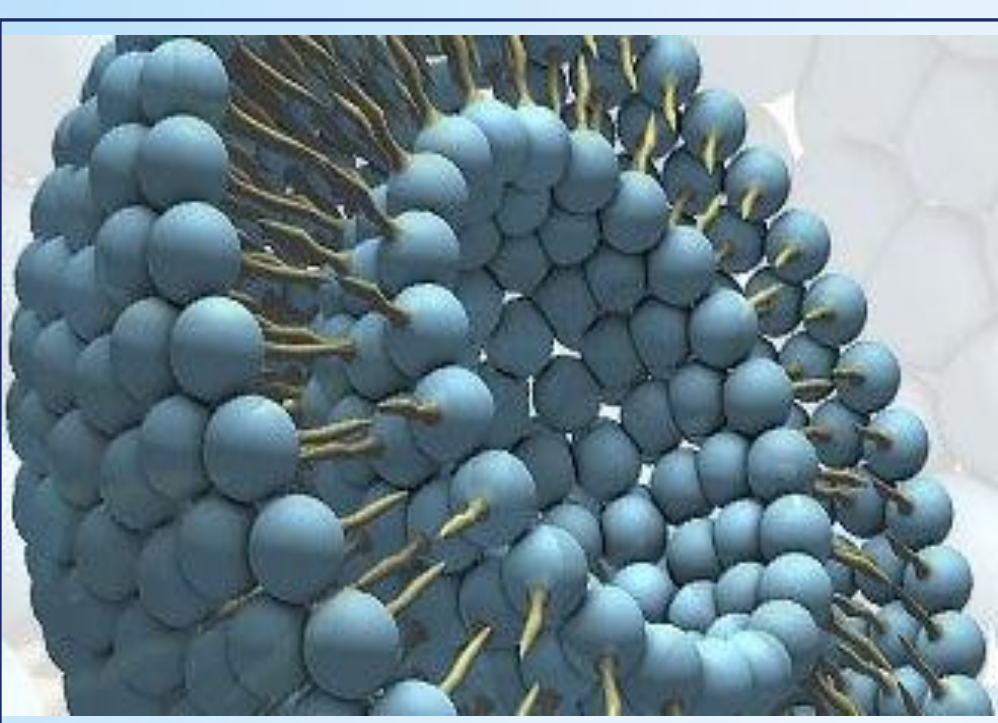
Investigation of the Preparation of Monodispersed Liposome Suspensions Using Microsieve Membranes



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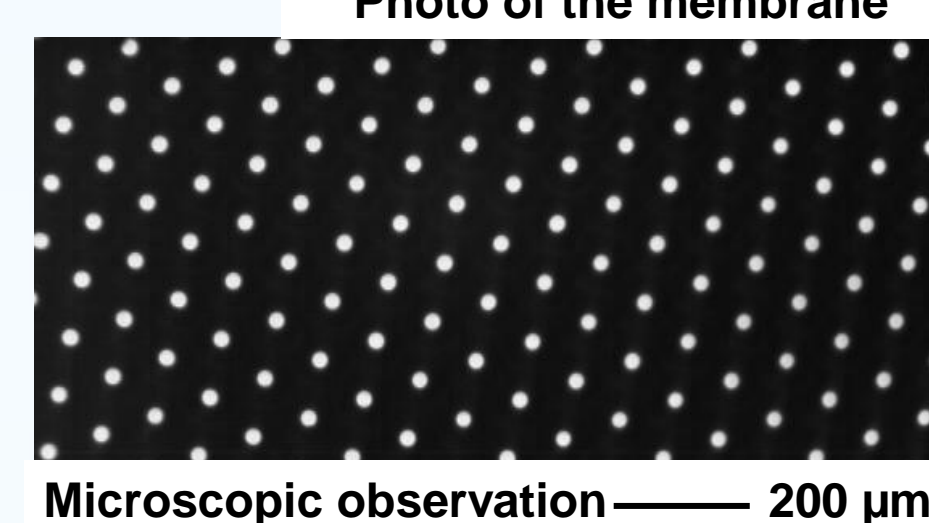
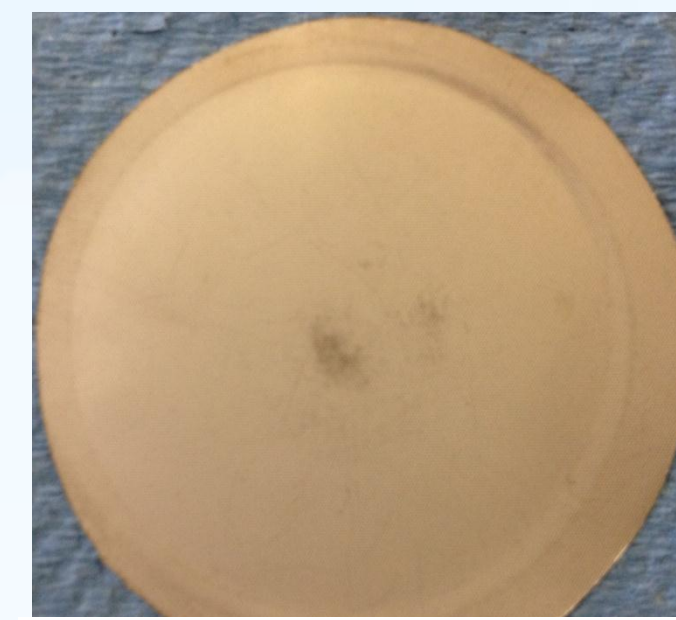


Background

- 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

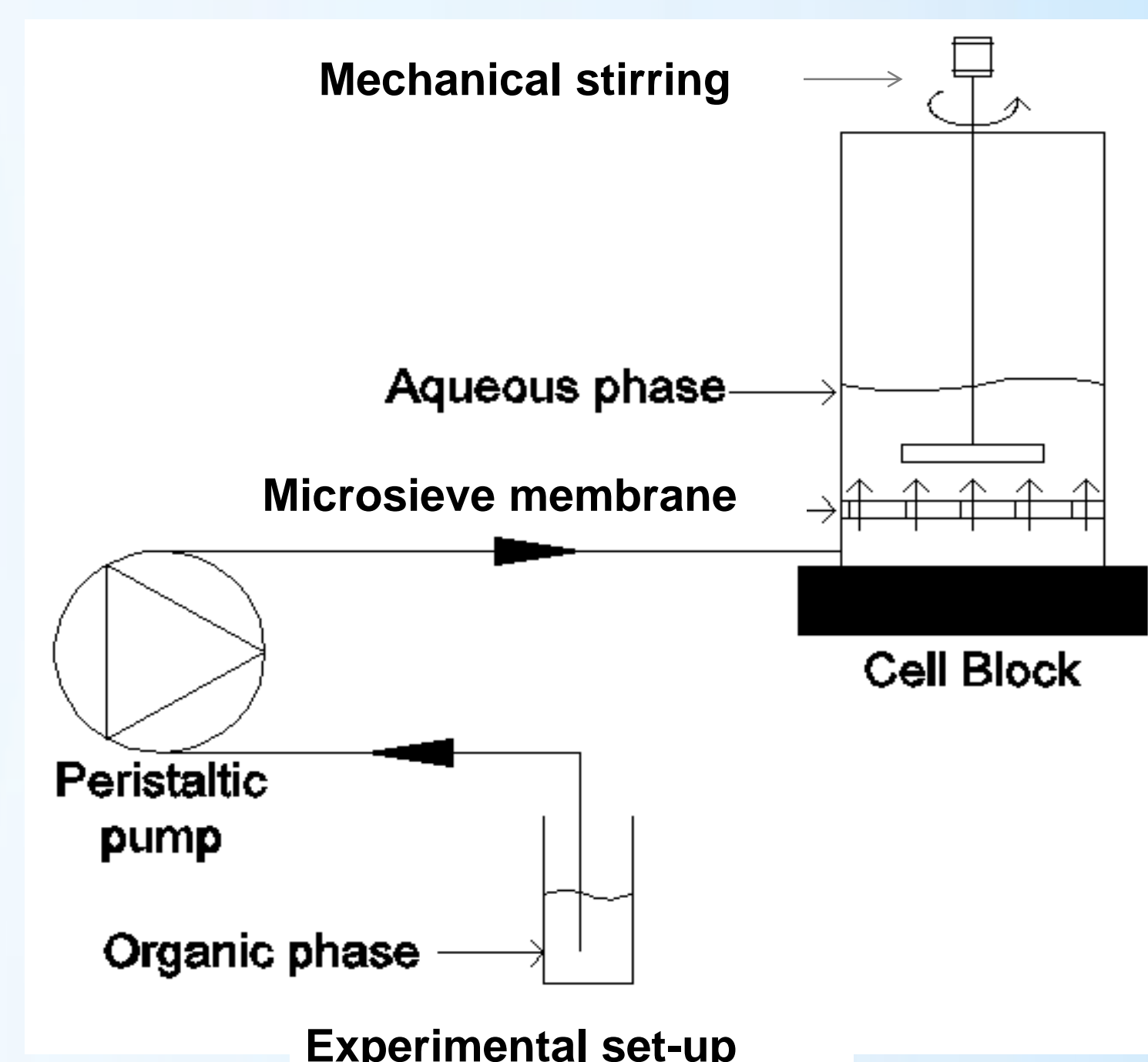
Aims of the study

- 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

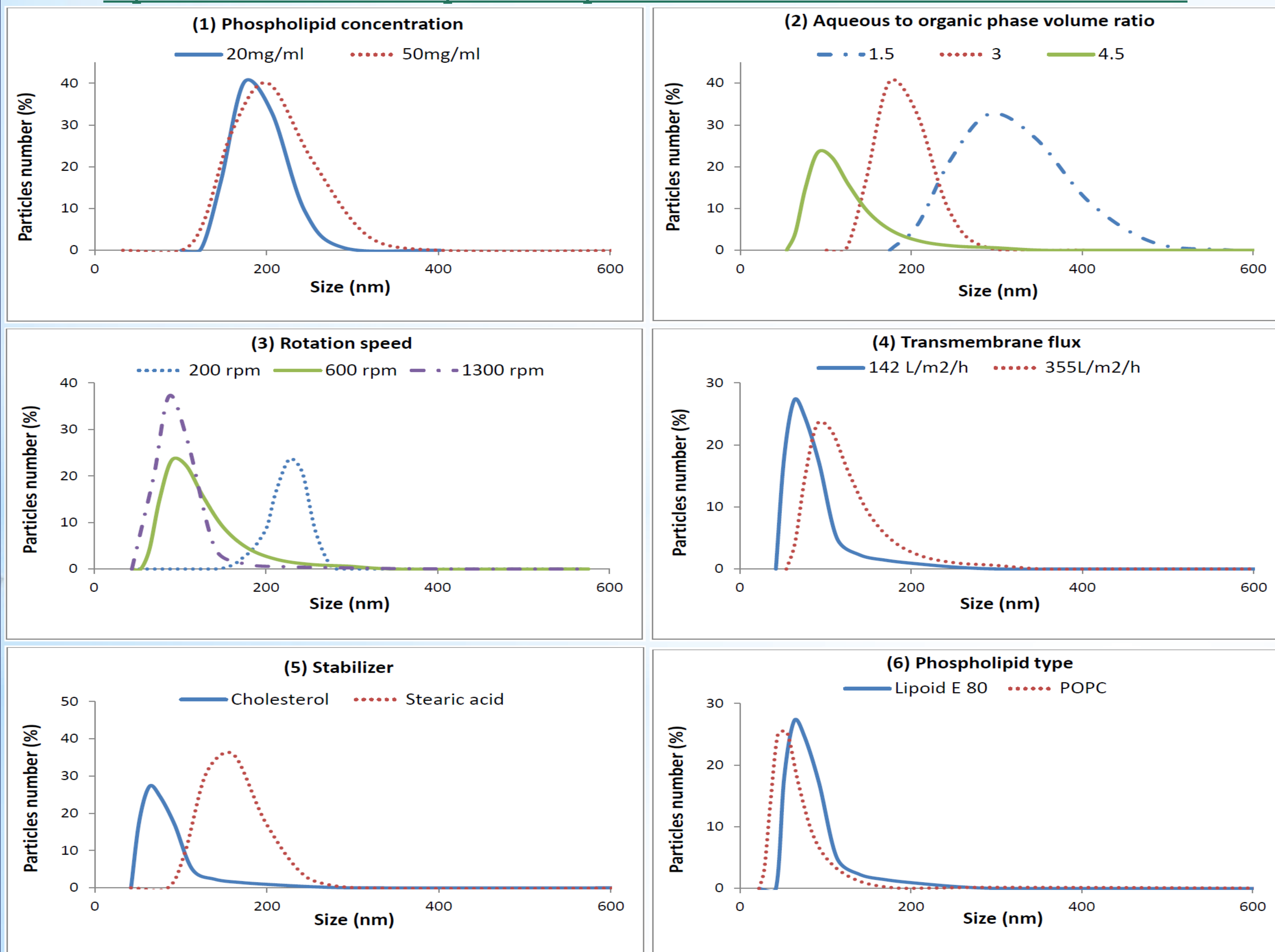


Liposomes preparation using a stirred cell

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.

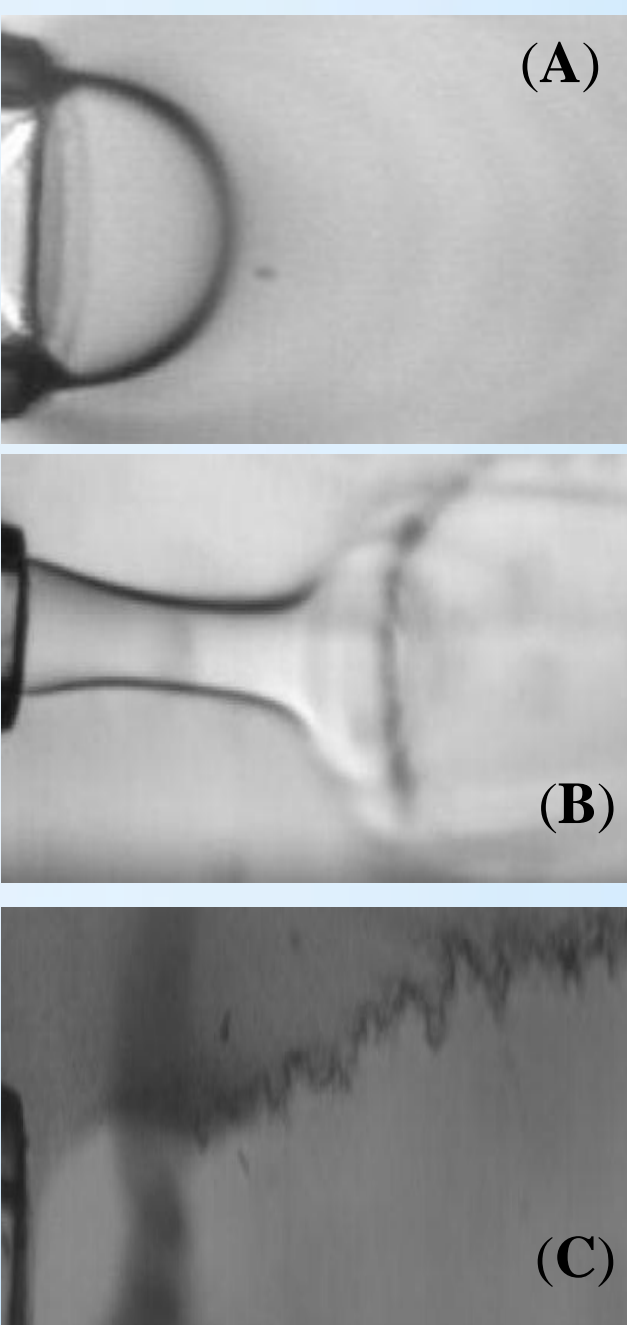


Optimisation of the process parameters and formulation factors



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:

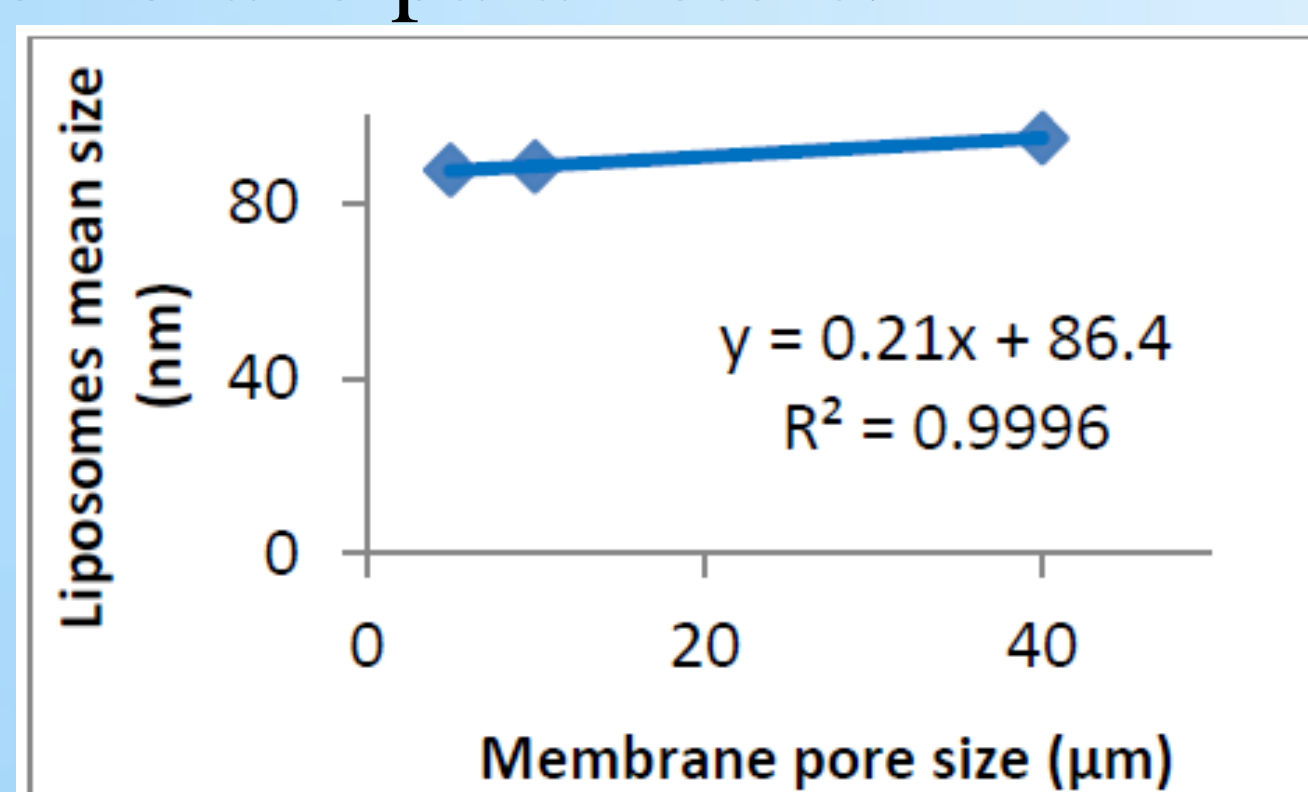
- (1) Phospholipids concentration = 20 mg/ml
- (2) Aqueous to organic phase volume ratio = 4.5
- (3) Agitation speed = 600 rpm
- (4) Transmembrane flux = 142 L/m²/h
- (5) Stabilizer: cholesterol 5 mg/ml
- (6) Both Lipid E80 and POPC could be used:

Phospholipid used	Lipoid E80	POPC
Mean size (nm)	84	59
Peak width (nm)	37.4	35.6
Polydispersity index	0.24	0.31

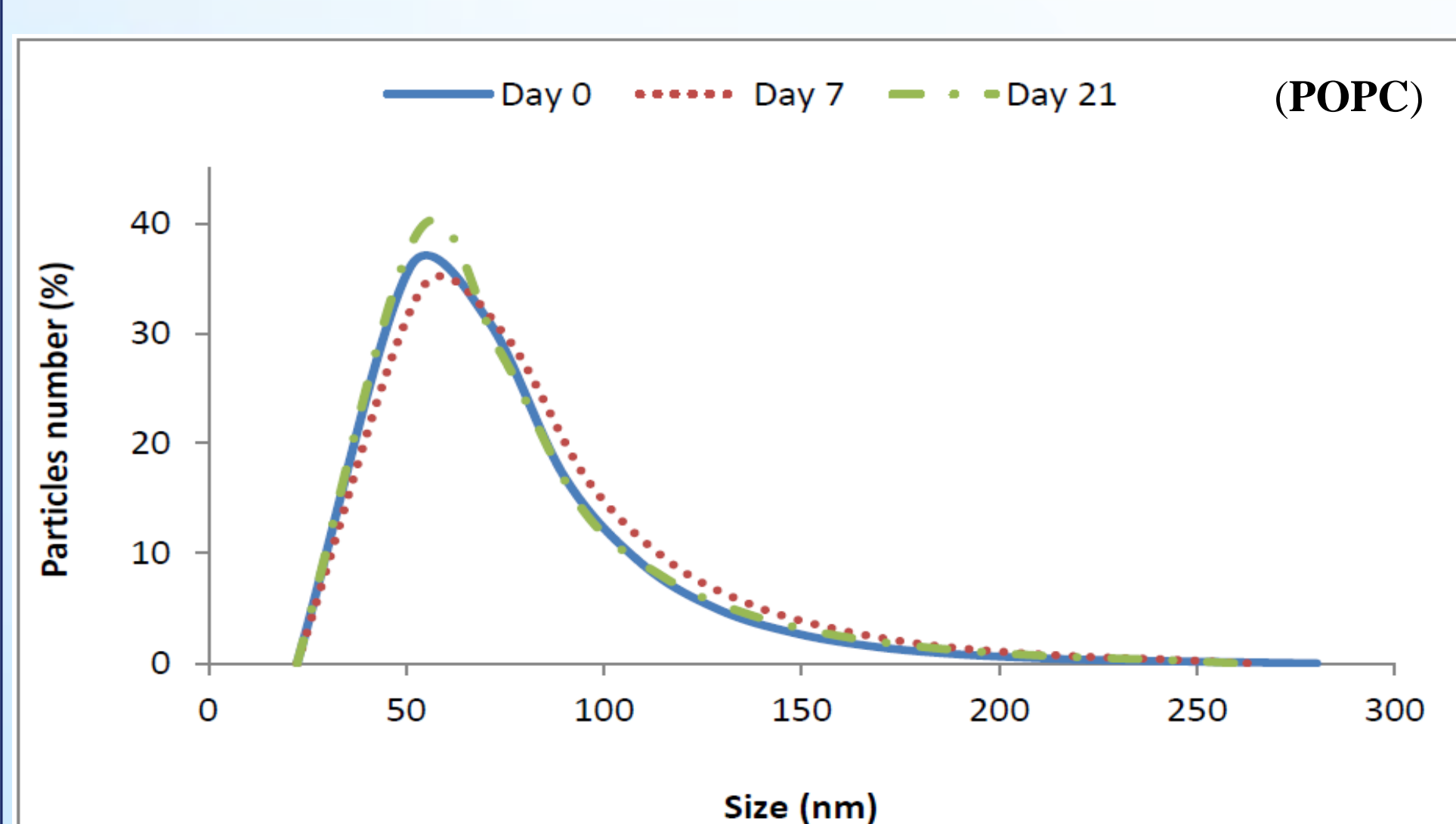
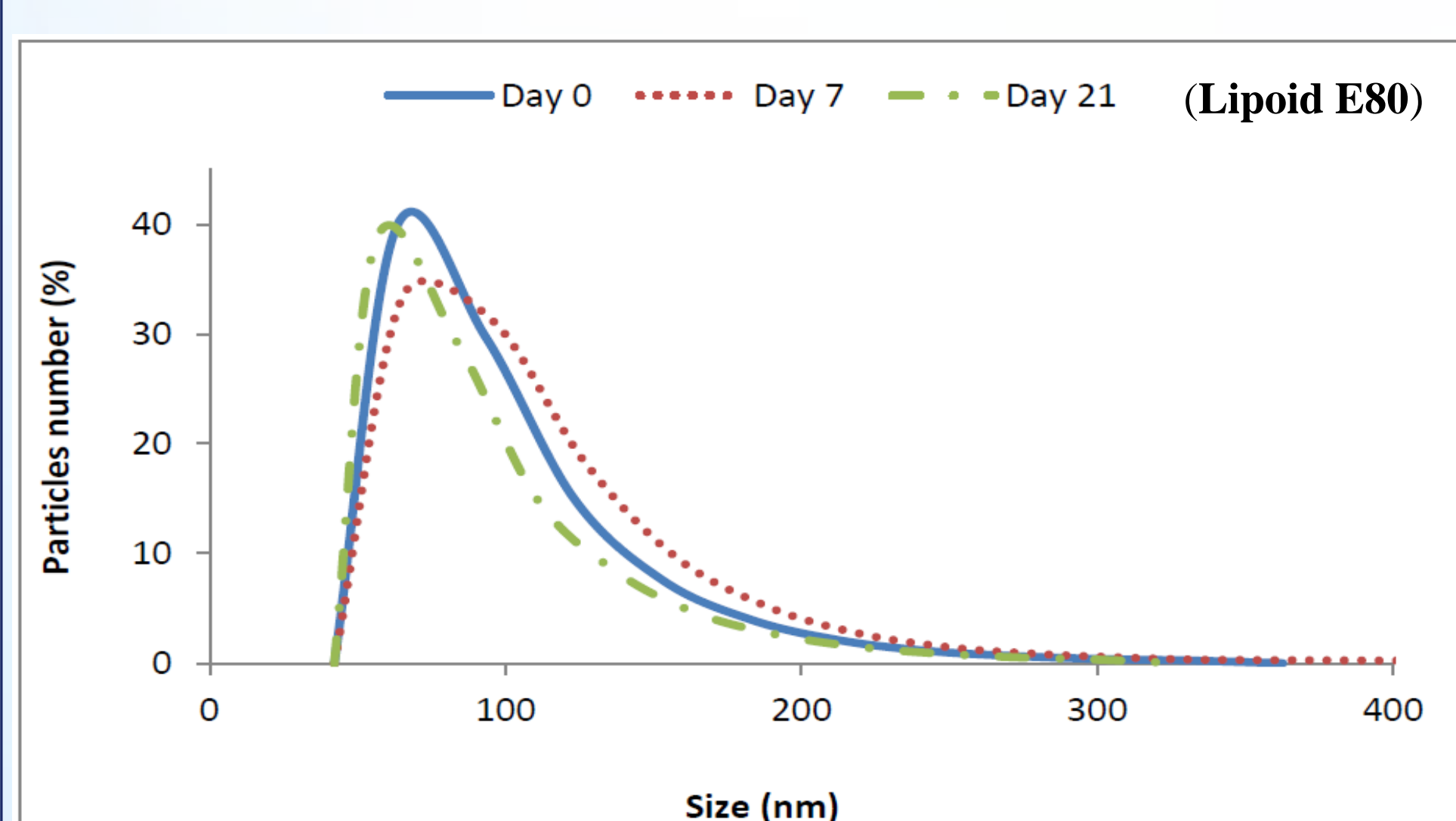
Effect of the membrane pore size

Membrane pore size (μm)	5	10	40
Liposomes mean size (nm)	87	88	95
Peak width (nm)	33.1	34.4	40.0
Polydispersity index	0.32	0.32	0.36

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.



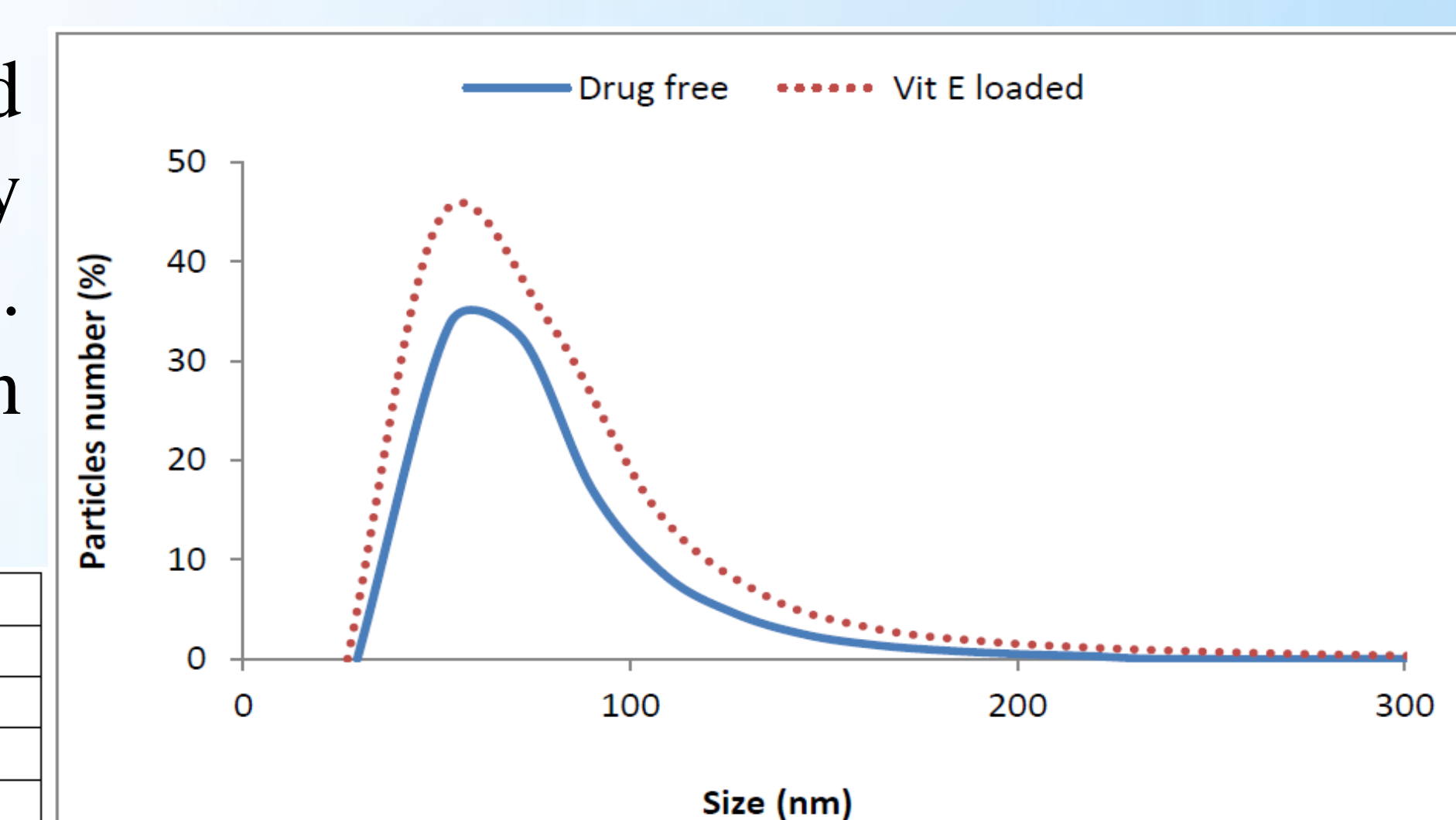
Storage stability study



Drug loading test

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.

Liposomes suspension	Drug free	Vitamin E loaded
Mean size (nm)	84	96
Peak width (nm)	37.4	44.3
Polydispersity index	0.24	0.44
Zeta potential (mV)	-28.0	-28.5



Conclusion

- ✓ 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

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