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Supercritical millifluidic process for the production of lipid-based formulations of anti-cancer drugs

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1. Introduction

Supercritical fluid technology applied to the elaboration of lipid-based formulations, especially liposomes, has been quite widely described in the literature over the last three decades. Many advantages of using supercritical carbon dioxide for liposome formation are often highlighted such as size control, stability enhancement and mitigation of organic solvent use. The main recent challenges in this field are the size reduction since vesicles smaller than 100 nm allow for a higher rate of cell internalization. Another point of attention, whatever the application field, is the development of less energy intensive processes, consuming less raw materials and solvents. The present study addresses all the different challenges mentioned above. A millifluidic process enabling fluid, equipment and energy savings has been applied to the formation of nanoliposomes. This process, previously applied to the encapsulation of small interfering RNA for gene therapy applications [1], has been used in this work for the elaboration of pegylated nanoliposomes encapsulating docetaxel, an anti-cancer drug used for the treatment of different types of cancer.

2. Materials and methods

2.1 Materials

Phosphatidylcholine (PC) (CAS: 97281-44-2, purity >99%), supplied by Sigma-Aldrich (Saint-Quentin-Fallavier, France) was used as main source of lipids. Cholesterol (CAS: 57-88-5) and polyethelene glycol (PEG) (CAS: 474922-22-0, Mw = 2941.605 g/mol) were supplied by Sigma-Aldrich (Saint-Quentin-Fallavier, France). Docetaxel (CAS: 114977-28-3, purity: 98%) was supplied by Sigma-Aldrich, Saint-Quentin-Fallavier, France. Carbon dioxide (purity > 99.7%) was supplied by Air Liquide (Marseille, France).

2.2 $ScCO_2$ encapsulation set-up

The main feature of the studied process is the use of a millifluidic device for mixing supercritical carbon dioxide with the aqueous ethanolic solution containing the drug, the lipids and polyethylene glycol (when used). The process is conducted in a continuous mode, enabling then the continuous production of a liposomal solution.

3. Results

Nanoliposomes have been formed at 150 bar and 35 °C, starting from an aqueous ethanolic solution (79/21 wt%) containing PC (0.1 wt%), docetaxel with a concentration of 34 $mg.L^{-1}$, cholesterol and PEG. The vesicle size is understood between 90 and 120 nm, with a drug encapsulation rate of 95 %. Drug-free liposomes with a similar size range have been formed.

4. Conclusion and perspectives

This work has highlighted that nanolipomes encapsulating an anti-cancer drug can be produced in a continuous and repeatable way. A unimodal population can be isolated enabling then the recovery of more stable formulations. Since the presence of drug in the liposome did not impact the vesicle size, nanoliposomes encapsulating different types of drugs may be successfully formed using a millifluidic device.

Acknowledgements

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References

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