LIPOSOME FOR THE TREATMENT OF COPD PRODUCED BY SUPERCRITICAL CARBON DIOXIDE-BASED TECHNOLOGIES

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INTRODUCTION

This study is aimed to produce an innovative liposomal formulation loaded with ciclesonide and encapsulated or free indacaterol used for the treatment of Chronic obstructive pulmonary disease (COPD). After deposition in bronchial tubes, PEGylated liposomes could enhance penetration of these active molecules through hypersecreted mucus layer, protect them from degradation by macrophages during the passage and control their liberation at target sites. Liposomes will be produced by the particles from gas-saturated solution process (PGSS) in which supercritical CO_2 ($scCO_2$) acts as a dispersing agent. This green approach allows us to remove use of organic solvent and improve the feasibility of fabricating the liposome at the industrial scale.

GOAL

At the beginning of the study, we investigated the potential of the PGSS to produce liposomes exhibiting adequate properties for the pulmonary delivery of indacaterol and ciclesonide.

METHODS

Liposome preparation:

The liposome was composed of SPC/CHOL/DSPE-PEG_{2000} (65/30/5, molar ratio). Firstly, lipids were dispersed in HEPES buffer (10 mM, pH 7.4) at 65 °C and stirred at 1200 rpm for 15 min. This dispersion was then added to a high pressure reactor. Afterward, the $scCO_2$ was pumped into the reactor under 2 conditions which shared some common parameters including time of contact (0.5 h), temperature (80 °C), and rotation speed (500 rpm)[1,2]. However, while the condition 1 used a lipid concentration of 45 mM and a volume of dispersion of 14 mL, these parameters for the condition 2 were 5 mM and 10 mL, respectively. Finally, the mixture was depressurized to remove CO_2 and resulted liposomes were collected in a recovery vial.

Liposome characterization :

For analysis by dynamic light scattering (DLS), the liposomes obtained from the condition 1 (L1) and 2 (L2) were diluted in HEPES buffer 100 and 10 times, respectively. Their mean size, polydispersity index (PdI), and zeta potential were then determined.

On the other hand, prior to analysis by the Nanoparticles Tracking Analysis (NTA) with a 642 nm laser, 10000000-fold and 10000-fold dilution in ultrapure water were also applied for L1 and L2, respectively. This technique gave information about particles sizes and concentrations.

RESULTS

Results derived from the DLS showed a bigger mean size for L1 (156 nm) as compared to L2 (139 nm). However, they displayed similar values of PdI (0.36 for L1 and 0.39 for L2) and zeta potential (-5 mV for L1 and -6 mV for L2).

As to the NTA, it demonstrated an expected higher particles concentration of L1 (5.26×10^{15}) in relative to that of L2 (4.58×10^{12}) while no difference in terms of mean size was observed (154 nm for L1 and 153 nm for L2).

DISCUSSION

Liposomes from both conditions possessed adequate sizes to theoretically bypass 'size filtering' by the mucus network and uptake by macrophages (< 200 nm). Their nearly neutral zeta potential would also help to avoid electrostatic interaction with negatively-charged mucins molecules. In addition, polyethylene glycol-covered surface is necessary to limit their hydrophobic interaction with the mucus network and the phagocytosis.

CONCLUSION

These preliminary results depicted the ability of the PGSS to produce liposomes that are suitable for the pulmonary administration. Further experiments focusing on their mucopenetration (based on a Transwell® model), phagocytosis and biocompatibility with lung epithelial cells will be performed to give more detailed information about their behavior in the lungs.

REFERENCES

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