Optimization of liposomal formulation to achieve sustained release of dexamethasone

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1. INTRODUCTION

Sensorineural hearing loss is a condition that can occur when hair cells in the inner ear are destroyed. These cells are protected by several physiological barriers and delivery of a drug by conventional routes does not appear to be optimal. Transtympanic injection of a drug would bypass most barriers, leaving the round window membrane (RWM) dividing the middle ear from the inner ear as the only remaining barrier. Also, the use of a sustained release (SR) formulation would decrease the number of such injections. The use of liposomes, lipid nanoparticles encapsulating active ingredients (APIs), in this formulation would provide a controlled release of these APIs [1]. Indeed, according to literature, modification of their lipid profile has an influence on their SR effect [2, 3]. The presence of saturated lipids (DPPC, DSPC, ...) or the addition of cholesterol (Chol) are known to stiffen the liposome structure and extend API release. **The aim of this work is therefore to test the impact of different liposome formulations on the release of dexamethasone (Dexa) or dexamethasone sodium phosphate (DexaPO_4) used as APIs. These will be compared to identify the best therapeutic option.**

2. MATERIALS & METHODS

a. Liposomes composition and production

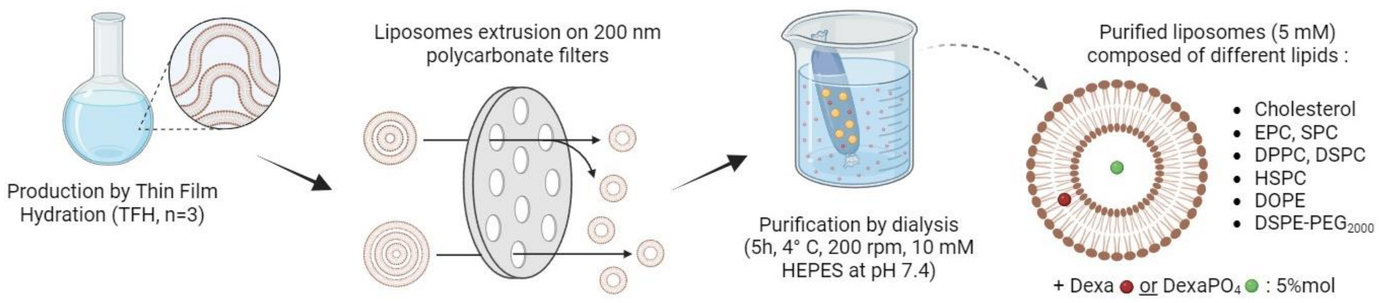

Figure 1. Production, extrusion and purification of liposomes composed of different types of lipids [4].

b. Release test

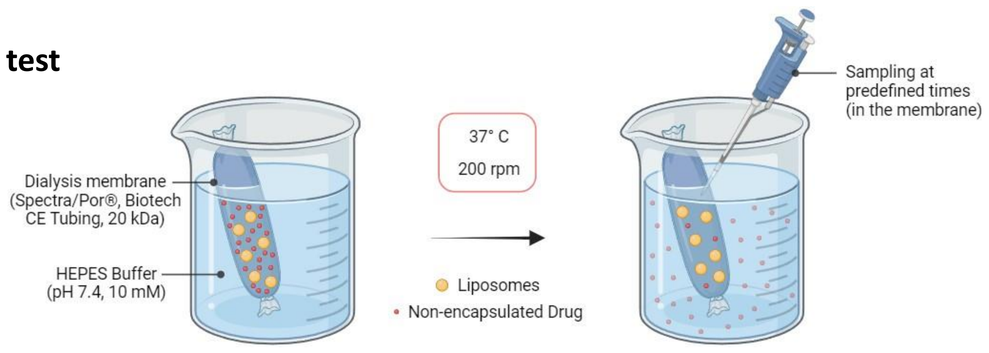

Figure 2. Release test based on a dialysis method [4].

3. RESULTS & DISCUSSION

The highest results in terms of encapsulation efficiency (EE) were obtained with 10% Chol for Dexa (Figure 3). Chol will thus be used at a low percentage due to its structural analogy with Dexa and their competitive effect for space in the liposome lipid bilayer. Among the various lipids tested, EPC exhibited significantly higher EE for Dexa-liposomes, while DSPC showed the best EE for DexaPO_4-liposomes. The longest release kinetics for Dexa-liposomes were obtained with EPC as the main lipid and 10% Chol (Figure 4). However, these components do not appear to substantially improve the SR, since the API is released over the same period of 3 hours for Dexa and 24 hours for DexaPO_4 (Figure 5). Similarly, addition of DSPE-PEG_{2000} or presence of DOPE in Dexa-liposomes did not greatly affect SR (Figure 4).

In terms of kinetics, the use of DexaPO_4 thus appears to be more interesting, since its release occurs over 24 hours. However, in terms of EE, results are significantly higher for encapsulated Dexa than for encapsulated DexaPO_4. The most promising approach therefore seems to be the use of Dexa, as it would allow reaching therapeutic concentrations more easily than with DexaPO_4. New strategies will then be required to sustain the release of Dexa (Figure 6).

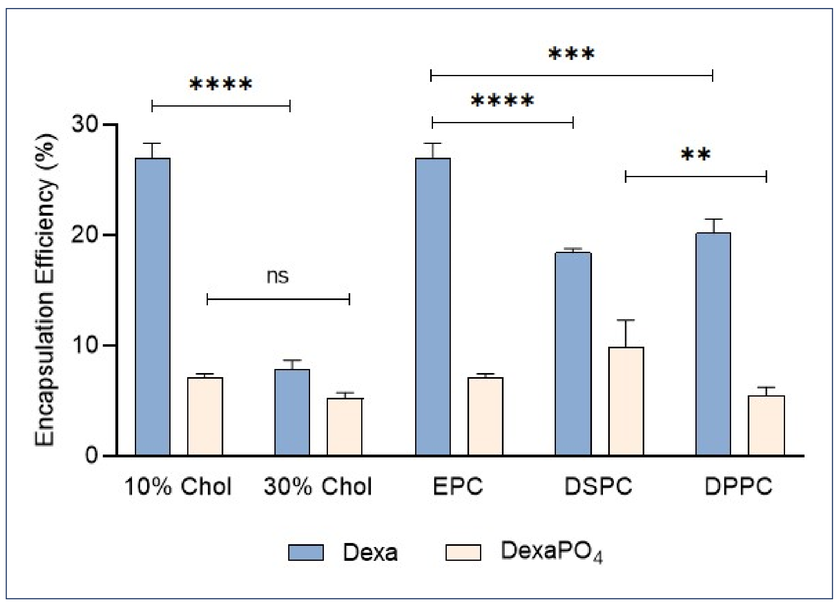

Figure 3. Comparison of Dexa and DexaPO_4 encapsulation efficiencies.

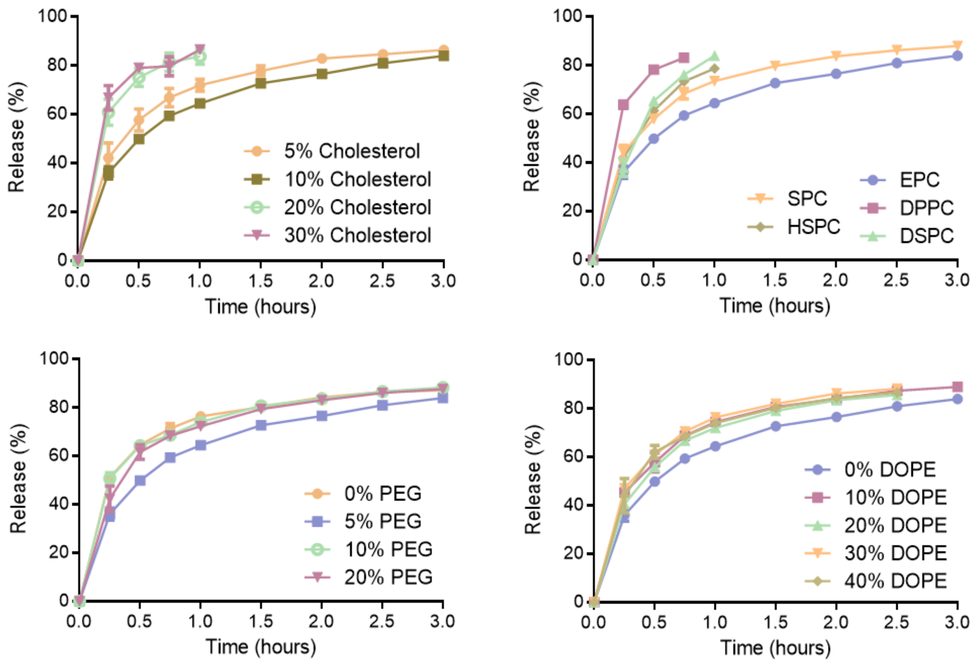

Figure 4. Impact of lipid composition on the release of **Dexa** encapsulated in liposomes in function of time.

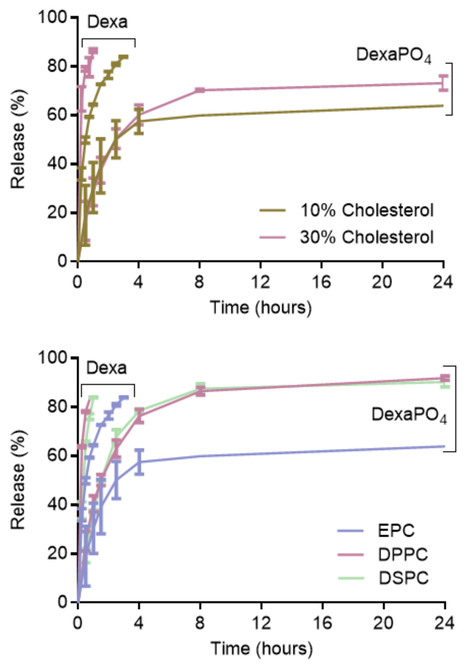

Figure 5. Comparison of Dexa- and DexaPO_4-liposomes SR.

4. CONCLUSION & PERSPECTIVES

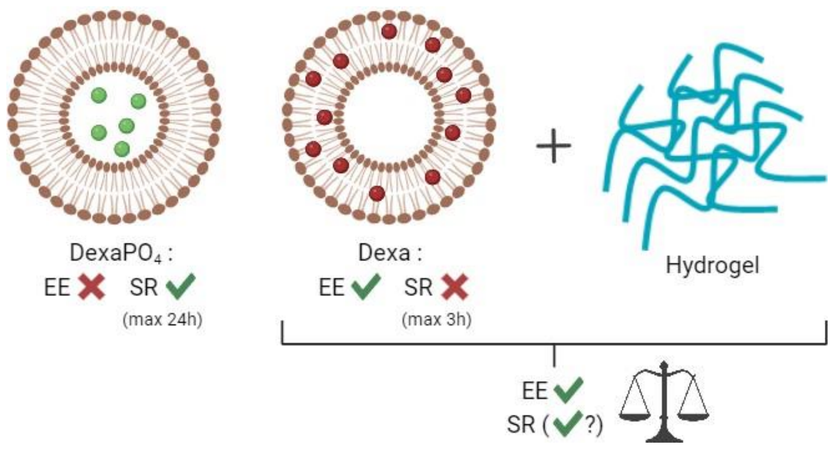

Figure 6. Dexa-liposomes will be dispersed in a hydrogel to improve the SR effect [4].

Changes in liposome composition

The lipids considered for liposome formulation optimization demonstrated no improvement in the release kinetics of encapsulated APIs. Some components, though, seemed useful to significantly improve EE (10% Chol, EPC, etc.). Some of these formulations will have to be tested *in vitro* to gauge their cytotoxicity on RWM cells, which will be modeled by HSAE cells, and inner ear hair cells, which will be modeled by HEI-OC1 cells. Most biocompatible lipids will be considered for the final liposome formulation.

5. REFERENCES

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[4] Created with BioRender.

6. ACKNOWLEDGMENTS

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