In vitro investigation of inhalation delivery of nebulized liposomes

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Introduction

- Liposomes can carry an active pharmaceutical ingredient inside the vesicle.
- Liposomal carrier = prospective carrier system (better retention in lungs, targeted delivery...)
- Liposomal drug delivery by nebulizer:
  - Can the vesicles survive the nebulization?
  - How to effectively deliver the system into the airways?

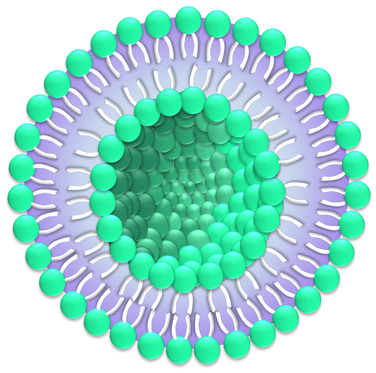

Figure 1: Liposomal vesicle

Goals

- *To measure the change of liposomal vesicle size distribution before and after the nebulization.*
- *To measure the fraction of aerosol able to penetrate below the upper airways using the realistic airway replica.*

Material & methods

Two liposomal systems:

- 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), Cholesterol (Chol), and 1,2-dilauroyl-sn-glycero-3-phosphate (PA)
- DPPC, Chol, and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-5000] (PEG)

Nebulizers:

  - Pari LC Sprint, (PARI GmbH, Starnberg, Germany)
  - Pari LC Sprint Star (PARI GmbH, Starnberg, Germany)

- Vesicle size distribution was measured by ZetaSizer Nano ZS (Malvern Instruments Ltd.) **before** and **after the nebulization**.

→ Vesicle damage

The *in vitro* deposition was measured in 3D printed **upper airway** and **trachea replicas** reported by *Lizal et al 2012* (figure 2) for the aerosol nebulized by Pari LC Sprint Star nebulizer. The phospholipid fluorescently labelled by ATTO 488 was used as a way of the vesicle labeling which enabled the evaluation of deposition Deposition fraction was evaluated from the mass of the ATTO 488 dye in the replica segment. The samples were measured by spectrofluorimeter FS5 (Edinburg Instruments Ltd, UK).

Inhalation flow rate:

1. Steady**: 20 l/min**
2. Realistic inhalation profile (Farkas et al, 2020)

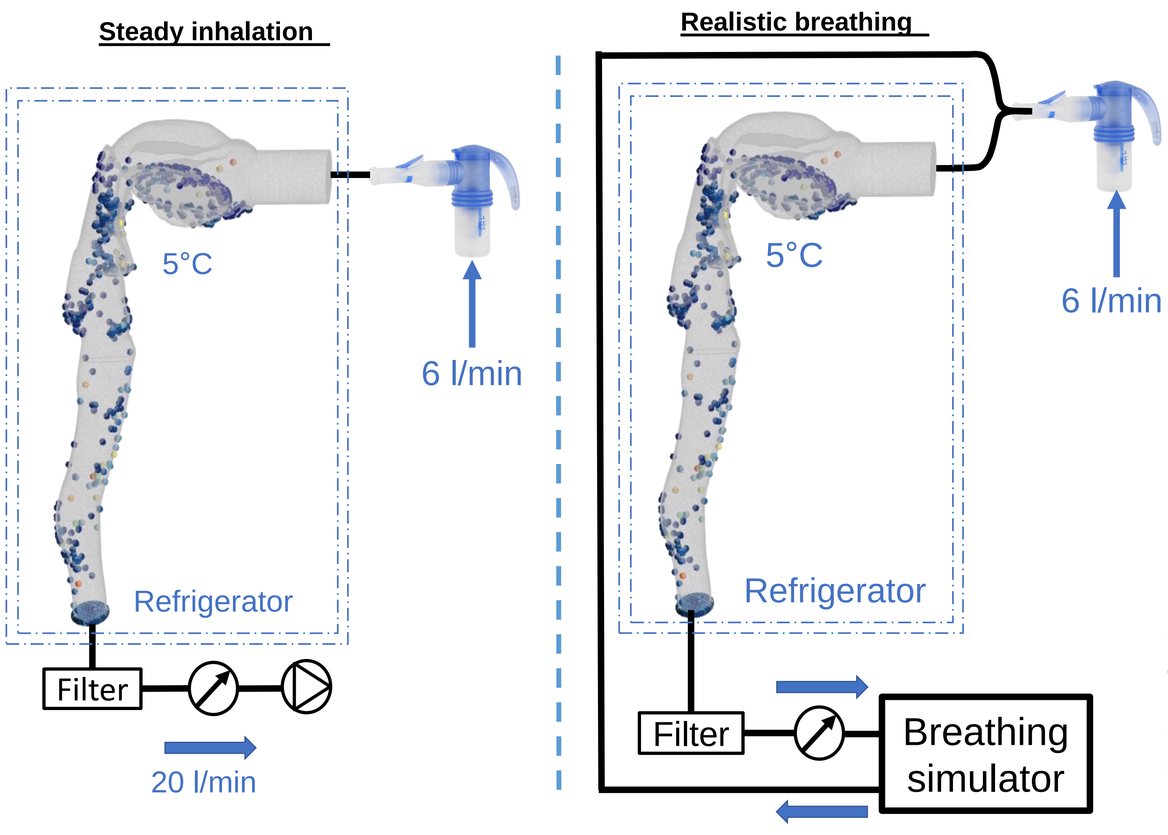

Figure 2: Scheme of the aerosol deposition measurement

Results

Table 1: MMAD of the nebulized aerosol

MMAD [µm]	DPPC-PEG-Chol	DPPC-PA-Chol
PARI LC Sprint	9.79 ± 0.41	10.43 ± 0.49
PARI LC Sprint Star	7.14 ± 0.31	7.39 ± 0.24

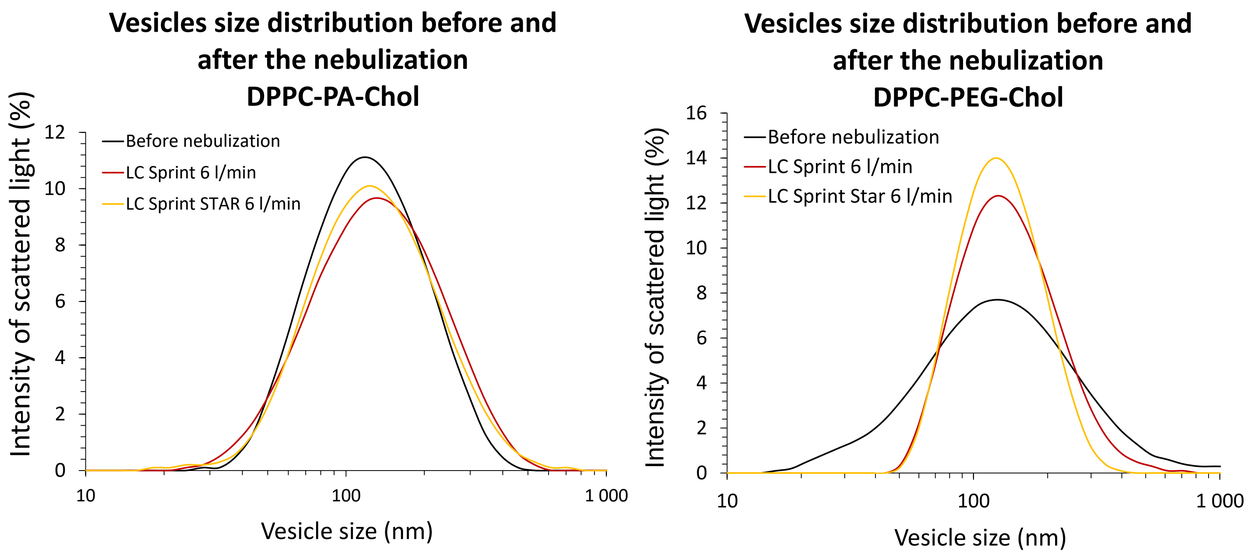

Figure 3: Change of vesicle size distribution of liposomal systems during the nebulization by 2 air-jet nebulizers.

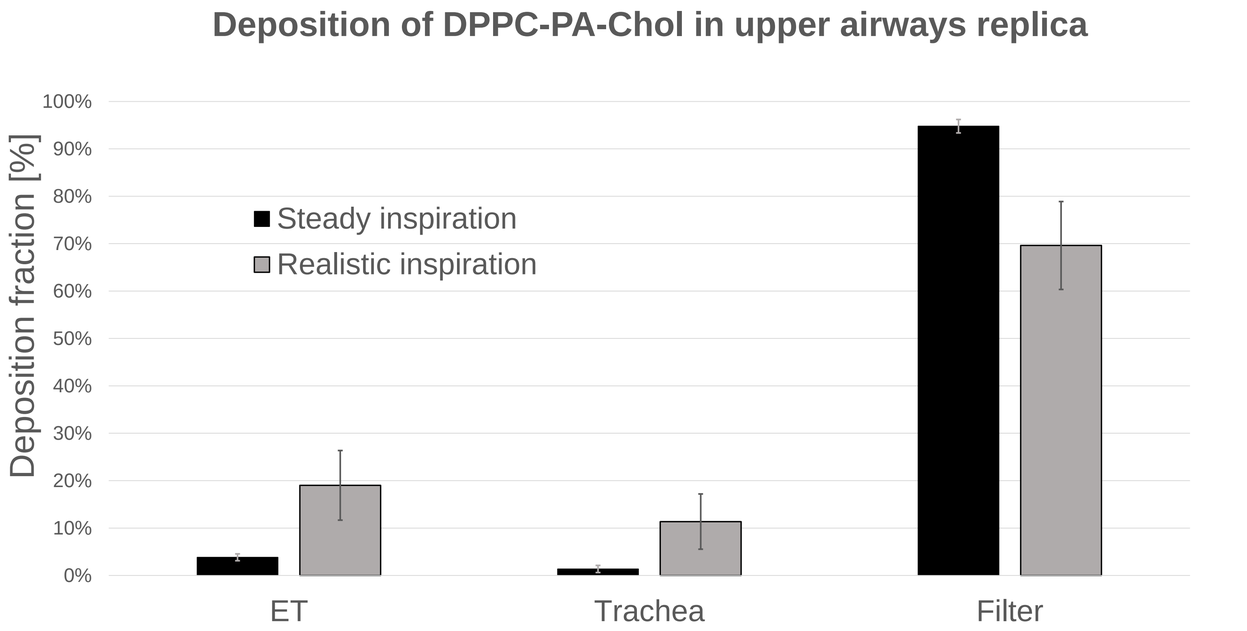

Figure 4: Deposition fraction within the airways model after steady inhalation and realistic breathing profile.

Conclusion

- The liposomal system DPPC-PA-Chol was more resistant to the nebulization.
- The aerosol nebulized by Pari LC Sprint Star had smaller MMAD (approx. 7 µm) than Pari LC Sprint (approx. 10 µm) but the liposomal system had no significant influence on aerodynamic particle size distribution.
  - The fraction of the aerosol mass which penetrated below the trachea was very high:
    - 94.79 ± 1.43 % for the steady inhalation,
    - 69.62 ± 9.28 % for the realistic inhalation.
- The liposomal system DPPC-PA-Chol can be effectively delivered into the lungs without significant damage of the

References

1. Farkas Á, Lizal F, Jedelsky J, et al. The role of the combined use of experimental and computational methods in revealing the differences between the micron-size particle deposition patterns in healthy and asthmatic subjects. *J Aerosol Sci*; 147. Epub ahead of print 2020. DOI: 10.1016/j.jaerosci.2020.105582.
2. Lizal F, Elcner J, Hopke PK, et al. Development of a realistic human airway model. *Proc Inst Mech Eng Part H J Eng Med* 2012; 226: 197–207

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