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Inhaled Nanomedicines Using a Vibrating-mesh Nebuliser: Particle Size Considerations

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SUMMARY

Vibrating-mesh nebulisers have a reputation for having a gentle and successful aerosolization process while preserving the integrity of biologic formulations. The main component of a vibrating-mesh nebuliser is the oscillating membrane. This is formed by thousands of micron-sized pores that oscillate to generate a fine mist. These pores have the potential to be blocked depending on the formulation, especially if it is not a homogeneous solution. In this experiment, poly-lactic-co-glycolic acid nanoparticles (PLGA-NPs) of three varied sizes (100, 200 and 500 nm) were nebulised. The aim was to understand the impact of particle size and concentration on nebulisation using the FOX® vibrating-mesh nebuliser. PLGA-NPs of 100 and 200 nm size were successfully nebulised over a wide concentration range (from 0.1 to 10 mg/ml) in terms of percentage aerosolised and nebulisation time. Particles of larger size (500 nm) showed a long nebulisation time which might correlate with membrane blockages. A substantial proportion of the nanomedicines in the market and under development have a particle size around 100-200 nm. The result of this study showed that the FOX® vibrating-mesh nebuliser can be a suitable platform to successfully deliver these types of nanomedicines to the lungs.

INTRODUCTION

Nebulisers can transform liquid formulation into fine inhalable aerosol droplets that can travel deep into the respiratory tract. Vibrating-mesh nebulisers are preferred over jet-nebulisers as they are low shear and gentler to formulations as well as portable. An example of mesh-nebuliser is the FOX®: a breath activated, hand-held device that is optimised to deliver formulations to the lung periphery (Munro, 2017). The critical aerosol generating component of a vibrating-mesh nebuliser is the membrane. There are thousands of micron size pores in a membrane that, upon oscillation in the 80-120 kHz range, convert a liquid into an inhalable aerosol. Due to the small diameter of the pores, they have the potential to become blocked by unoptimised nanomedicines. In this study, the effect of different solid particle sizes on nebulisation efficiency was investigated. With special interest in establishing critical success factors for inhaled nanomedicines such as vaccines or nanoparticles.

MATERIALS AND METHODS

Degradex® fluorescent PLGA-NPs were purchased from Sigma Aldrich at different particle sizes (100, 200 and 500 nm). The lyophilised powder was reconstituted with sodium chloride (0.9% w/v) and polysorbate 80 (0.02% w/v) to achieve concentrations from 0.1 to 10 mg/ml. The FOX® vibrating-mesh nebuliser was filled with 300 µl of each formulation

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and nebulised in a continuous mode until empty detection was triggered (continuous mode is a laboratory research mode, whereas the FOX® devices used by patients are breath actuated i.e. only nebulised on inspiration). Nebulisation time was recorded, and particles aerosolised collected for fluorescence quantification (SpectraMax®-445/500 nm). Salbutamol sulphate solution was nebulised as a positive control - unchallenging liquid solution with no suspended solid particles. Additionally, budesonide suspension was nebulised as a negative control. Particles of budesonide were significantly larger than the nebuliser's pores with a d(90) of 6.9 µm as measured by laser diffraction. Salbutamol and budesonide concentrations were quantified by HPLC-UV.

RESULTS AND DISCUSSION

Initially, PLGA-NPs freeze-dried cakes were resuspended in different solution and the presence of polysorbate 80 (0.02% w/v) was critical to establish a stable suspension. The particle size was measured before and after nebulisation and physical properties remained unchanged (data not shown). Figure 1 represents the percentage of PLGA-NPs nebulised depending on concentration and particle size. Overall, all the PLGA-NPs sizes and concentrations went through the vibrating-mesh of the FOX® at a percentage comparable to salbutamol solution (positive control). The percentage of budesonide nebulised was much lower, suggesting that those particles were not able to pass through the micron-sized pores of the device (negative control).

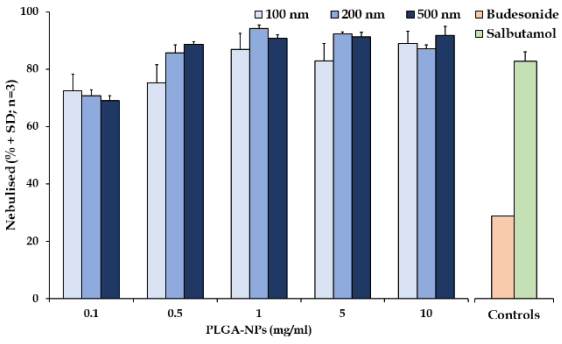

Fig. 1. *Percentage of nebulised formulations at different concentrations and particle size.*

The main differences in formulation performance were represented in Figure 2. Time to nebulise 300 µl of formulation in a continuous mode is plotted as a function of particle size and particle concentration. Particle size of 100 and 200 nm nebulised at a consistent speed independent of the concentration of the formulation. However, larger particles of 500 nm increased in total nebulisation time. This aligns with the negative control (budesonide) and indicates that PLGA-NPs around 500 nm were not successfully nebulised with the mesh-nebuliser and may result in blockage of the micron-sized pores. Alongside particle size, there are other physicochemical properties that need to be taken into consideration when developing a formulation for vibrating-mesh nebulisation, such as viscosity, surface tension or conductivity (Lock, 2023).

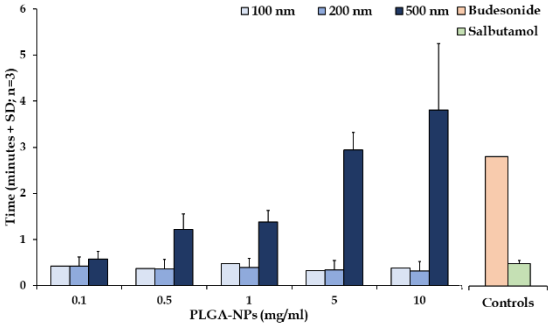

Fig. 2. *Time to continuous nebulise 300 µl of formulations at different concentrations and particle size*

CONCLUSIONS

Nanomedicines can be successfully nebulised using a vibrating-mesh nebuliser such as the FOX®. The particle size of the nanomedicine is critical to achieve successful delivery of the formulations with particles of 200 nm or lower being successfully nebulised. Thus, it is feasible to use mesh nebulisation as a mechanism to deliver nanomedicines to the lungs for either local effect or delivery to the systemic circulation via the pulmonary route.

REFERENCES

Lock, D., 2023. Multi-Factor Understanding of Vibrating-Mesh Nebulization: Placing Patient Needs at the Center of the Combination Product Development Process. RDD23, 2023: 437-442

Munro, S., Main, M., Vos, W., 2017. Matching delivery device to a patient's condition: Use of lung deposition modelling to optimise delivery in idiopathic pulmonary fibrosis. BJPharm, 1, 1-13.