Multi-factor understanding of vibrating-mesh nebulization: Placing patient needs at the center of the combination product development process

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INTRODUCTION

- The delivery of orally inhaled drug products (OIDPs) by nebulization is a long-standing mode of administration for the treatment of respiratory disease, with numerous marketed drug-device device combinations administered at home and in controlled clinical settings [1].
- Unlike typical dry powder inhalers (DPI) and pressurized metered dose inhalers (pMDIs) nebulizer performance is measured in terms of treatment duration. Reducing treatment time is crucially important for all patients, especially for those with high treatment burden disease, such as cystic fibrosis and pulmonary arterial hypertension [2].
- This study evaluated the aspects of nebulized drug delivery that can be optimized by the formulator and device engineer to ensure OIDPs can be effectively delivered in the shortest possible time, using Vectura's FOX® vibrating-mesh nebulizer (VMN)

METHODS

Scanning electron microscopy

- The median diameter of FOX meshes was determined by scanning electron microscope (SEM, EVO 25) using SmartSEM touch software.
- Image analysis was performed using ZEN Core 3.5 (Carl Zeiss Ltd, Warwickshire, UK)

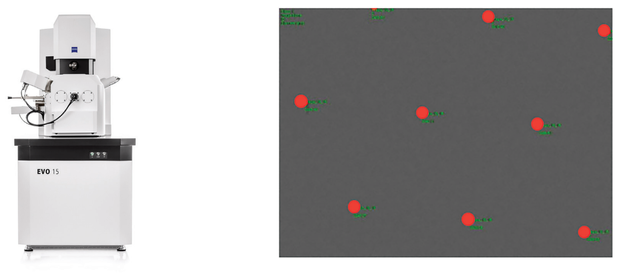


Figure 1: SEM, EVO25 and an example image of a membrane with highlighted membranes

Laser diffraction

- The volume median diameter when nebulising 0.9% saline (VMD_S) was determined using a Sympatec HELOS (Sympatec GmbH, Germany)
- An R3 lens was used and the aerosol was created with successive device actuations similar to patient simulated use

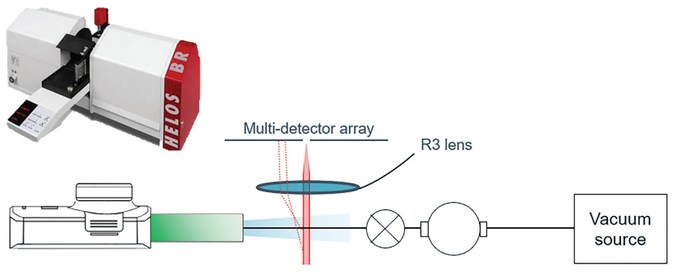


Figure 2: Sympatec instrument and illustration of experimental set-up

Viscosity and model inputs

- The Viscosity (m-VROC viscometer, Rheosense, Inc. CA, USA) of solutions prepared with defined concentrations of PEG4000 was determined and tested in a matrix design with nebulizers stratified by the VMD_S

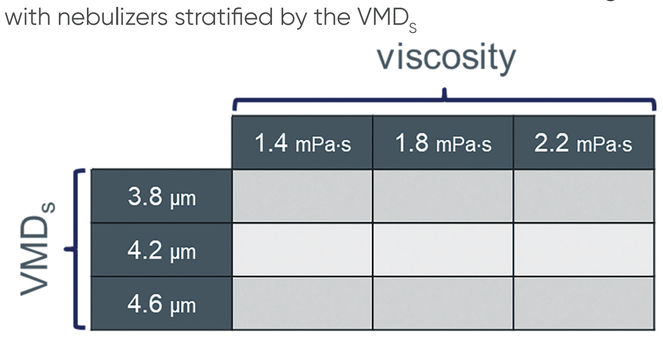
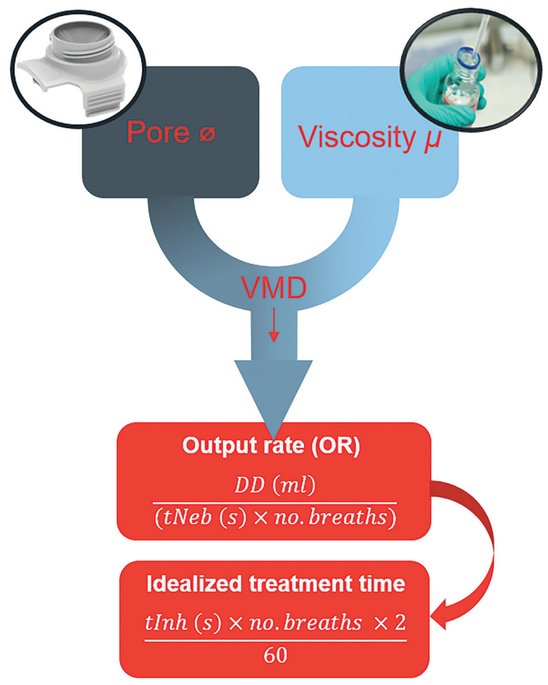


Figure 3: Matrix testing approach for input to the model with equally distanced values for VMD_S and viscosity

COMPONENTS OF THE MODEL



KEY SUMMARY

- Understanding of product critical factors is essential for making optimal development decisions
- Models of drug/device combination products can be used to ensure that
  1. The Target Product Profile (TTP) is met
  2. Early development is efficient
  3. Risks to success e.g. long treatment times can be actively managed
- Using a model of performance which considers patient factors such as treatment time as an output, both formulators and device engineers can optimize performance with respect to the patient as a key stakeholder in development.

RESULTS

1. Correlation between pore diameter and VMD_S

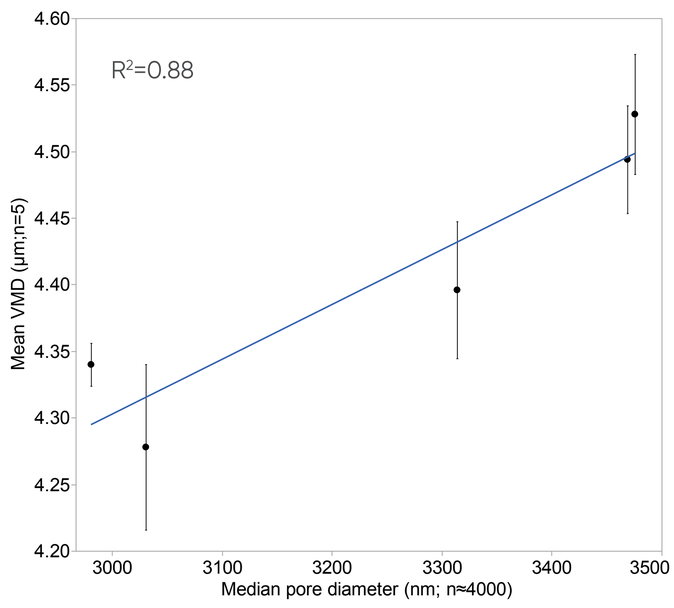


Figure 4: Pore diameter measured by SEM correlated against VMD_S determined by laser diffraction

RESULTS

2. VMD and output rates achieved with solutions of differing viscosity

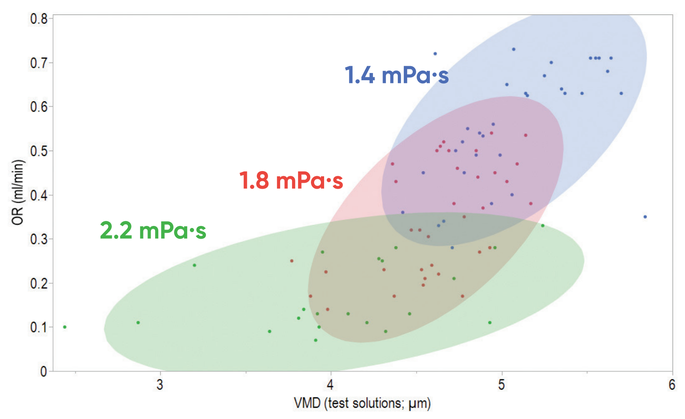


Figure 5: The VMD values obtained using test solutions plotted against output rate

A fixed effect regression model was created using VMD_S and solution viscosity as inputs and output rate and treatment time as outputs

CONCLUSIONS

- Pore geometry and solution properties strongly influence the performance of vibrating-mesh nebulizer products.
- Where treatment time is to be minimized, a model of performance can be utilized to directly relate fundamental device and formulation properties to the patient experience.

Table 1: Estimated treatment times for a 1.8 mPa·s solution at a fill volume of 2 ml

Viscosity (mPa·s)	VMD_S (µm)	Predicted OR (ml min-1) ± 95% CI	t to deliver 2 ml (min)
1.8	3.8	0.25 ± 0.13	14 – 44
1.8	4.2	0.33 ± 0.05	14 – 19
1.8	4.6	0.43 ± 0.08	10 - 15

- Importantly, both viscosity and VMD_S can be controlled and understood to direct development towards an optimal configuration to reduce patient treatment burden.
- In addition, the benefits of breath actuated delivery with slow and deep inhalation – such as employed using FOX – may increase the effective lung dose and thereby further reduce treatment time [3][4].

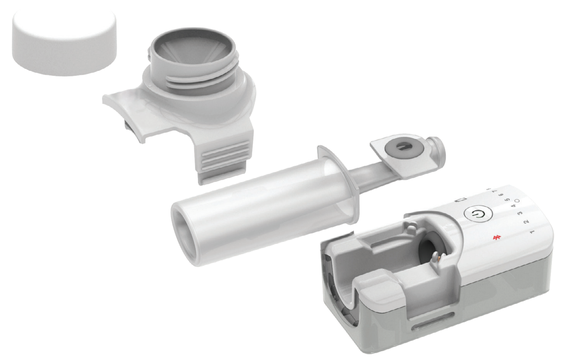


Figure 6: Vectura's FOX vibrating-mesh nebulizer

REFERENCES
1. Martin AR, Finlay WH; Nebulizers for drug delivery to the lungs, *Expert opinion on drug delivery* 2015, 12: 889-900
1. Dobler CC, Harb N, Maguire CA, Armour CL, Coleman C; Treatment burden should be included in clinical practice guidelines, *BMJ (clinical research ed.)* 2018, 363
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