Benchmarking of Particle Engineering Strategies for Nasal Powder Delivery: Characterization of Nasal Deposition using the Alberta Idealized Nasal Inlet

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Introduction

Powder formulations of a drug and mucoadhesive polymer have increased residence time in the nasal cavity and can be manufactured by blending, spray-drying or agglomeration of primary particles into chimeral agglomerates[1].

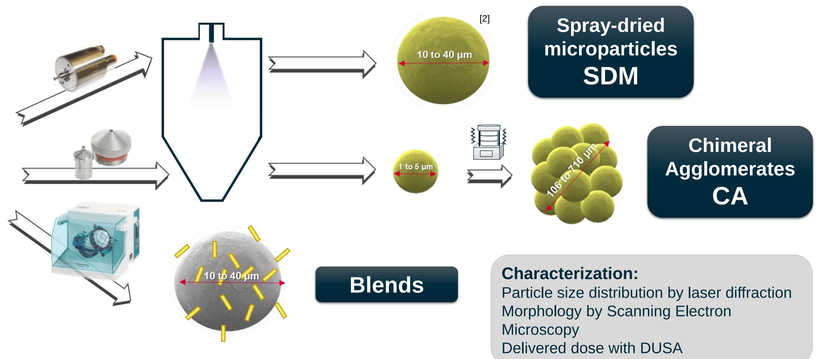
While spray-drying allows particle size control and generation of amorphous solid dispersions (ASD), blending is simpler and CA should allow faster dissolution after breakup into smaller particles.

The objective of this study was to characterize nasal deposition and benchmark nasal powders manufactured by different particle engineering strategies, namely **spray dried microparticles (SDM), chimeral agglomerates (CA) and blends**, using the **Alberta Idealized Nasal Inlet (AINI)**. The AINI method conditions were firstly optimized by selecting appropriate angle of actuation and flow rate. Then, six different formulations prepared with distinct polymers and particle engineering strategies were evaluated.

Methods

Drug	Polymer
Piroxicam 20%	PVP/VA or HPMC E3

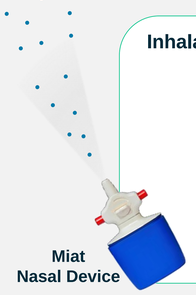
HPMC - hydroxypropyl methylcellulose E3
PVP/VA - polyvinylpyrrolidone/vinyl acetate



Characterization:
Particle size distribution by laser diffraction
Morphology by Scanning Electron Microscopy
Delivered dose with DUSA

Nasal deposition studies with Alberta Idealized Nasal Inlet (AINI)

1) Method optimization with formulation with highest and most reproducible delivered dose



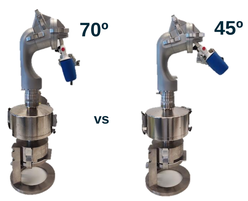
Inhalation flow rate

7.5 L/min

vs

15 L/min

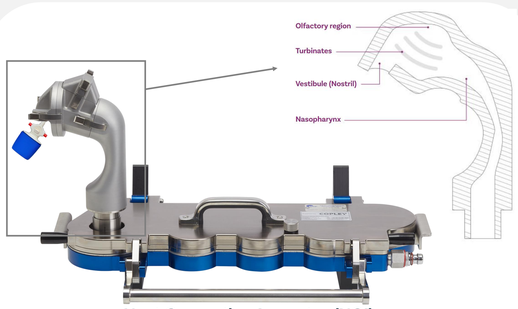
Angle of actuation



Fixed variables

- Coating with Brij solution (0.15 g/ml Brij in ethanol) in glycerol (1mL Brij solution for 5 g glycerol)[3];
- 3 actuations of 2 seconds each.

2) Formulation testing



Next Generation Impactor (NGI)

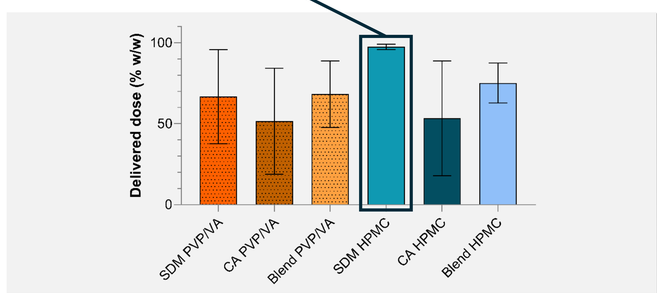
Results and Discussion

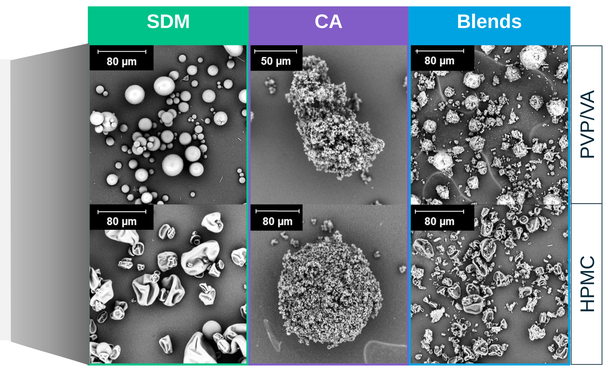
Physicochemical characterization and delivered dose

Formulation	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)
SDM PVP/VA	13.10 ± 0.39	28.40 ± 0.62	50.31 ± 0.61
SDM HPMC	17.43 ± 0.47	44.60 ± 0.33	82.92 ± 0.29
Primary particles for CA PVP/VA	0.50 ± 0.01	2.01 ± 0.03	4.97 ± 0.03
Primary particles for CA HPMC	0.61 ± 0.01	2.86 ± 0.12	6.74 ± 0.41
Blend PVP/VA	2.98 ± 0.02	20.72 ± 0.05	47.29 ± 0.73
Blend HPMC	3.95 ± 0.03	16.42 ± 0.05	33.66 ± 0.13

Results and Discussion

High and reproducible delivered dose (97.5 ± 1.6 %)



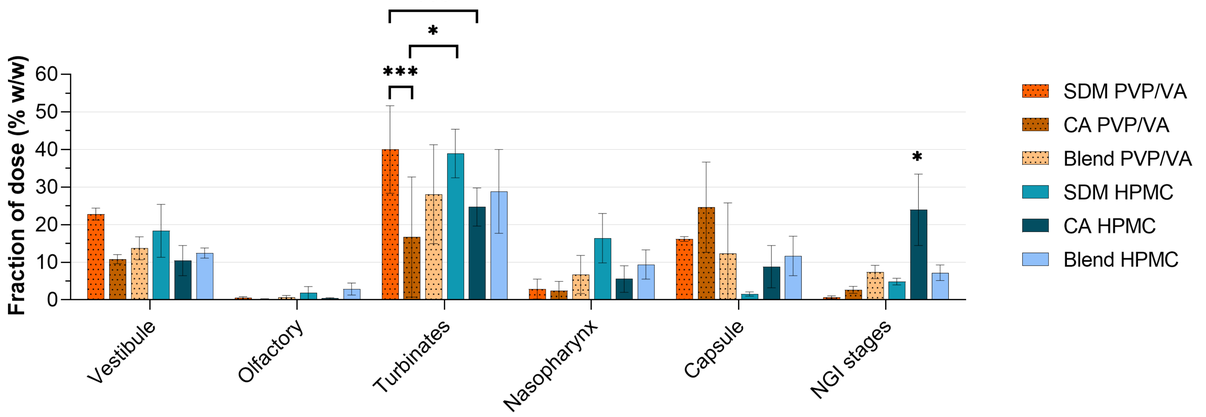


Method Optimization

Administration angle	Inhalation Flow (L/min)	Mass Balance (%)	Dose Fraction (%)				
			Vestibule	Turbinates	Olfatory region	Nasopharynx	Preseparator + Filter
45º	7.5	89.6 ± 6.0	16.9 ± 4.0	50.2 ± 1.5	5.5 ± 2.4	9.5 ± 2.8	6.2 ± 0.5
45º	15	96.6 ± 3.2	11.0 ± 0.9	55.3 ± 7.0	1.3 ± 0.7	20.7 ± 1.5	4.8 ± 0.4
70º	7.5	82.8 ± 3.9	33.7 ± 4.3	27.5 ± 5.8	5.7 ± 1.4	7.3 ± 4.4	4.7 ± 1.7
70º	15	103.5 ± 4.9	35.3 ± 6.8	41.3 ± 0.8	6.8 ± 1.8	14.5 ± 7.6	4.0 ± 1.0

- Angle of 45º - lower vestibule deposition and higher turbinates deposition, indicating better suitability for drug systemic delivery [4];
- Inhalation flow rate 15 L/min - higher mass balances indicating better suitability of the analytical procedure.

Formulation evaluation



Particle engineering strategy

- The average deposition on the vestibule and turbinates was higher for SDM, followed by blends and CA, evidencing SDM as an advantageous particle engineering strategy for nasal targeted systemic delivery.
- HPMC based CA showed high deposition on the NGI stages (24.0 ± 9.5 %), suggesting that the agglomerates may break into fragments that can reach the lungs

Polymer

- For the same particle engineering strategy, PVP/VA based formulations had higher average deposition on the vestibule and lower average deposition on the nasopharynx, compared with HPMC based formulations.
- There is a tendency for higher deposition of PVP/VA based formulations on the anterior part of the AINI, possibly as a result of the higher particle agglomeration and cohesion.

Conclusions

- The present work aimed to develop and characterize nasal deposition of nasal powders manufactured by 3 different particle engineering approaches.
- SDM exhibited higher deposition on the **turbinates area** of the AINI, evidencing spray-drying as an advantageous technology for **nasal targeted systemic delivery**. CA required an extra manufacturing step and presented higher risk of lung deposition since the size of primary particles is in the inhalation size range.
- Due to the high delivered dose and high turbinates deposition, HPMC based SDM seem to be the lead candidate for further performance studies as *in vitro* release and permeation.
- To the best of our knowledge, this is the first study benchmarking manufacturing strategies regarding nasal powder deposition.

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