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 (CA) [1]. While spray-drying allows particle size control and generation of amorphous solid dispersions, 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), 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

Piroxicam was selected as model drug for systemic delivery, and polyvinylpyrrolidone/vinyl acetate (PVP/VA) and hydroxypropyl methylcellulose E3 (HPMC) as polymers. Spray-drying was performed using ultra-sonic (USN) and two-fluid nozzle (TFN) to produce microparticles within the nasal size range and primary particles for agglomeration, respectively, in a Büchi model B-290 unit. Chimeral

agglomerates were produced by vibrating primary particles in a sieve shaker equipped with 106 μm and 710 μm mesh size sieves. Agglomerates retained on top of the 106 μm sieve were collected. Physical blends were obtained by mixing neat polymer microparticles with piroxicam raw material in a Turbula blender. All formulations were produced at 20% (w/w) drug load.

Particle size of the powder formulations was assessed by laser diffraction. Powders (20 mg) were filled in QUALI-V®-I capsules size 3 which were placed on the active device Miat nasal insufflator. The delivered dose during insufflation was determined using a Dosage Unit Sampling Apparatus, applying a 15 L/min flow rate for 2 seconds in 3 actuations. The formulation with the highest and most reproducible delivered dose was used to optimize nasal deposition method.

Nasal deposition was evaluated using the AINI. To mitigate particle bounce, the AINI was coated with Brij solution (0.15 g/ml Brij in ethanol) in glycerol (1mL Brij solution for 5 g glycerol) [2]. For method optimization, the AINI was coupled with a Fast Screening Impactor (FSI), and the impact of angle of actuation (45º and 70º) and inhalation flow rate (7.5 L/min and 15 L/min) were evaluated in 3 actuations of 2 seconds each. Absence of airflow could not be tested since the large tip of the device could not be fully inserted in the nostril, and great losses of powder were observed. For formulation deposition evaluation, the AINI was coupled with Next Generation Impactor (NGI). Drug quantification was performed by High Performance Liquid Chromatography with absorbance detector. Experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Physicochemical characterization and delivered dose

SDM and blends presented a Dv50 within the nasal size range of 10 to 45 μm [3] (Table 1).

Table 1 – Particle size of powder formulations.

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

CA – chimeral agglomerates; HPMC – hydroxypropyl methylcellulose PVP/VA - polyvinylpyrrolidone/vinyl acetate SDM – spray dried microparticles.

Delivered dose was high and reproducible for SDM of HPMC (97.5 ± 1.6 %). For the rest of the formulations, it was lower (51.6 to 75.1 %) and highly variable (standard deviations of 12.3 to 35.5 %). Consequently, SDM of HPMC was the formulation used for AINI method optimization.

AINI Method Optimization

Two method variables were studied, namely administration angle and inhalation flow (Table 2). The lower administration angle of 45º resulted in consistently lower vestibule deposition and higher turbinates deposition (Table 2), which is in agreement with a study by Chen *et al.* [4] using other nasal devices. These results indicate that a 45º angle has better suitability for drug systemic delivery.

Regarding the inhalation flow, a 15 L/min flow led to higher mass balances (percentage of mass of drug recovered on AINI, FSI and capsule) (Table 2), indicating better suitability of the analytical procedure. Accordingly, a 45º angle and 15 L/min inhalation flow were the experimental conditions selected for nasal deposition studies.

Table 2 – Mass balance and deposition profile of SDM HPMC formulation under the experimental conditions tested

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

Nasal Deposition Profile of Powder Formulations

The results show that the particle engineering strategy has impact on nasal deposition profile (Figure 1). The average deposition on the vestibule and turbinates was higher for SDM, followed by blends and CA, with statistically significant differences between SDM and CA on the turbinates ($p < 0.05$, two-way ANOVA) except between SDM HPMC and CA HPMC ($p = 0.077$), 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 (Figure 1).

The polymer also showed impact on powder deposition (Figure 1). 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. Even though no statistically significant differences were observed, 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. Due to low dose fraction retained in the capsule (1.6 ± 0.6 %) and high dose deposited on the turbinates region (38.9 ± 6.5 %), HPMC based SDM would be the lead formulation candidate for further studies.

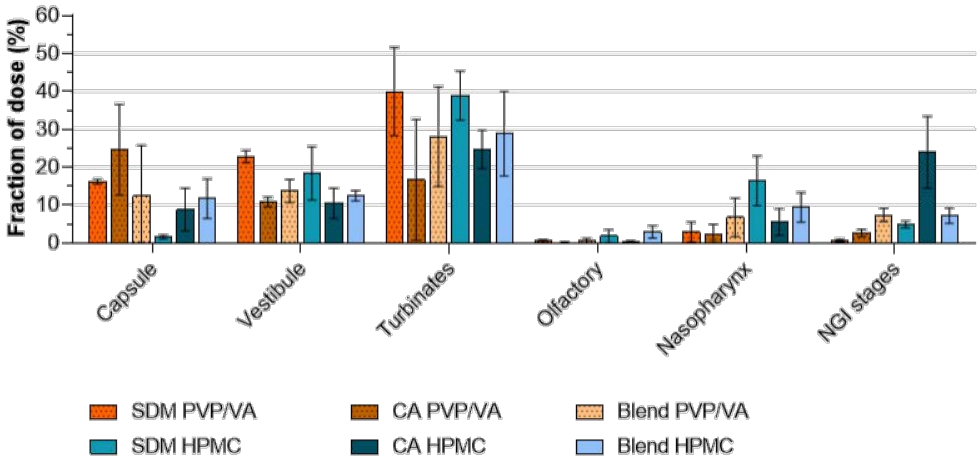

Figure 1 – Nasal deposition profile of powder formulations using AINI coupled with NGI. CA – chimeral agglomerates; HPMC – hydroxypropyl methylcellulose; PVP/VA - polyvinylpyrrolidone/vinyl acetate; SDM – spray dried microparticles.

CONCLUSIONS

The present work aimed to develop and characterize nasal deposition of nasal powders manufactured by three different particle engineering approaches. SDM within the nasal size range were successfully produced and exhibited higher deposition on the turbinates area, 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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