Amorphous solid dispersions for nasal delivery

Powder formulation and particle engineering considerations

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Nasal delivery is the primary option for the treatment of topical nasal disorders. However, there has been growing interest in using this route for systemic treatments. This is due to fast and direct drug absorption that circumvents pre-systemic gastrointestinal and hepatic first-pass metabolism, allowing quick onset of action and possible reduction of dose [1]. Therefore, systemic delivery through nasal administration is particularly relevant for drugs that require fast onset of action in acute or emergency conditions [2].

Due to its large surface area and extensive vascularization, the respiratory region of the nasal cavity, where the turbinates are located, is the target for systemic drug delivery [3]. Additionally, the olfactory epithelium in the olfactory region of the nasal cavity allows unique contact between the external environment and the central nervous system (CNS) and can enable an intranasal drug to directly target the brain. This strategy can circumvent the blood-brain barrier and it is commonly referred to as nose-to-brain delivery. The targeted delivery through this pathway, with direct nose-to-brain drug transport, can reduce side effects related to systemic delivery and improve the efficacy of neurotherapeutics [4].

Powders for nasal delivery have been recognized as advantageous dosage forms compared to liquids, due to their increased stability and residence time on nasal mucosa as well as improved bioavailability. Nasal powders also represent an opportunity to administer poorly soluble drugs, which have been emerging in the drug discovery pipeline [5], namely through the development of amorphous solid dispersions (ASD). This approach can improve drug dissolution and, subsequently, systemic absorption [6, 7].

Nasal powders can be manufactured by utilizing diverse methodologies including lyophilization [8-13], spray drying [14-20], supercritical fluid-assisted spray drying [21], spray freeze drying [22-24] and agglomeration of micronized powders [25-30]. Spray drying is one of the techniques used most often for nasal powder preparation, as it allows continuous processing and produces well-controlled particle characteristics such as size and shape [31], which may impact therapeutic outcomes [32]. A diverse range of particle sizes and morphologies can be designed, including microencapsulated particles and large porous particles with varying aerodynamic particle sizes. In addition, the technology is scalable and equipment sizes range from research-scale to commercial-scale.

Despite these opportunities, nasal powder research and development is a new area compared to nasal sprays. Only two nasal powders for systemic action have been approved by the United States Food and Drug Administration (FDA), both within the last seven years: Onzetra® Xsail®, a sumatriptan product for migraine approved in 2016 [33] and Baqsimi®, a glucagon powder for severe hypoglycemia approved in 2019 [34].

In fact, the scientific community still struggles with the existing gaps among formulation composition, particle engineering and nasal absorption. The complex interplay among particle deposition, mucoadhesion, drug release and permeation is generally difficult to mimic *in vitro* and strongly dependent on formulation and particle design.

The aforementioned challenges and the opportunity for nasal powders to improve bioavailability are leveraging research in developing formulation and process strategies, along with advanced performance characterization methodologies that can predict *in vivo* behavior in nasal powder early development. In the following sections, two case studies are presented, where different particle engineering and formulation strategies were evaluated, focusing on nasal delivery of poorly soluble drugs.

Benchmarking of particle engineering strategies for nasal powder delivery

Polymeric nasal powders can be manufactured by different particle engineering strategies including blending of drug and excipient(s), spray drying or agglomeration of primary particles into chimeral agglomerates (CA) [35]. While spray drying allows particle size control and generation of amorphous solid dispersions, blending is simpler and CA may 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 Idealised Nasal Inlet (AINI, Copley Scientific, Nottingham, UK).

The AINI (Figure 1) is an idealized nasal airway geometry constructed of aluminum, developed according to computational fluid dynamics simulations performed in a set of realistic nasal geometries, in order to mimic human nasal deposition [36, 37]. It has four different regions, namely the vestibule (nostril), the turbinates, the olfactory region and the nasopharynx, which can be separated, allowing drug quantification. The AINI can be coupled with a Next Generation Impactor (NGI), providing additional information about lung deposition [38].

In total, six different formulations of a model drug were prepared using two polymers and three particle engineering strategies. The non-steroidal anti-inflammatory drug (NSAID) piroxicam was selected as a model poorly soluble drug with analgesic characteristics, due to its potential for rapid pain relief when administered through nasal delivery, compared to the conventional oral route. Polyvinylpyrrolidone/vinyl acetate (PVP/VA) and hydroxypropyl methylcellulose E3 (HPMC) were selected as polymers. Spray drying was performed using an ultrasonic (USN) and two-fluid nozzle (TFN) to produce microparticles within the nasal size range (Dv50 of 10 to 45 µm) [39] and primary particles for agglomeration (Dv50 of 2 to 3 µm). Chimeral agglomerates were produced by vibrating primary particles in a sieve shaker equipped with 106 µm and 710 µm mesh size sieves, and collecting the agglomerates retained on top of the 106 µm sieve. Physical blends were obtained by mixing neat polymer microparticles with piroxicam raw material in a Turbula® blender (WAB-Group. Muttenz, Switzerland). All formulations were produced at 20% (w/w) drug load.

Figure 1

Alberta Idealised Nasal Inlet (AINI) coupled with the Next Generation Impactor (NGI). Reproduced with permission from Copley Scientific, Limited [38].

Nasal deposition was evaluated using the AINI coated with Brij solution and coupled with a Next Generation Impactor (NGI, Copley Scientific). A 45° administration angle and 15 L/min inhalation flow were the experimental conditions selected for the nasal deposition studies.

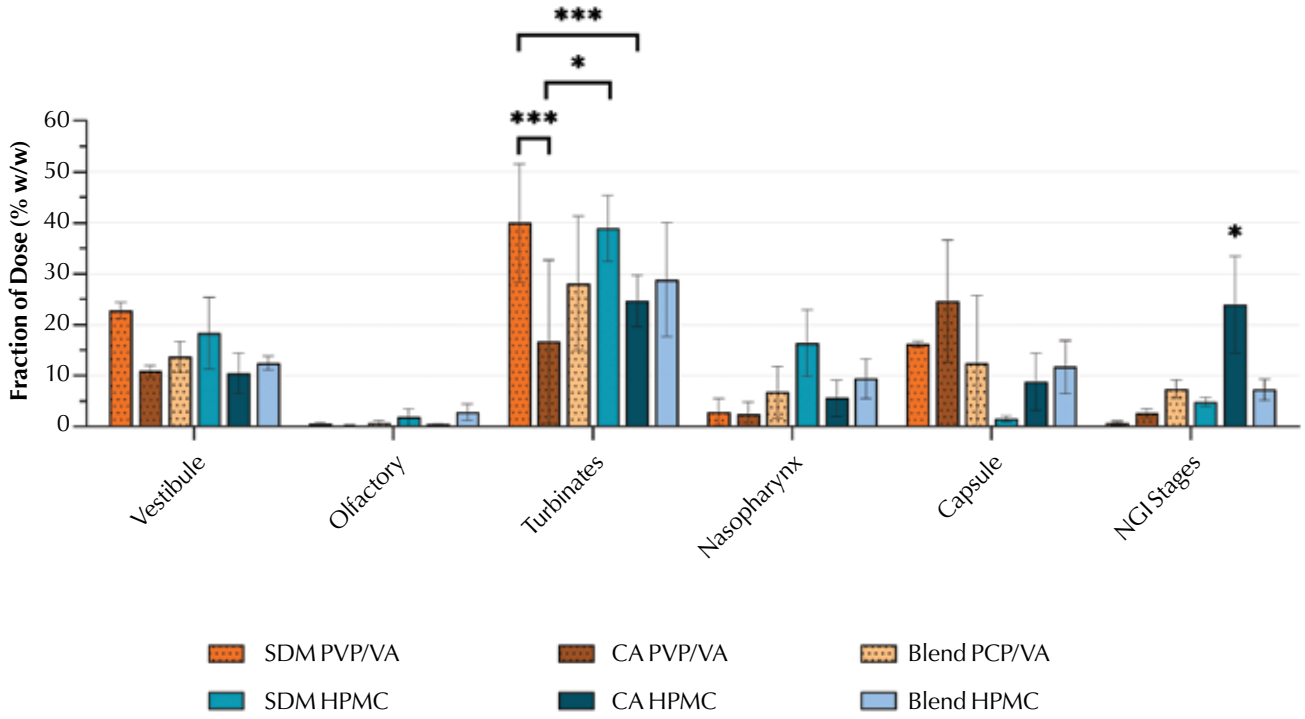
The nasal deposition results show that the particle engineering strategy affects the nasal deposition profile (Figure 2). The average deposition on the vestibule and turbinates was higher for SDM, followed by blends and CA, with statistically significant differences between SDM and CA on the turbinates ($p < 0.05$, two-way ANOVA) except between SDM, HPMC and CA HPMC ($p = 0.077$), demonstrating SDM to be an advantageous particle engineering strategy for nasal targeted systemic delivery. HPMC-based CA showed high deposition on the NGI stages (24.0 ± 9.5%), with 12.9% deposition on NGI stage 1 ($d50 > 14.1$ µm) and 3.7% deposition on NGI stages 5 and 6 ($1.36 < d50 < 3.3$ µm). This last fraction of the formulation can deposit on small airways and the alveoli region since particles are within the aerodynamic size range of 1 to 5 µm. This suggests the agglomerates may break into fragments that can reach the lungs (Figure 2). CA required an extra manufacturing step and presented a higher risk of lung deposition since the size of primary particles was in the inhalation size range. Overall, SDM within the nasal size range was the most promising particle engineering strategy to target nasal systemic absorption.

Supersaturating ASD for fast onset of action through the nasal mucosa

A large number of lipophilic compounds with poor solubility have been emerging in the drug discovery pipeline. In fact, more than three-quarters of new drugs in development are poorly soluble [5], a characteristic that negatively affects drug dissolution and, subsequently, systemic absorption. Therefore, many technologies have been developed to enhance drug solubility such as amorphous solid dispersion (ASD), where a drug is homogenously dispersed in an excipient matrix in an amorphous state. An amorphous form of drug occurs in a higher free-energy state compared to its crystalline counterpart, providing enhanced solubility and dissolution rate [40]. Additionally, amorphous solids can promote super-

Figure 2

Nasal deposition profile of powder formulations using the AINI coupled with the NGI. CA: chimeral agglomerates; HPMC: hydroxypropyl methylcellulose; PVP/VA: polyvinylpyrrolidone/vinyl acetate; SDM: spray-dried microparticles. *p < 0.05 and ***p < 0.001 were considered statistically significant.



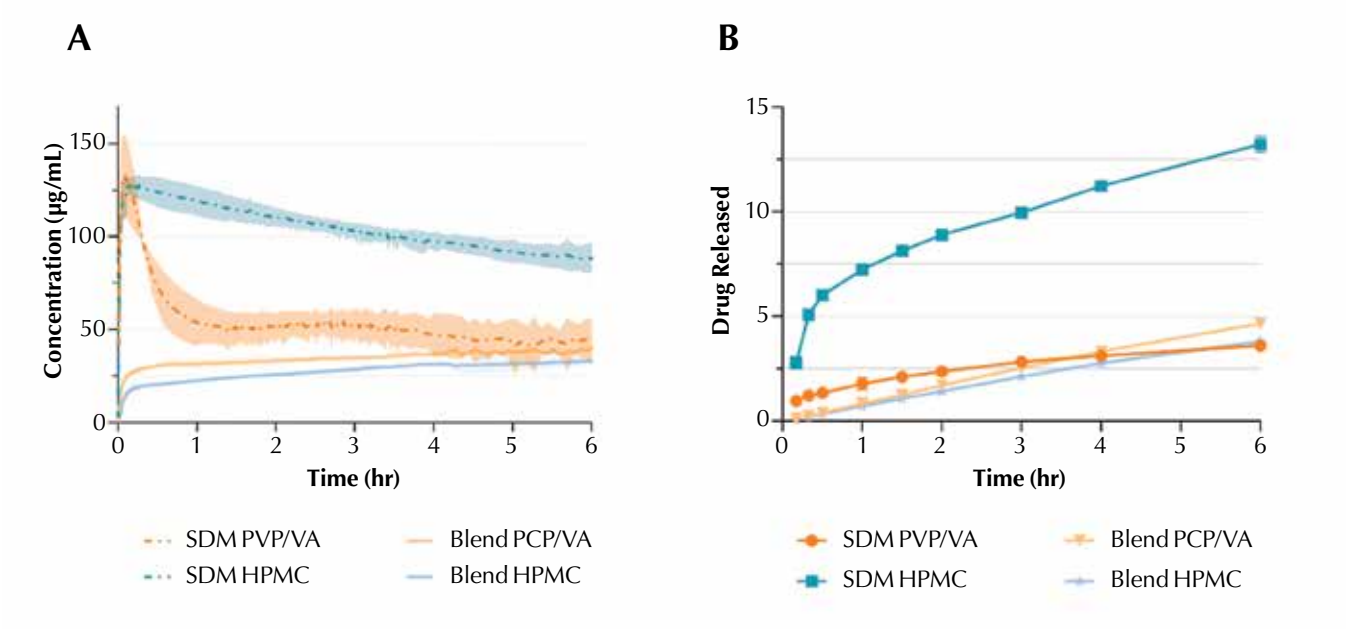
saturation of the drug during dissolution [41]. The supersaturated solution in the nasal mucosa may enhance drug permeation and bioavailability, particularly when absorption is limited by drug solubility [20, 42, 43].

An ASD can be manufactured by spray drying, a scalable process that allows particle size control. Polymers commonly used in ASD, such as HPMC and PVP/VA [7], have mucoadhesive properties [44-46] and, therefore, a dual function: stabilizing the drug amorphous form and enhancing mucoadhesion, which increases both dissolution and residence time of the formulation. However, the impact of different polymers on drug release performance, in many instances, is still not clear and the methodologies available to evaluate the behavior of these formulations are limited. Guidelines from European and US regulators lack recommendations on advanced nasal powder performance characterization, namely regarding drug release, mucoadhesion and permeation. Accordingly, the objective of this study was to characterize the *in vitro* and *in vivo* performance of amorphous spray-dried microparticles (SDM) comprising a model poorly soluble drug piroxicam (PXC) and either HPMC or PVP/VA, at 20% drug load, while comparing with the corresponding physical blends [47]. To achieve this, the SDM and blend formulations manufactured as described in the previous study were evaluated regarding their *in vitro* dissolution and drug release profile, using simulated nasal fluid [47]. Subsequently, *in vivo* pharmacokinetic studies were carried out in Wistar rats for select formulations. The SDM of PXC presented no crystalline peaks on X-ray powder diffraction diffractograms, confirming the formation of an ASD.

Small volume dissolution testing in a MicroDiss Profiler (Pion, Inc., Billerica, MA, US) was carried out to investigate the supersaturation potential of the formulations varying in manufacturing strategy and polymeric composition. The results (Figure 3A) show that the amorphous formulations comprising PVP/VA or HPMC generate a supersaturated solution when in contact with the medium. A PXC concentration of approximately 130 µg/mL was attained for both SDM formulations at 5 minutes, which was about 7 times higher than the concentration attained with the blends. However, this supersaturated state was transient with recrystallization of metastable supersaturated PXC. For PVP/VA SDM, this occurred quickly, with an abrupt reduction of dissolved PXC after 5 minutes, leading to low PXC concentrations that were similar to blends after 4 hours. For HPMC SDM, the decrease was slower and concentrations were maintained higher than those dissolved from blends for the 6 hours of the test. This indicates that HPMC has higher capacity to maintain the supersaturated state of PXC in solution.

Figure 3

Dissolution profile (A) and *in vitro* drug release profile (B) of piroxicam powder formulations. Results are expressed as mean ± standard deviation (n = 3). HPMC: hydroxypropyl methylcellulose; PVP/VA: polyvinylpyrrolidone/vinyl acetate; SDM: spray-dried microparticles.



Franz diffusion cells (PermeGear, Inc., Hellertown, PA, US) were then applied to study the drug release profile of the PXC powder formulations. Contrary to the dissolution experiment, this methodology allows mimicking physiological conditions of the nasal cavity, including temperature, medium and slow powder hydration in a humid environment similar to that encountered in the nasal cavity [48]. The percentage of PXC released was plotted as a function of time (Figure 3B). The PVP/VA-based SDM showed higher percentages of drug release than the corresponding blend for the first 3 hours, while for the HPMC-based SDM this was valid for the 8 hours of the test. Additionally, from the 20-minute timepoint onward, the SDM of HPMC exhibited significantly ($p < 0.001$, ANOVA) higher percentage of drug release, when compared to all other formulations. Blend formulations presented a slower release, with major differences seen in the first 2 hours, most likely due to the crystalline state of the drug. A supersaturated solution generated by the amorphous form of the drug can increase the amount of drug available to cross the artificial membrane, where the polymer plays a major role in the ability to achieve and maintain supersaturation [7]. As observed in dissolution experiments, HPMC sustains the supersaturated drug for a longer period of time, allowing a higher drug release. Even though PVP/VA may promote some degree of supersaturation, the faster drug precipitation hinders the release rate. The small volume used in the MicroDiss Profiler dissolution experiments proved to be helpful in characterizing the "spring and parachute" behavior of ASD [49] and ranking the formulations correctly.

Three formulations, namely HPMC SDM, PVP/VA SDM and HPMC blend formulations, were characterized for pharmacokinetic profile after nasal administration to Wistar rats. Considering the similar dissolution profiles of the blends, only the blend with HPMC was selected for the *in vivo* studies, in order to minimize the number of animals used. Plasma samples were collected for 30 hours after administration. The main pharmacokinetic parameters of the concentration-time profile are summarized in Table 1, as estimated by non-compartmental analysis. SDM of HPMC presented the highest C_{max} and shortest t_{max}, suggesting a faster absorption of PXC. For this formulation, PXC plasma concentration at 20 minutes was significantly higher ($p < 0.01$) than the other formulations. This indicates that SDM of HPMC could provide a faster onset of action with quicker and effective therapeutic action. The amorphous SDM formulations provided lower t_{max} than the blend containing crystalline drug, indicating that the faster drug release provided by these formulations has, as expected, impact on drug absorption. SDM of PVP/VA provided the second highest C_{max}, followed by the blend with HPMC. This indicates that ASD for nasal delivery of poorly soluble drugs could be a suitable strategy to provide a faster onset of action and especially useful in therapeutic indications such as pain management, migraine or angina pectoris [1].

The formulation rankings obtained in dissolution and drug release studies at early timepoints (up to 1 hour) were predictive regarding *in vivo* t_{max} (shorter for formulations with higher dissolution performance) and C_{max} (higher for formulations with higher dissolu-

Table 1

Pharmacokinetic parameters following intranasal or intravenous administration of piroxicam, evaluated by non-compartmental analysis.

Pharmacokinetic Parameters	SDM PVP/VA[a]	SDM HPMC[a]	Blend HPMC[a]
t_{max} (h)	2.33	0.89	3.33
C_{max} (µg/mL)	3.35	4.68	3.26
AUC_{1h} (µg.h/mL)	2.16	3.63	1.78
AUC_{30h} (µg.h/mL)	46.05	41.06	44.70

[a] Parameters estimated considering a normalized PXC dose of 0.3 mg

AUC_{1h}: area under the concentration time-curve from time zero to 1 hour

AUC_{30h}: area under the concentration time-curve from time zero to 30 hours

CA: chimeral agglomerates

C_{max}: maximum peak concentration

HPMC: hydroxypropyl methylcellulose

PVP/VA: polyvinylpyrrolidone/vinyl acetate

SDM: spray-dried microparticles

t_{max}: time to achieve the maximum peak concentration

tion performance), indicating that the combination of dissolution and biorelevant drug release testing can represent a robust screening methodology for ASD for nasal delivery.

Conclusion

Nasal powders have been recognized as an opportunity to improve stability and residence time on the nasal mucosa compared with liquids, where amorphous powders favor the formulation of poorly soluble drugs with improved biopharmaceutical profile, namely faster onset of action. However, regulatory recommendations and consensus in the scientific community on how to evaluate nasal powder performance are limited. Moreover, the industry and academia face gaps among particle engineering, formulation and product *in vitro* and *in vivo* performance. Therefore, this article presents two case studies focused on particle engineering strategies and nasal powder formulation of a model poorly soluble drug for systemic delivery, while evaluating performance methodologies.

The results confirm the suitability of spray drying to manufacture particles for nasal delivery. This process is scalable and can be fine-tuned to meet particle size requirements. Spray-dried microparticles of the model poorly soluble drug exhibited higher deposition on the turbinates area than chimeral agglomerates and blend formulations, evidencing spray drying as a suitable technology for nasal targeted systemic delivery. The findings also showed that amorphous solid dispersions generate supersaturated solutions, resulting in enhanced *in vitro* release performance using a biorelevant methodology. Pharmacokinetic studies conducted in Wistar rats confirmed the potential of ASD to provide faster onset of action for poorly soluble drugs, given the shorter t_{max} of the model amorphous formulations. This indicates that supersaturation, even when maintained for a short period of time, affects and promotes absorption. *In vitro* nasal deposition and drug release methodologies proved to be helpful in selecting lead formulations. Formulation screening and *in vitro*/*in vivo* correlations are valuable in early phase formulation development, reducing *in vitro* and *in vivo* testing in later stage formulation development.

The product complexity and limited regulatory guidance in nasal powder development demands collaboration and input from multiple areas in order to expedite progress in this field. Despite the challenges, the studies performed can foster better comprehension of formulation, process and performance evaluation of nasal powders.

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