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Opportunity and challenges of nasal powders: Drug formulation and delivery

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ABSTRACT

In the field of nasal drug delivery, among the preparations defined by the European Pharmacopoeia, nasal powders facilitate the formulation of poorly water-soluble active compounds. They often display a simple composition in excipients (if any), allow for the administration of larger drug doses and enhance drug diffusion and absorption across the mucosa, improving bioavailability compared to nasal liquids. Despite the positive features, however, nasal products in this form still struggle to enter the market: the few available on the market are Onzetra Xsail® (sumatriptan) for migraine relief and, for the treatment of rhinitis, Rhinocort® Turbuhaler® (budesonide), Teijin Rhinocort® (beclomethasone dipropionate) and Erizas® (dexamethasone cipecilate).

Hence, this review tries to understand why nasal powder formulations are still less common than liquid ones by analyzing whether this depends on the lack of (i) real evidence of superior therapeutic benefit of powders, (ii) therapeutic and/or commercial interest, (iii) efficient manufacturing methods or (iv) availability of suitable and affordable delivery devices. To this purpose, the reader's attention will be guided through nasal powder formulation strategies and manufacturing techniques, eventually giving up-to-date evidences of therapeutic efficacy in vivo. Advancements in the technology of insufflation devices will also be provided as nasal drug products are typical drug-device combinations.

1. Introduction

Nowadays, the majority of nasal pharmaceutical products on the market are liquids, delivered as sprays or drops (less frequently), regardless of whether they are for local or systemic action. In this area, product development focuses on simple formulation strategy and convenience of the delivery system. However, chemical and microbiological instability, the relatively high formulation's volume administered to ensure the drug dosage, and the rapid clearance from the nasal cavity are significant drawbacks of nasal liquids. When it comes to peptide and protein delivery, nasal formulations need additives and stabilizing agents, and proper storage conditions to assure the intended shelf life. Moreover, when administered in solution, the absorption of some drugs across the nasal biological barrier was demonstrated low and variable, with bioavailability not exceeding 10% for small molecular weight drugs such as alniditan and morphine, and < 1% for peptides such as insulin and leuprolide (Illum et al., 2002).

It is known that solid dosage forms, which for nasal administration are mainly represented by powders, are more stable than liquids. Formulation-wise, powders denote a simpler composition in excipients (if any), allowing for the administration of larger drug doses. Powders also facilitate the formulation of poorly water-soluble compounds (Buttini et al., 2012; Pozzoli et al., 2016; Vasa et al., 2015). Moreover, nasal powder dosage forms can enhance drug diffusion and absorption across the mucosa, thus improving drug bioavailability at the site of action compared to liquids (Vasa et al., 2017). In a study in humans comparing different formulations of desmopressin, a nasal powder was superior to a commercial nasal liquid spray and also to a sublingual tablet with respect to both bioavailability and patient's compliance (Fransén et al., 2009).

Despite the above-listed positive features, however, nasal powders still struggle to enter the market. The only approved product for

Abbreviations: API, Active pharmaceutical ingredient; AUC, Area under the curve; BCS, Biopharmaceutical classification system; GRAS, Generally recognized as safe; MRI, Magnetic resonance imaging; NSAID, Non steroidal anti-inflammatory drug

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systemic action is Onzetra Xsail® (Avanir Pharmaceuticals Inc., Aliso Viejo, CA, USA), containing sumatriptan for migraine (approved by the Food and Drug Administration, FDA, in January 2016) (Silberstein, 2017). In Europe, Rhinocort® Turbuhaler® (budesonide, AstraZeneca, London, UK) is marketed for topical treatment of seasonal and perennial allergic and vasomotor rhinitis and of nasal polyps. Other two locally-acting products, Teijin Rhinocort® (beclomethasone dipropionate, Teijin, Tokyo, Japan) and Erizas® (dexamethasone cipecilate, Nippon Shnyaku, Kyoto, Japan), are commercially available in Japan.

Thus, some questions may be raised: is there a lack of therapeutic and/or commercial interest? Isn't there yet a real evidence of a superior therapeutic benefit of nasal powders? Is it difficult to manufacture a nasal powder? Is a suitable and affordable delivery device still not available?

Many remarkable reference papers have already illustrated the anatomy and physiology of the nasal cavity with respect to drug delivery via this route (Dhuria et al., 2010; Illum, 2003, 2002; Pires et al., 2009). The present review aims to focus on the opportunities and challenges of developing powders for nasal drug delivery and answer the above questions. Nasal powder formulation strategies and manufacturing techniques will be illustrated, eventually giving up-to-date evidence of therapeutic efficacy in vivo. Advancements in the technology of insufflation devices will be addressed too, as nasal drug products are typical drug-device combinations. No nasal formulation works by itself without its paired delivery device. Since the delivery technologies for nasal dry powder vaccines have been treated recently, readers are referred elsewhere for further information (Hickey et al., 2014).

2. Powder engineering

Nasal powders are defined in the European Pharmacopoeia (Ph. Eur, 9th Ed.) as *powders for insufflation into the nasal cavity by means of a suitable device*. Despite such quite general definition, nasal powders comprise a number of dosage forms spacing from the pure active pharmaceutical ingredient (API) raw material to micronized powders, where the API can be formulated alone or with excipients (Colombo et al., 2016; Dalpiaz et al., 2015; Gavini et al., 2006) (Fig. 1A–B). Moreover, both the raw material and micronized powders can be the building blocks to produce new physical entities, named soft or chimera agglomerates (Balducci et al., 2013) (Fig. 1C–E).

It is noteworthy that composition and manufacturing method influence the structure and fundamental properties of the powder's particles. The combination of the fundamental properties of a powder, i.e., particle size and shape, then determines the powder derived properties: packing, apparent density, and flow. Fine tuning of fundamental and derived properties of a powder is required as they impact on the manufacturing process and biopharmaceutical behavior of the finished nasal product, ultimately determining the therapeutic outcome (Fig. 2). For example, micronized particles tend to be highly cohesive and adhesive, hence not flowing and difficult to be dosed and delivered accurately by the nasal insufflator device.

2.1. Dosage forms

2.1.1. API raw material

In principle, the API raw material in powder form could be per se suitable as a solid nasal dosage form, but in most cases this is not true. One reason is that most unprocessed solid APIs are poorly flowing, thus difficult to dose in the insufflator device during the “manufacturing phase” of the nasal drug product. On the other hand, coming to the “patient phase”, therapy can fail if the pure drug powder is:

1) unable to be quantitatively delivered from the device and deposit in the nasal cavity, again due to the effect of particle size and morphology on powder flow and deposition mechanism;
2) scarcely dissolving in contact with the mucosa, because of poor drug solubility in the mucus;
3) susceptible to degradation in the nasal cavity.

To overcome some of these drawbacks, a pure drug raw material can be processed by lyophilization. Actually, **lyophilized powders** have been proposed as nasal products since the ‘80s when Tsuneji and colleagues first applied the use of dry powders to the nasal delivery of insulin for diabetes (Tsuneji et al., 1984). Being very porous and fast-dissolving in contact with the nasal fluid, lyophilized powders allow for prompt drug release and diffusion across the mucosa. The in vivo data (dogs) by Tsuneji and co-workers allowed to estimate that an insulin-Carbopol 934 co-freeze-dried powder gave the same hypoglycemic effect at 3-fold the intravenous (IV) dose. However, nowadays lyophilized powders for nasal drug delivery have been largely overcome, due to limitations of lyophilization as manufacturing method and the

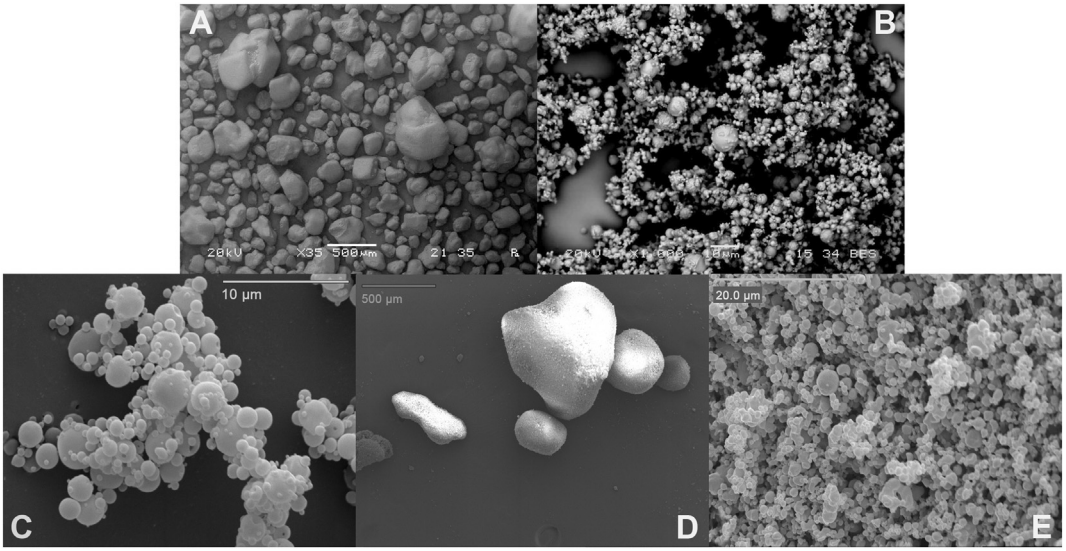

Fig. 1. Examples of nasal powders: A) Carbamazepine raw material; B) Chitosan glutamate carbamazepine microspheres; C) Desmopressin spray-dried microparticles; D) Desmopressin agglomerates of the microparticles in C; E) Detail of the surface of the desmopressin agglomerate in D.
(Reproduced with permission from: A–B) Gavini et al., 2006; C–E) Balducci et al., 2013).