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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), allowing 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), Rhinocort® Puvlizer (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.

KEYWORDS

Nasal drug delivery; nose-to-brain; microparticle; powder; device; particle engineering.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient

AUC: Area Under the Curve

BCS: Biopharmaceutical Classification System

GRAS: Generally Recognized As Safe

NSAID: Non Steroidal Anti-Inflammatory Drug

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 less than 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 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, Rhinocort® Teijin (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).

< Figure 1 near here>

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 behaviour 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.

<Figure 2 near here>

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 the effect of particle size and morphology on powder flowability 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 introduction of alternative powder manufacturing technologies like spray drying (Rassu et al., 2015).

Another option to face the solubility issue could be to modify the drug chemical structure and make a pro-drug, as it was done with levodopa (L-dopa) (Lee et al., 2014). Levodopa methyl ester hydrochloride, formulated as nasal powder, was administered intranasally *in vivo* to rats and increased the drug absolute bioavailability from 16% of the oral administration to 82%. Moreover, nasal delivery of the pro-drug also increased brain targeting efficiency as expressed by the higher AUC in brain/AUC in plasma. An obvious drawback, possibly discouraging the pro-drug approach, is that the chemical modification

may result in a burden of work to demonstrate that the pharmacological action and safety of the drug are preserved.

The use of the API as raw material is certainly relevant in research, to carry out preliminary studies before developing the actual nasal drug formulation. Typically these experiments aim to characterize *in vitro* the drug powder dissolution profile in simulated nasal fluid or compare the diffusion across a barrier (artificial or biological) between a liquid formulation of the drug *versus* its solid form. For example, ribavirin, a drug candidate for the treatment of viral neurological disorders in dogs, was nose-to-brain delivered in rats as aqueous solution and as powder raw material to investigate whether its brain distribution was affected by the physical state. Differences in brain drug accumulation were found, with 3-fold higher drug levels in the olfactory bulb with ribavirin powder compared to the solution: the stronger and longer contact between powder and mucosa and the higher concentration gradient across the mucosa explained the increased drug absorption and brain bioavailability detected with drug powder. In fact, *in vitro* permeation experiments of ribavirin across rabbit nasal mucosa confirmed that the drug permeated from the powder was significantly higher than from the solution at the same applied dose (5 mg, of which 85 ± 2% and 34 ± 4% permeated across the tissue in 4 hours of experiment from the powder and the solution) (Colombo et al., 2011).

2.1.2 Micronized powders

Micronized powders are composed of “microparticles” that is a general word identifying particles in the micrometer size range (1-1000 μm) and manufactured by different methods (Table I). Spray-dried and spray freeze-dried drug microparticles can be in certain cases excipient-free. Microparticles can be called “microspheres” if they have spherical shape and matrix structure.

Table I. Examples of nasal microparticle powders.

Drug	Microparticle Type	Excipient/s	Manufacturing method	Ref.
Gentamicin	microsphere	Hyaluronic acid Chitosan glutamate Hyaluronic acid/chitosan glutamate	Solvent evaporation	(Lim et al., 2000)
	microparticle	Chitosan hydroglutamate Hyaluronic acid Chitosan hydroglutamate/hyaluronic acid	Solvent evaporation	(Lim et al., 2002)
Granisetron	microparticle	Hydroxypropyl-β-cyclodextrin Hydroxypropyl-β-cyclodextrin and sodium carboxymethylcellulose	Freeze drying	(Cho et al., 2010)
Insulin	microparticle	Thiolated chitosan-4-thiobutylamidine	Emulsification solvent evaporation	(Krauland et al., 2006a)

	microsphere	Starch with lysophosphatidyl choline Starch with glycodeoxycholate Starch with sodium taurodihydroxyfusidate	Freeze drying	(Illum et al., 2001)
Lorazepam	microparticle	Hydroxypropyl-β-cyclodextrin + mucoadhesive polymer (hydroxypropyl methylcellulose and/or carbomer)	Spray drying	(Jug and Bećirević-Laćan, 2008)
	microparticle	Poly(vinyl alcohol) Poly(vinyl pyrrolidone)	Spray drying	(Zhao et al., 2012)
Metoclopramide	microsphere	Sodium alginate Chitosan hydrochloride Sodium alginate/chitosan hydrochloride	Spray drying	(Gavini et al., 2005)
Ropinirole	microparticle	Poly(lactic-co-glycolic) acid)/dipalmitoylphospatidylcholine/trimethylchitosan	Spray drying	(Karavasili et al., 2016)
Tacrine	microparticle	Chitosan/pectin polyelectrolyte	Spray drying	(Saladini et al., 2013)
Verapamil	microsphere	Chitosan	Spray drying and precipitation	(Abdel Mouez et al., 2014)

Micronized powders represent the majority of nasal solid formulations studied so far in the literature. In fact, microparticles are interesting for reasons including fast dissolution in the nasal mucus when they are made of soluble excipients for the majority of their composition. This favors nasal transport and bioavailability leading to rapid therapeutic effect. Moreover, microparticles can be made of polymers encapsulating the drug active in a matrix structure (Table I). In this case, they may sustain drug release over prolonged time. Lipids may also be used as matrix formers (Martignoni et al., 2016). Micronized powders allow for adequate nasal deposition if the particle size falls in the range 10-45 μm. On the other hand, they can show difficult handling during manufacturing (e.g. cohesiveness, adhesiveness and limited fluidity) and, for patients, the risk of lung inhalation during administration if the powder contains a significant fraction of particles below 10 μm diameter.

2.1.3 Agglomerates of micronized powders

Agglomeration is a technological strategy implemented to counteract the handling drawbacks of small microparticles while preserving their positive features in terms of dissolution rate. It is a way to have, although transiently, bigger particles for improved handling during manufacturing and dose delivery. In fact, the agglomeration process consists in establishing weak bonds between the particles of a micronized powder, alone or blended with other microparticles (e.g. a drug or an excipient) to get soft clusters. The resulting agglomerates have bigger size than the original microparticles, measuring tenths to hundreds of microns in diameter. The bonds between the microparticles must be strong enough for the agglomerates to sustain handling, but weak for the agglomerates to break into fragments during insufflation. Fragments that are deposited on the nasal mucosa

release immediately the primary microparticles, which behave as if they have never been agglomerated (Balducci et al., 2013; Russo et al., 2006, 2004; Sacchetti et al., 2002).

2.2 Excipients in powder formulation

From a safety perspective, insufflation of the pure drug powder would be the best option for nasally administered APIs. Similarly to inhalation products, nasal products should contain the lowest possible number/amount of non-active ingredients. Furthermore, if the drug is not very potent (e.g. antibiotics like gentamicin; NSAIDs like flurbiprofen), the unit dose can be in the order of tenths of milligrams of powder to insufflate in a cavity whose volume is relatively small. It is reasonable to consider that the human nose can accommodate about 10-25 mg of powder *per* nostril *per* shot (Elmowafy et al., 2014). In a recent randomized clinical trial comparing intranasal sumatriptan powder with oral treatment, an 11-mg shot was insufflated in each nostril (Cady et al., 2015; Tepper et al., 2015). In spite of this, excipients have often been used to formulate non potent drugs as nasal powders.

In contrast, potent drugs (<1-5 mg per unit dose) compulsorily require filler excipients (also called carriers) to guarantee accurate dosing and delivery.

Excipients in nasal powders can be:

- physically mixed with the API in solid form (Callens et al., 2003): an interesting example has been recently provided by Khan and co-workers in which the GRAS substance nicotinamide was triturated with zolmitriptan to form an eutectic (Khan et al., 2016). The new physical form was given to rats by nasal aerosol in comparison with nasal administration and intravenous injection of pure zolmitriptan. Superior drug levels in brain compartments such as olfactory bulb, cerebral cortex and cerebellum, were found with the eutectic formulation as a consequence of its faster dissolution than the pure drug.
- co-lyophilized or co-spray-dried with the active ingredient (Ambrus et al., 2014; Cho et al., 2015; Coucke et al., 2009b; Quadir et al., 2000).
- forming a matrix in which the drug is dispersed, such as in the case of the polymeric microspheres (Krauland et al., 2006a);
- forming a protective shell around the active ingredient such as in microcapsules and liposomes (Chen et al., 2013; Lim et al., 2000).

Non-active ingredients play different roles in the formulation and may be classified as fillers, mucoadhesive agents and absorption enhancers that also include enzyme inhibitors.

2.2.1 Fillers

These are ingredients added as bulk agents to simplify handling and administration of the active principle. However, fillers can affect the nasal bioavailability of drugs, taking into account the peculiar physical and physiological environment of the nasal cavity. For instance, if the filler is hygroscopic, it may influence the drug dissolution; the filler's particle size distribution could affect the area of distribution of the drug particles on the mucosa and consequently the absorption. Some fillers may adsorb drug molecules on their surface (Matsuyama et al., 2007).

Both water-soluble and water-insoluble fillers can be used in nasal powder formulation. Water-soluble excipients (e.g. lactose, mannitol, and sorbitol) are expected to ease the wetting of the powder formulation by the aqueous liquid lining the mucosa. These fillers also tend to dissolve rapidly. Whether this affects the dissolution of the drug positively or negatively, it depends on the drug characteristics, particularly its water solubility. Tanaka and co-workers studied whether the mucosal fluid volume has an effect on drug dissolution and absorption from nasal powders (Tanaka et al., 2017a). The mucosal fluid volume was modified by adding lactose and sodium chloride as excipients to the powder formulation. Their solubility in water and small molecular weight cause them to withdraw water from the epithelial cells or underneath tissues due to the osmotic pressure that is generated by their dissolution. As the mucosal fluid volume increased following the excipient's dissolution, it enhanced the absorption of the poorly soluble drugs whose dissolution was promoted. At the same time, however, the formulation's fast dissolution resulted in its rapid clearance by the mucociliary system and short time available for drug absorption.

On the other hand, insoluble fillers are useful for prolonging the residence time of the formulation on the nasal mucosa in comparison with soluble ones that, once dissolved, make the whole formulation more easily cleared by cilia's movement. A work of Ishikawa and colleagues demonstrated that water insoluble fillers, such as calcium carbonate, talc, barium sulphate or ethyl cellulose provided excellent nasal bioavailability of drugs with molecular weights ranging from 354 to 77,000 daltons (Ishikawa et al., 2001).

A relationship was evidenced between drug solubility/permeability and nasal absorption depending on the presence in the powder formulation of cellulose derivatives like

hydroxypropylcellulose and sodium carboxymethylcellulose (Tanaka et al., 2017b, 2016b). Three model drugs (warfarin, piroxicam and sumatriptan, belonging respectively to BCS classes I, II and III) were blended with the hydrophilic polymer HPC (1:1), also evaluating the effect of the polymer's molecular weight. The higher the molecular weight, the longer the formulation's residence time in the nasal cavity, which favors absorption. In fact, the polymer hydrates in the nasal cavity and creates a viscous layer of fluid on the mucosa in which the drug's solid particles must dissolve. Then, the dissolved drug molecules diffuse through this layer toward the mucosa. In this frame, *in vivo* nasal absorption of the highly soluble and highly permeable warfarin decreased due to hydroxypropylcellulose, likely limited in its diffusivity by the viscosity of the formulation. In the case of piroxicam (high permeability, low solubility), the negative effect of hydroxypropylcellulose on nasal absorption was ascribed to the viscous polymer layer delaying drug dissolution particularly at the highest molecular weight. The take-home-message underlying this and the other studies by the Japanese group is that the selection of a particular excipient must take into account that the excipient behavior (hydration and gelification in this case) may affect drug bioavailability differently depending on the drug physico-chemical properties.

Fillers may influence drug absorption also via ion-binding. In a study by Oechslein and collaborators, powder formulations of the peptide octreotide associated with different particulate carriers (microcrystalline cellulose, semi crystalline cellulose, hydroxyethyl starch, cross-linked dextran, microcrystalline chitosan, pectin and alginic acid) were tested *in vivo*. No correlation was found between water absorption by the carrier and nasal bioavailability of octreotide in rats. Indeed, the absorption-enhancing effect of the various carriers was attributed to binding of Ca^{2+} ions by the carrier. Although Ca^{2+}-binding capacity differed among the considered polymers, the decrease in Ca^{2+} availability in the nasal mucosa loosened the tight junctions between epithelial cells and affected the mucociliary clearance, as the ciliary beat frequency is Ca^{2+}-dependent (Oechslein et al., 1996). This is an example of how tight junction modulators can improve transmembrane drug delivery. The topic has been reviewed recently by Deli, M.A. (Deli, 2009).

2.2.2 Mucoadhesive agents

To prolong the residence time in the nasal cavity, powder formulations may contain mucoadhesive excipients, such as polymers like gelatin, starch, chitosan, cellulose derivatives and others. Some polymers are employed with the double function of carrier (filler) and promoters of mucoadhesion.

As already mentioned, when dry particles containing these polymers get in contact with the nasal secretions, the polymer chains hydrate, while nasal secretions consequently de-hydrate, creating regions where mucus viscosity is increased, which provides greater resistance to the ciliary beat (Illum, 2012). For example, lorazepam (a sedative/hypnotic benzodiazepine) nasally administered alone in powder form to rabbits was rapidly cleared from the nose into the esophagus producing a pharmacokinetic profile compatible with rapid nasal and secondary (slower) oral absorption. In contrast, by formulating lorazepam as spray-dried microparticles in presence of N-vinyl-2-pyrrolidone (PVP) and polyvinyl alcohol (PVA), the drug was retained by the polymer in contact with the nasal epithelium favouring its absorption only through the nose. Moreover, the polymer matrix did not delay drug release, thus the effect was rapid (Zhao et al., 2012).

The increase of the formulation's nasal residence time is particularly favorable when macromolecules are administered, as shown by Tanaka et al. (Tanaka et al., 2016a). Alhalaweh and co-workers have proposed an interesting theoretical approach to evaluate the adhesive potential of materials potentially suitable for formulating a nasal powder (Alhalaweh et al., 2011). The applied theory allowed to establish that adhesion is more likely to occur to mucin than to the mucosal tissue and to relate adhesion with the polymer molecular weight and its content in the formulation.

2.2.3 Absorption enhancers

Absorption enhancers include several substances, differing for their mechanisms of action and required when the powder formulation produces sub-optimal nasal transport of the API (e.g. poorly permeable macromolecular biologics).

Examples are:

- surfactants (e.g. sodium laurylsulfate, saponin, polisorbate 80, laureth-9);
- bile salts and derivatives (e.g. sodium glycocholate, sodium taurocholate, sodium deoxycholate);
- fatty acids and derivatives (e.g. sodium caprylate, sodium laurate, oleic acid);
- phospholipids (e.g. lysophosphatidylcholine, didecanoylphosphatidylcholine);
- glycyrrhetinic acid derivatives (e.g. carbenoxolone, glycyrrhizinate);
- chelating agents (e.g. ethylenediaminetetraacetic acid, salicylates);
- cyclodextrins (α-, β-, γ-cyclodextrins and their derivatives);
- cationic compounds (e.g. chitosan and derivatives, poly-L-arginine, poly-L-lysine).

Surfactants, bile salts, fatty acids and cyclodextrins can alter the permeability of the nasal epithelium modifying the structure of the phospholipid bilayer of cells or removing the proteins from cell membranes. Chelating agents, but also bile salts, cationic agents and cyclodextrins, impair the tight junctions between the epithelial cells, allowing macromolecules weighing above 1000 Daltons to diffuse through (Casettari and Illum, 2014; Ghori et al., 2015). Moreover, some enhancers work by increasing the aqueous solubility of poorly soluble drugs. By the latter mechanism hydroxypropyl-β-cyclodextrin improved the extent of the *in vitro* release of budesonide from a powder formulation (Kim et al., 2014), while β-cyclodextrin promoted thalidomide *in vitro* accumulation within nasal tissue without significant transmucosal transport, a result deemed suitable for the desired local action of this drug on nasal bleeding without systemic drug exposure (Colombo et al., 2016).

Enzyme inhibitors compounds (e.g. bestatin, amastatin) are considered permeation enhancers as they inhibit the metabolic enzymes in the nasal mucosa and allow sensitive APIs to be absorbed.

Despite the advantages for the absorption of such critical drugs, none of the marketed nasal powder products contain a penetration enhancer as excipient. Animal studies showed that there is a direct correlation between enhancing effect and damage to the nasal mucosa (e.g. irritation, ciliotoxic effects). This is true for bile salts, surfactants, fatty acids and most phospholipids that act by modifying the phospholipid bilayer structure of cell membrane, leaching out proteins or stripping off the outer layer of the mucosa. Only for enhancers that work by loosening the tight junctions, the permeation enhancement effect seems to outweigh the damage caused to the mucosa (Casettari and Illum, 2014). Hence, the approval of nasal products containing these excipients subordinates to full clinical and toxicological safety data (Illum, 2012).

3. PROOF-OF-CONCEPT OF THE EFFICACY OF NASAL POWDERS *IN VIVO*

Particularly for systemic therapeutic action, the literature widely reports on the improvements of *in vivo* drug absorption and bioavailability obtained using nasal powder formulations compared to liquid dosage forms that in some cases are already marketed. Some studies also compare the nasal administration of powders with other administration routes. Examples are provided in the following sections, not only considering drugs, but also non-pharmacologically active substances.

3.1 Small molecule drugs

Nasal delivery of low molecular weight drugs for systemic effect shares in part the challenges of topical treatments: for instance, the drug's lipophilic nature and scarce solubility in biological fluids, make the absorption across the mucosa poorly efficient. In addition to local metabolism in the nasal cavity, hepatic first-pass metabolism can decrease the bioavailability and shorten the half-life. For drugs targeting the central nervous system, protein binding and the presence of the blood brain barrier limit the passage from the blood circulation to the brain.

The above challenges can be addressed by nasal administration, but the superiority of powders over liquids can be appreciated only with respect to the first one that refers to the pre-absorption phase. Examples of small molecules successfully administered as nasal powders are given.

Carvedilol

Oral administration leads to low bioavailability of carvedilol (around 25%) as a consequence of considerable first pass metabolism (Patil et al., 2010). Mucoadhesive microspheres of alginate or chitosan loaded with carvedilol and produced by emulsification cross-linking, administered nasally to rabbits in dry form, showed a drug bioavailability close to 70% of that obtained after intravenous (IV) injection for both types of polymeric microspheres. Based on gamma scintigraphy data, the high drug bioavailability was explained by the fact that the polymers limited nasal drug clearance and extended the time available for absorption (Patil et al., 2012, 2010).

Repaglinide

Low bioavailability upon oral administration and short duration of action of repaglinide result in inadequate control of mealtime glucose excursion of diabetic patients treated with this anti-diabetic drug. Elmowafy and collaborators studied three nasal powders in which repaglinide was formulated with dextran, gellan gum, and pectin as non-diabetogenic polysaccharides. Spray-dried microparticles of dextran or gellan gum loaded with repaglinide produced prolonged hypoglycemic effect in diabetic rats: hypoglycemia lasted from 2 to 6 hours with the nasal powders, depending on the formulation. In contrast, the effect lasted only 1 hour when the same drug dose (0.1 mg/kg) was given nasally as a solution and 2 hours after IV administration (dose not disclosed). The favorable role of the

polymers in terms of mucoadhesion and drug dissolution was claimed to be at the base of such conclusive result (Elmowafy et al., 2014).

Anti-migraine drugs

Three agents have been approved by the FDA for the intranasal first-line treatment of migraine, namely two triptans and dihydroergotamine.

Triptans. Sumatriptan was the first triptan approved (1997) by the FDA for nasal use and is currently available both as nasal spray solution (Imitrex®/Imigran®, GSK, Uxbridge, UK) and nasal powder (Onzetra Xsail®, Avanir Pharmaceuticals Inc., Aliso Viejo, CA, USA). For an in depth analysis of the pharmacokinetics and clinical efficacy as well as tolerability of the sumatriptan nasal powder delivered by the Breath-Powered™ Intranasal Delivery System, the reader is referred to the relevant literature reporting the outcomes of the TARGET and COMPASS clinical trials that led to the marketing authorization of Onzetra Xsail® (Cady et al., 2015; Obaidi et al., 2013; Silberstein et al., 2017; Tepper et al., 2015). Nasal zolmitriptan, approved in 2003, is marketed as a single-dose liquid spray under two brands (AscoTop®, AstraZeneca Gmbh, Wedel, Germany; Zomig®, Impax Pharmaceuticals, Hayward, CA, USA; both available in dosage unit packages of 2.5 mg and 5 mg). Pharmacokinetics data in humans reported that 30% of a 2.5 mg zolmitriptan dose delivered as nasal spray is absorbed into the bloodstream (Rapoport et al., 2006). Gavini and co-workers studied nasal spray-dried polymeric microcarriers encapsulating zolmitriptan and found that a drug formulation containing chitosan promoted zolmitriptan delivery to the rat brain similar to the drug intravenous (IV) injection and enhanced compared to the nasal delivery of the simple drug suspension. After the administration of a drug dose of 100 µg, the drug concentration in the cerebrospinal fluid was found to be 0.605 ± 0.025 µg/ml for the nasal powder, 0.582 ± 0.029 µg/ml after IV injection and 0.387 ± 0.030 µg/ml for a nasal drug suspension. The main advantage of the nasal powder compared to IV injection was the zolmitriptan low plasma levels, suggesting reduced peripheral distribution and potentially a reduction in adverse drug effects (Gavini et al., 2013). Chitosan was recognized as the key factor in the powder formulation allowing to transiently open the tight junctions in the mucosal tissues allowing for drug nose-to-brain transport. In fact, other nasal powders formulated with different polymers were not equally efficient in delivering zolmitriptan to the brain.

Dihydroergotamine, an ergot alkaloid approved by the FDA since 1997 as intranasal anti-migraine drug, is available as liquid nasal spray (dihydroergotamine mesylate, Migranal®,

Valeant, West Laval, Canada). Only few studies have investigated the nasal delivery of dihydroergotamine using powder-based formulations in the ‘90s. Marttin and co-workers proposed a lyophilized powder composed of dihydroergotamine and methyl-β-cyclodextrin (Marttin et al., 1997), while Fransén and collaborators worked on an interactive mixture powder of micronized dihydroergotamine particles and sodium starch glycolate (Fransén et al., 2007). In both cases, the powder formulation did not significantly differ in promoting the drug absorption over the liquid product. After the ’90s, no innovative powder formulations for nasal dihydroergotamine have been proposed. One possible reason could be the conflict between the necessity to address the patient’s need for rapid relief from migraine symptoms and the pharmacokinetic of dihydroergotamine: it was reported that after intranasal administration as a solution, dihydroergotamine plasma levels were detectable after 30-60 minutes compared to only 15 minutes required to detect zolmitriptan. A slow drug absorption delays the anti-migraine effect. Nevertheless, in clinical practice dihydroergotamine appears more effective than triptans at extending the period between two consecutive migraine attacks (Rapoport and Winner, 2006). In light of this, the optimization of nasal dihydroergotamine powder formulations could remain of interest, at least for some groups of patients.

3.2 Macromolecular drugs

Macromolecular drugs like peptides and proteins, which represent the majority of recently developed biotechnological APIs, permeate limitedly across biological tissues due to their hydrophilic nature and high molecular weight. Also, they are prone to metabolic degradation by enzymes in biological liquids and tissues, thus oral administration is not possible or characterized by very low bioavailability. For this reason, the preferred approach for the administration of biopharmacetuicals is the injection. Even then, maintaining the chemical stability of these biotech APIs is a formulation challenge, especially when they are formulated in liquid form. In this regard, nasal powder dosage forms may be expected to protect sensitive APIs from nasal endo- and exo-peptidases metabolisms at the same time providing a better chemical stability. Four paradigmatic examples are presented here below, distinguishing between small peptides (<35 aminoacids) and proteins.

Desmopressin

Nasal administration of the small cyclic peptide desmopressin enables higher systemic absorption compared to other non-injection routes of administration and enhances bioavailability (i.e., 3-5% bioavailability from liquid nasal sprays, 0.25% for a sublingual freeze-dried tablet and 0.08-0.16% for an oral tablet, respectively) (De Bruyne et al., 2014; Vande Walle et al., 2007).

Interestingly, nasal powder agglomerates of spray-dried microparticles made of desmopressin together with mannitol and lecithin, led to a significantly higher drug permeation across excised rabbit nasal mucosa *in vitro* than a commercial liquid nasal spray loaded at the same dose (the cumulative amount of desmopressin permeated in 4 hours from the powder was 7.7 ± 0.8 µg, i.e., about 20% of the loaded dose, whereas it was 2.3 ± 0.4 µg from the solution, i.e., just above 5% of loaded dose). *In vitro* data found good correlation *in vivo,* as a more pronounced antidiuretic effect was obtained by nasal administration to rats of the powder agglomerates *versus* drug solution. Moreover, the nasal powder did not significantly differ in its effect from an IV injection of the peptide at a ten-fold lower dose (Balducci et al., 2013).

Glucagon

Glucagon is a 29-amino acid peptide hormone, used as a rescue medication (intramuscular injection) to treat insulin-induced severe hypoglycemia in diabetic patients. A nasal powder of glucagon (GNP, formerly referred to as AMG504-1; Locemia Solutions, Montreal, Canada) is being developed that contains synthetic glucagon (10 % w/w), beta-cyclodextrin, and dodecylphosphocholine. At the preclinical level, the safety of this formulation was evaluated with respect to 28-day sub-chronic toxicology in rats and dogs treated intranasally. Acute toxicology following intra-tracheal administration was studied in rats, while local tolerance was evaluated by direct administration into the eyes of rabbits (Reno et al., 2015). The overall safety profile raised no concerns in any of the animal species. The subsequent clinical trial involved subjects receiving this intranasal glucagon powder, to be compared with subjects treated with the conventional marketed glucagon intramuscular injection. Nasal administration of this glucagon powder in youth resulted in a therapeutic blood glucose increase with a lower incidence of gastrointestinal adverse effects (42% transient nausea in the “nasal group” versus 67% in the “injection group”) (Sherr et al., 2016). An additional advantage of the intranasal treatment is that the nasal product would be ready for use at any time severe hypoglycemia occurs as a typical emergency condition. In contrast, the injectable form requires extemporaneous

reconstitution, which may be unfeasible outside the home, and is usually administered by non trained medical professional, possibly leading to suboptimal use.

Calcitonin

Calcitonin has been on the market in Europe and the US for several years as liquid nasal spray (Miacalcin®, Novartis, Basel, Switzerland and Fortical®, Upsher-Smith Laboratories, Inc., Maple Grove, MN USA, containing synthetic salmon calcitonin and recombinant salmon calcitonin, respectively), indicated for the treatment of postmenopausal osteoporosis. Matsuyama et al. (2006) selected it as model peptide drug and studied a nasal powder *in vivo* (rats and dogs). The calcitonin powder formulated with ethylcellulose as carrier and delivered intranasally to rats, improved absorption compared to the administration of the peptide at the same dose (0.1 mg) dissolved in saline, although not significantly. When N-acetyl-L-cysteine, a mucolytic agent, was included in the powder formulation, calcitonin bioavailability was 4-fold that of the solution. The bioavailability-enhancing effect was mainly attributed to the mucolytic agent by a combination of mechanisms, including the reduction of the viscosity of the nasal mucus facilitating peptide diffusion across the mucus layer towards the mucosa surface. In addition, the high drug concentration gradient produced by the powder and a prolonged contact with the mucosa due to the water-insoluble filler were also in favor of a more extensive absorption (Matsuyama et al., 2006).

In recent years, the interest in the nasal delivery of calcitonin has decreased after the European Medicines Agency (EMA) in 2012 was requested by the United Kingdom to express an opinion on whether the marketing authorizations for medicinal products containing calcitonin should be maintained, varied, suspended or withdrawn (EMA, 2013). The request was motivated upon concerns were raised of a possible association between calcitonin use and prostate cancer. The Committee for Medicinal Products for Human Use (CHMP) considered all the available data on the efficacy and safety of calcitonin-containing medicines (injections, nasal and an oral medicinal product under clinical investigation at that time) and the new data in relation to the risk of cancer. It was concluded that the benefit-risk balance of the intranasal formulations of calcitonin-containing medicinal products was not positive under normal conditions of use. Therefore, the CHMP recommended the suspension of the Marketing Authorisations for the intranasal formulations of calcitonin. The products are still in use in the US, as the FDA decided that there was no conclusive evidence of a causal relationship between the use of these

products and cancer. Keeping these products on the market would provide options for those patients who cannot or do not want to use other treatments for osteoporosis (U.S. Food and Drug Administration, 2015).

High molecular weight peptides

The first and most extensively studied protein for nasal delivery by powder formulations has been insulin to be administered in diabetic patients. The majority of the studies were conducted between the late '80s and the first decade of the years 2000s, likely comparing the research on insulin delivery by pulmonary inhalation. In the last years, the number of studies has decreased, as if somehow the "holy grail" of non invasive insulin administration had faded away with the commercial "failure" of the first approved human insulin product for pulmonary administration. In fact, Exubera® by Pfizer, a dry powder inhaler approved in the US in January 2006 for the pulmonary administration of insulin was withdrawn from the market 18 months later. Beside this, it is worth highlighting that in many of the reported studies, the simple concept of increasing insulin bioavailability by using a solid product instead of a liquid (to create a higher concentration gradient) proved not effective enough. Absorption-enhancing strategies had to be adopted to impact significantly on insulin bioavailability compared to liquid formulations. Mucoadhesion, tight-junction modulation, use of surfactants, cyclodextrins or anionic resins are some of the strategies proposed (Illum et al., 2001; Krauland et al., 2006b; Pringels et al., 2008; Varshosaz et al., 2004). Apart from insulin, a recent clinical study by Lewis and colleagues tested a spray-dried powder for the administration of human Growth Hormone (hGH), containing an innovative permeation enhancer with low irritation potential (CriticalSorb™). Even though hGH bioavailability was lower compared with subcutaneous injection, the induction of IGF-1, which was chosen as main outcome for this study, was similar, with the advantage of a lower systemic exposure to the drug: this is considered a promising result on the path toward non-invasive administration of hGH (Lewis et al., 2015).

3.3 Non-pharmacologically active substances

The concept of applying inert cellulose powder to the inside of the nose as a remedy for seasonal allergic rhinitis (AR; also referred to as hay fever) symptoms is not new (Emberlin and Lewis, 2007, 2006; Josling and Steadman, 2003). A nasal spray is registered as a medical device in the US under the trade name of FastBlock® Allergy Relief (EuroPharma, Green Bay, WI, USA) containing cellulose in the form of fine-powder. Boots Allergy Barrier

Nasal Spray 800 mg (Boots, Nottingham, UK) is a similar drug-free product on the market in the UK. As the powder deposits on the mucosa, it gelifies forming a protective layer that hinders airborne allergens to reach their receptors in the nasal tissues. Further scientific evidences have become available owing to more recent clinical trials that investigated the efficacy of these products in adults and children (Åberg et al., 2014, 2011). However, contrasting data have been just published following a randomized, double-blind trial in 60 dust mite-sensitized AR children comparing the nasal cellulose powder with placebo (Manuyakorn et al., 2017). The placebo was a lactose powder having the same particle size and appearance as the cellulose powder. This study demonstrated that the treatment with cellulose at 1 powder puff per nostril 3 times a day for 4 weeks did not improve the nasal symptoms more than treatment with the placebo. One reason could be that the dosage of the nasal cellulose powder was lower than that used in previous studies, but it was the actual one recommended by the manufacturer.

It has also been shown that the mucoprotective action of hydroxypropylmethylcellulose (HPMC) enhanced the topical decongestant action of oxymetazoline in patients with persistent allergic rhinitis (Valerieva et al., 2015). HPMC-dependent mucoadehsion coupled to the barrier effect prolonged the efficacy of oxymetazoline even beyond its discontinuation.

New potential applications are emerging with respect to the nasal use of cellulose. In a randomised clinical trial, Al-Shaikh et al. found that an oxidised cellulose powder can effectively stop nasal bleeding following sinus surgery and its application is less painful compared to the use of non-absorbable packing (Al-Shaikh et al., 2014).

3.4 Nasal powder "failures"

Few, but worth mentioning, are the reports of non superiority or even failure of nasal drug powders to achieve benefits when compared to a nasal liquid formulation or to alternative administration routes. Most of these "failures" date back to the early years 2000s.

In the comparison of nasal liquids *versus* solids, ketorolac is a case of unsatisfactory delivery of the drug as nasal powder. SPRIX® (Egalet Corp., Wayne, PA, USA), a nasal ketorolac tromethamine spray for short-term treatment of pain in adults, has been approved recently by the FDA, indicated for moderate-to-severe pain control. In a pharmacokinetic study in rabbits both ketorolac and ketorolac tromethamine as nasal lyophilized powders were less bioavailable than their liquid counterparts despite equal drug dose administered. Reduction of powder's particle size or inclusion of microcrystalline

cellulose as mucoadhesive polymer still did not improve ketorolac bioavailability *versus* liquids. Slow drug dissolution in the mucus and incomplete release from the polymer-drug matrix before the powder was cleared from the nasal cavity were deemed responsible for the lower performance of powders (Quadir et al., 2000).

Qvarnberg and co-workers reported the uneffectiveness of the use of beclomethasone dipropionate intranasal powder in the treatment of common cold (Qvarnberg et al., 2001). Differently from allergic rhinitis or nasal polyposis, the corticosteroid was unable to reduce the cold's symptoms caused by inflammation nor to accelerate recovery. However, these results are unlikely to depend on the fact that the drug was given in powder form. They should be related to the current evidence yet not supporting the use of intranasal corticosteroids for the common cold (Hayward et al., 2015).

An apomorphine nasal powder was the object of an European clinical trial in subjects with Parkinson's disease (PD). The trial aimed to assess the efficacy, safety and tolerability of apomorphine in alleviating the acute episodes of motor symptoms typical of the disease. After being approved in 2006, the trial prematurely ended in February 2007 (The European Union Clinical Trials Register, 2006). Although the reasons for the trial's interruption are not disclosed in the EU Clinical Trial Register, the history of intranasal apomorphine in PD had not been particularly successful since the 90s. In fact, most of the *in vivo* studies published in those years using intranasal apomorphine solutions, had shown a reduction in motor symptoms comparable to oral levodopa and subcutaneous apomorphine, but with significant systemic and local adverse effects (Gálvez-Jiménez et al., 2016).

More recently, as mentioned, a glucagon nasal powder is being developed as needle-free treatment to manage hypoglycemia in type 1 diabetes alternative to the conventional intramuscular injection. The clinical trials that compared the intramuscular (IM) *versus* intranasal (IN) treatments did not actually evidence a superiority nor inferiority of the latter, (Rickels et al., 2016; Sherr et al., 2016). Indeed, from a pharmacokinetic point of view, peak glucagon levels were slightly delayed with IN glucagon (about 5 minutes). This caused average glucose concentrations and time to meet the primary end point (time to plasma glucose concentration ≥70 mg/dl or an increase ≥20 mg/dl from nadir concentration in subjects with nadir glucose <50 mg/dl) after IN glucagon to lag about 3 min compared to glucose concentrations after IM glucagon. These differences were deemed clinically unrelevant. As for the treatments' safety, gastrointestinal adverse events were reported with similar frequency, whereas head/facial discomfort was more frequent with IN glucagon (25% *versus* 9% with IM glucagon).

Although nasal immunotherapy and vaccination were out of the scope of the present review, an *in vivo* study reported no humoral response after nasal administration to mice of dry powder vaccine formulations containing ovoalbumin as model antigen (Scherließ et al., 2015). Three powders were studied, namely chitosan or agarose nanoparticles embedded in a mannitol matrix and chitosan microparticles, and only the last two evoked a local cellular response. This response was modest though and attributed to the low antigen load and imited immunogenicity of the powders.

4. NASAL POWDER MANUFACTURING METHODS

Nasal powders can be manufactured by means of various techniques. For example, different chitosan-based microspheres have been produced by emulsification-cross linking (Patil et al., 2010; Varshosaz et al., 2004), spray drying (Gavini et al., 2011, 2005; Martinac et al., 2005), precipitation (Abdel Mouez et al., 2014) or solvent evaporation processes (Jain et al., 2004; Lim et al., 2000; Nagda et al., 2011). Any method should work to obtain a powder whose size falls in the suitable range for nasal delivery. Physico-chemical methods, based on solvent evaporation or sublimation, will be considered in detail here as they are proposed most frequently in the literature. One reason is that they can count on well-established technologies relatively easy to scale-up.

4.1 Freeze drying

In freeze drying, the API is dissolved alone or with excipients in a liquid vehicle, water in most cases. The solution is then frozen and transferred to a vacuum chamber. The combined effect of low pressure and progressive temperature increase makes the solvent sublimate. The solid components, no more dissolved, will constitute the freeze-dried powder.

Several process-related limitations have hindered extensive application of freeze drying to manufacture nasal powders. For example, as the vehicle is mainly aqueous, many drugs may show low water solubility. In this case, the lyophilization of an aqueous drug suspension may not bring significant improvements over the unprocessed material. Organic solvents, which could act as co-solvents for water-insoluble drugs, are avoided because they require lower temperatures for the freezing phase. Then, solvent vapors must be collected by condensation and if the vapors escape the condenser, they could damage some freeze dryer's parts (e.g. vacuum pump, plastic and rubber parts, etc.) (Millrock Technology, 2017; Silverman, 2011; SP Scientific, 2017). Moreover, freeze drying

is not applicable to all drug-excipient combinations, especially in the case of polymeric carriers: in this regard, Rassu and co-authors observed that the inclusion of polymers in the feed led to lyophilized powders with non homogeneous drug content or too high residual humidity. In addition, yields of production are low when small (lower than 5 μm) particles are formed and aspirated from the vacuum system of the freeze dryer (Rassu et al., 2015).

The properties of lyophilized powders relevant to nasal drug delivery have appeared less suitable compared to powders obtained by other methods. Rassu and co-workers prepared spray-dried particles loaded with deferoxamine using methyl-β-cyclodextrin or chitosan as carrier. These particles were homogeneous with respect to surface characteristics and showed smaller particle size with narrow size distribution. Volume-surface diameter was $d_{v,s}$: 3.47 ± 0.05 μm and 1.77 ± 0.06 μm, and coefficient of uniformity (CU), i.e., the ratio between $d_{v,10}$ and $d_{v,90}$: 0.17 ± 0.00 and 0.26 ± 0.01, respectively for methyl-β-cyclodextrin and chitosan microparticles. The mass median aerodynamic diameter, calculated from particle size and density, supported an aerodynamic behavior in favor of deposition on the nose's roof. These spray-dried microparticles were compared to a lyophilized powder obtained by freeze drying of the same feed solutions used for spray drying. The lyophilizates were characterized by variable particle surface and, in the case of methyl-β-cyclodextrin microspheres, the size was significantly larger ($d_{v,s}$: 9.29 ± 0.50 μm) and more heterogeneous (CU 0.07 ± 0.01, at $p<0.05$) than its counterpart produced by spray-drying. The chitosan lyophilized particles could not be analyzed due to the formation of a sponge-like film during size analysis. Based on this, the authors concluded that the spray-dried powder was more suitable for nasal drug deposition in the olfactory region for the nose-to-brain delivery of deferoxamine (Rassu et al., 2015).

Freeze drying can be exploited as a method to produce solid solutions/dispersions for improving drug aqueous solubility, as it was recently done by processing the corticosteroid budesonide with Soluplus®, an excipient with excellent capability to form solid solutions (Pozzoli et al., 2017). A solid solution/amorphous solid dispersion was obtained as confirmed by X-ray powder diffraction and thermal analysis. The freeze-dried product was characterized by higher surface area per budesonide dose than micronized budesonide as a reference. These physico-chemical properties and the presence of Soluplus® in the formulation significantly increased *in vitro* dissolution rate and permeation across a model of the nasal mucosa.

4.2 Spray drying

This is a widely applied technology, not only in the pharmaceutical field. A feed solution containing the API dissolved or dispersed in a liquid vehicle (both alone or in the presence of excipients), is sprayed and converted into a dried particulate upon evaporation of the vehicle. Nasal drug powder formulations by spray drying include those produced for the delivery of carbamazepine (Gavini et al., 2006), cyanocobalamin (García-Arieta et al., 2001), deferoxamine (Rassu et al., 2015), desmopressin (Balducci et al., 2013), gentamicin (Hasçiçek et al., 2003), insulin, metoprolol tartrate, salmon calcitonin, somatotropin (Coucke et al., 2009a), lorazepam (Zhao et al., 2012), metoclopramide (Gavini et al., 2005), morphine (Russo et al., 2006), ondansetron (Mahajan et al., 2012; Mahajan and Gattani, 2010; Suryawanshi et al., 2015), repaglinide (Elmowafy et al., 2014), rokitamycin (Gavini et al., 2011), ropinirole (Karavasili et al., 2016), tacrine (Saladini et al., 2013), tramadol (Belgamwar et al., 2011), valsartan (Pardeshi et al., 2012), zidovudine (Dalpiaz et al., 2015).

The principal advantages of the technique are:

- processing of both drug solutions and disperse systems, at different total solid concentration;
- multiple options with respect to the liquid feed composition, spacing from aqueous to organic solvents, the latter being not always suitable to be used in other processes;
- possibility to tune process parameters such as feed rate and evaporation temperature, according to the drug to process (e.g. lower temperature for temperature-sensitive APIs).

Spray drying allows for the optimization of particle characteristics like size, shape and density (Pilcer and Amighi, 2010). For example, both nozzle design and mechanism of atomization influence the droplet size of the spray, enabling to control the particle size distribution of the final product. For instance, aiming to realize dry powders for nasal deposition, caffeine microparticles were spray-dried using a 1 mm nozzle diameter (Sacchetti et al., 2002).

However, the technique does not go beyond 50-60% as production yields due to powder sticking to the equipment's parts (nozzle, drying chamber, cyclone, filter or collector vessel wall). This could be a drawback of the method, especially when the process variables are not controlled and the parameters concerning both the spray dryer and the feed formulation have not been optimized (Walters et al., 2014). Different spray drying

equipments may also impact on the yield. A recent ongoing study has shown low yields (maximum 70%) in laboratory scale production using spray drier models such as the Mini spray driers B-190 or B-290 of Büchi (Flawil, Switzerland) (Fig. 3A), which are very common spray driers in research laboratories (Haggag and Faheem, 2015). Compared to the Mini spray driers by Büchi, the recent Nano spray driers B-90 or B-90HP by the same producer (Fig. 3B) have made possible to process minimal (few ml) quantities of liquid samples into dry powder at high yields (up to 90%) (Aquino et al., 2013; Del Gaudio et al., 2017; Haggag et al., 2015). In particular, there are three main claims in the patented technology: (1) a laminar airflow to decrease sample loss with minimal dead volume; (2) a spray head system to produce small particles with very narrow size distribution; (3) an electrostatic particle collector to obtain high yields and recover even the smallest particles (Bürki et al., 2011; Sosnik et al., 2015). Until now the Nano Spray Drier has found application in the field of powders for inhalation that are produced with high nano (>300 nm) - low micrometer size (<5 μm) (Büchi Labortechnic, 2017) round shape, good aerodynamic properties. Nevertheless, it could also be applied for spray drying microparticles to be agglomerated for nasal delivery.

<Figure 3 near here>

4.3 Supercritical fluid-assisted spray drying

Supercritical fluids are defined as compressed gases or liquids above their critical pressures and temperatures. The supercritical fluid-based processes exploit the specific properties of a gas in supercritical conditions, such as the modulation of the solubilizing power, large diffusivity, solvent-less or organic solvent-reduced operation. These processes have emerged as a promising technique for the production of powders for inhalation delivery, as they enable to control powder size and distribution. Recently, they have been employed also for nasal powder manufacturing. In fact, Cho and colleagues studied nasal powder formulations of calcitonin containing different absorption enhancers and some stabilizers comparing two preparation methods: the conventional spray drying and a novel supercritical fluid-assisted spray drying (Fig. 3C). Regardless of the manufacturing method, powders were chemically stable, fine and spherical. The presence of chitosan in the formulations acted as absorption enhancer, improving the bioavailability of the peptide upon nasal administration compared to unprocessed salmon calcitonin powder without the excipient. However, the supercritical fluid-assisted spray-dried powder

with its 3-fold lower particle size, was found to produce an even higher nasal absorption versus the conventional spray-dried formulation (Cho et al., 2015). This was attributed to the faster dissolution of the smaller particles in the mucus, allowing for higher calcitonin transmucosal absorption before clearance from the animal's nose. The suitability for nasal delivery of particles measuring approximately 700-800 nm in diameter, as those obtained by supercritical fluid-assisted process, should be evaluated also taking into consideration the risk of lung inhalation.

4.4 Spray freeze drying

This innovative technique has been developed aiming to combine the advantages of spray drying and freeze drying techniques. Spray freeze drying is a three-step process, consisting of dispersion of a bulk liquid (drug solution/dispersion) into droplets, droplet freezing and drying by sublimation of the frozen liquid (Fig. 3D) (Ishwarya et al., 2015; Wanning et al., 2015). This technology allows to:

- formulate low water soluble APIs by processing a solid dispersion;
- in complex formulations, like those containing more APIs and non-active ingredients, minimize the phase separation between the drugs or drug and excipients by ultra-fast freezing;
- encapsulate sensitive APIs into polymeric microspheres (Vo et al., 2013).

Currently, spray freeze drying is widely applied in food processing, whereas in pharmaceutical applications it is mainly proposed for formulating pulmonary drugs into porous powders with high aerodynamic performance. For nasal drug products, the actual few applications of spray freeze drying are related to vaccines, e.g. anthrax, influenza, plague vaccines (Garmise et al., 2007, 2006; Huang et al., 2009; Jiang et al., 2006; Mikszta et al., 2005; Wang et al., 2012). However, it should be considered as an option in case of low water soluble or temperature-labile APIs, as many of those produced by medicinal chemistry in the last years.

4.5 Agglomeration of micronized powders

In principle, any microparticle powder manufactured by one of the methods above discussed is suitable to construct agglomerates as the final nasal dosage form. Agglomeration occurs spontaneously in powders when particle size goes below 100 µm due to the high surface area to volume ratio and increased cohesive forces. This phenomenon can be exploited to form round-shaped clusters of microparticles when these

microparticles are subjected to tumbling or mechanical vibration on sieves. With the sieving method, agglomerate formation may depend on the size of microparticles with respect to the sieve's mesh size: particles in the lower micrometer range (e.g. <5 μm particle size) could require sieve's mesh <100 μm to make sure that the first agglomerated nuclei are retained on the sieve and can further enlarge.

If the original (or primary) microparticles to be agglomerated are made of pure drug, they may be not sticky enough and lead to fragile agglomerates, easily broken during handling. It has been shown that soybean lecithin acted as binder in the agglomerate's construction, increasing its mechanical resistance. The binder can be either embedded in the structure of the primary drug microparticle or be included in the composition of a second microparticle population (referred to as excipient microparticles) to be blended with the drug microparticles before agglomeration (Fig. 4).

Nasal agglomerates of spray-dried microparticles have been described for both low molecular weight active molecules (caffeine and morphine) and a small peptide (desmopressin) (Balducci et al., 2013; Russo et al., 2006, 2004; Sacchetti et al., 2002).

<Figure 4 near here>

5. DELIVERY DEVICES FOR NASAL POWDER INSUFFLATION

According to the Ph. Eur. definition of nasal powders, the formulation must be combined with a device for nasal insufflation for use. Table II lists the marketed products with their respective device.

Table II. *Marketed nasal powder products for local or systemic action.*

Product brand name	Drug active (metered dose)	Excipient/s	Device
Rhinocort® Turbuhaler®	Budesonide (100 µg)	None	Multi-dose breath-actuated metering device
Rhinocort® Puvlizer	Beclomethasone dipropionate (50 µg)	Hydroxypropylcellulose, magnesium stearate, stearic acid	Single dose patient-operated capsule-based device
Erizas®	Dexamethasone cipecilate (400 µg or 200 µg, according to the device)	Lactose	Device for 400 µg: capsule-based breath-actuated Device for 200 µg: multi-dose nasal spray

Onzetra Xsail®	Sumatriptan succinate (11 mg)	None	OptiNose's Bi-Directional Breath Powered™ technology

The joint effect of nasal powder properties and device design and mechanism of insufflation is largely responsible for the nasal drug bioavailability, due to the influence on particle deposition in the nasal cavity. Figure 5 qualitatively shows device-dependent coverage of the various regions of the nasal cavity in a silicon cast of the human nose. The effect of the delivery device on drug bioavailability has been studied by Pringels and co-workers using a freeze-dried powder formulation of insulin with starch and Carbopol® (Pringels et al., 2006). Three insufflators were selected, namely Monopowder® (Valois, Marly-le-Roi, France), Pfeiffer® system (Pfeiffer, Radolfzell, Germany) and an experimental device composed of a polyethylene tube filled with the nasal powder formulation. When the device allowed the formulation to deposit in the anterior part of the nasal cavity of the rabbit, slower mucociliary clearance and increased insulin bioavailability were observed.

<Figure 5 near here>

As some device's parts will enter in contact with the nasal mucosa during product's use, the device's development requires to assess possible consequences of such contact. This evaluation may start early during product development, even to drive the selection of the optimal device for the subsequent clinical trials. For instance, *in vitro* cytotoxicity and *in vivo* skin sensitization and irritation tests were carried out on the polypropylene resin used for the delivery device of the glucagon nasal powder (Reno et al., 2016).
Based on their mechanism of function, nasal devices for powder insufflation are classified in sprayers, inhalers, and insufflators (Djupesland, 2013).

Powder sprayers

They produce a plume of particles when a compressible compartment containing the formulation is pressed and then released. For example, Bespak's Unidose-DP® (Bespak, Norfolk, UK) dry powder nasal device is composed of a capillary perforator and an airtight bellow for the powder expulsion. This device has been used to test a powder formulation of a model antibody, a human IgG, in a nasal cast model built from human MRI images. It was found that 95% of the loaded dose was deposited into the nasal cavity, even though only 45% effectively reached the deeper compartments of the cavity (turbinates, olfactory

region, and nasal-pharynx) (Kaye et al., 2009). Similarly, Monopowder®, originally developed by Valois and today acquired by Aptar (Crystal Lake, IL, USA), is a reservoir-based system allowing spraying the drug powder into the nose when a plunger is pressed and creates a positive pressure that breaks a membrane in the powder reservoir. In the above-mentioned study by Pringels, low bioavailability of an insulin powder delivered by the Monopowder® was reported in comparison to that obtained when the same powder was conveyed by an experimental device. A deposition study in the human nose silicon model showed that Monopowder® made the powder to deposit in the upper turbinate region and the nasopharynx, close to the exit of the nasal cavity. This deposition pattern was responsible for the lower bioavailability *in vivo* compared to the other devices (Pringels et al., 2006).

Breath-actuated powder inhalers

Devices activated by patient's breath work based on a passive mechanism of powder emission that may be suitable to limit powder dispersion in the environment. If the device is single-dose, the powder is contained in a blister or a capsule that is emptied as the subject inhales through with the nose. Rhinocort® Turbuhaler® (AstraZeneca, London, UK) is another passive device, designed as a multi-dose device modified for nasal use from the corresponding inhaler for pulmonary use. It has been chosen for nasal delivery of a budesonide powder approved for allergic rhinitis and nasal polyps. Even though the marketed powder product is an alternative to the liquid spray, there are practically no differences between the two products in terms of efficacy, at least for the nasal polyps treatment (Agertoft et al., 1993; Tos et al., 1998). Nevertheless, the powder can be easier to use by the patient who for instance does not need to remember to shake the product before use.

Aptar group has developed several nasal inhalers, including Prohaler®, a blister-based multi-dose powder inhaler that is claimed to have a patient-friendly design to improve the compliance to the therapy. UDS® (Unit Dose System) contains pre-loaded cartridges with aerosolizing air jet upon mechanical actuation and is intended for targeting the drug to the olfactory region for the nose-to-brain delivery. BDS® (Bi Dose System) is similar to the previous one, but delivers two nasal shots or two half-doses (when used for intranasal vaccination) (AptarGroup, 2017).

Nasal powder insufflators

Insufflators are made of two pieces fluidly connected, named mouthpiece and nosepiece. Similar to nasal powder inhalers, they are activated by the patient, but in this case, the subject has to blow into the mouthpiece producing an airflow through the system that makes the powder particles enter the nose via the nosepiece. This system was studied to exploit the fact that the act of blowing naturally causes the soft palate to close. In this way, during powder delivery, there is no possibility for the powder to pass from the nose to the deeper airways. Bi-Directional® Breath Powered, developed by OptiNose (Yardley, PA, USA), is based on this concept. Djupesland and co-workers proved that this device has the potential for the nasal delivery of systemic active compounds, since it broadens the powder deposition in the nasal cavity allowing for fast and efficient drug absorption. By deposition studies *in vivo* in humans with gamma scintigraphy imaging, the researchers have found that the OptiNose Breath Powered device broadly deposited a lactose powder covering the posterior and superior areas of the nasal cavity, whereas a traditional liquid spray concentrated most of the dose (around 60%) in the lower areas of the nasal cavity (Fig. 6). Nasal delivery of a low dose of sumatriptan by OptiNose device in pharmacokinetic studies confirmed the large lining of nasal mucosa surface by drug formulation was associated with high rate and efficiency of drug absorption (Djupesland et al., 2013). Currently, Bi-Directional® is the device combined with the sumatriptan succinate powder in Onzetra Xsail®. Moreover, it is now under clinical evaluation for delivery of fluticasone propionate for the treatment of chronic rhinosinusitis (Djupesland, 2013; Hansen et al., 2010).

<Figure 6 near here>

Shin Nippon Biomedical Laboratories (SNBL, Tokyo, Japan) has recently developed μco® System, a nasal delivery technology composed of a combination of a mucoadhesive powder drug carrier and a nasal delivery device. Milewski and collaborators prepared the first intranasal oxytocin dry powder formulation combined with a device exploiting the SNBL technology for the treatment of post-partum hemorrhage in the developing world. Pharmacokinetic studies in monkeys have revealed good *in vivo* absorption rate of oxytocin from the dry powder of the active with μco® carrier, rapid onset of the effect and reasonable nasal bioavailability (12% of intramuscular bioavailability) (Milewski et al., 2016).

6. CONCLUSIONS

This review confirms that nasal delivery of active compounds has been and still is of great interest for locally/systemically acting drugs and also for drugs targeting the central nervous system via the nose-to-brain transport. Many studies and clinical evidence have corroborated the advantages of nasal powder dosage forms. The higher stability over liquids eliminates the need for preservatives in the formulation, increasing safety. In addition, drug bioavailability *in vivo* of various active compounds delivered nasally by powders has been generally higher than by nasal liquids used as reference.

Recently developed devices for insufflation can deliver the nasal powder more efficiently, in particular depositing the formulation to cover a larger surface of nasal mucosa compared to liquids. Both local and systemic diseases may benefit from such broader nasal drug deposition that counteracts the short drug residence time in the cavity. Especially for systemically-acting drugs, this enhances the rate and efficiency of drug absorption, reasonably leading to faster and greater therapeutic effect in patients. Rapid relief from disease symptoms as for pain and migraine, may be a key driver to improve patient's compliance to the therapy.

However, liquids are still much more diffused among the marketed nasal products, and a drug solution/suspension is the first-choice dosage form. From a manufacturing point of view, the production of liquid dosage forms may be easier and cheaper than that of a solid dosage form for nasal delivery. From the patient's point of view, liquids could be considered more acceptable, somehow perceived as more "physiological" and less irritating. It is also true that there are not many data about the local tolerability of nasal powders, neither in the short nor the long-term, possibly raising concerns related to the toxicity towards physiological functions of the nose.

The enhanced bioavailability that powders give may be unnecessary for potent active ingredients, which can be easily administered at low doses by liquid formulations to give the desired effect. Furthermore, as seen, the formulation of such drugs in powder form would require dilution in an inert carrier for administration. On the other hand, for less potent systemically-acting APIs, drug absorption from the powder may be insufficient for the effect without adding mucoadhesive excipients and/or absorption enhancers. Concerns about such excipients and lack of safety data may be among the reasons still preventing the market availability of drug powders with absorption enhancers.

Device-wise, the technology for the nasal delivery of liquids has advanced and offers nowadays systems that deliver a range of unit volumes with high accuracy, control droplet

size distribution and even protect the content from microbial contamination. Technologies for nasal powder delivery are available as well, but not yet fully studied, with some devices already in clinical trials and others at the development stage or only existing as blueprints. It must be added that in some cases patients have expressed a preference for liquid sprays over powder devices (Kivisaari et al., 2001).

In summary, it is recognized that future development of nasal powder formulations requires optimization of powder manufacturing, characterization of the combination between powder and device and a deeper understanding of the local effects of powder insufflation in the nasal environment. Nevertheless, the evidences with respect to stability and shelf-life, bioavailability and efficient administration by newly designed devices, make further research on this path worth of efforts in the perspective of increasing the number of nasal powder products on the market, especially looking at the opportunities offered by the administration of biotech products via an alternative, but viable and attractive administration route such as nasal delivery.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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FIGURE AND TABLE LEGENDS

Figure 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).

Figure 2

Biopharmaceutics of nasal powders, from insufflation to effect. The therapeutic outcome depends sequentially on steps (1) to (5). Steps 1-3 are influenced by powder properties. Steps 4 and 5 involve drug molecules with their characteristics of lipophilicity, ionization, molecular weight, etc.(adapted with permission from Dean, 2005; Dhuria et al., 2010; Mygind and Dahl, 1998; Wikimedia Commons, 2017).

Figure 3

Manufacturing methods of nasal microparticles (adapted with permission from Büchi Labortechnic, 2017, Cho et al., 2015 and Ishwarya et al. 2015).

Figure 4

Strategies for nasal microparticle agglomeration: 1) single-drug agglomerates. One-drug agglomerates can be blended with agglomerates of another drug in a combined final nasal product. 2) multi-drug agglomerates. Microparticles of different APIs (with excipient microparticles, as required) can be firstly blended and then agglomerated to obtain multi-drug agglomerates. Both strategies could be used to prepare nasal products for drug combined therapy (e.g. synergism of drugs for the same disease, multi-drug therapy in patients suffering from different disease, etc.).

Figure 5

Deposition patterns of a thalidomide/hydroxypropyl-β-cyclodextrin powder in a silicon nasal cast obtained with different devices: A) passive bi-dose device (Aptar, Louveciennes Cedex, France); B) active single dose (MIAT, Milan, Italy); C) active multi-dose (Teijin Ltd., Tokyo, Japan). Aptar and MIAT devices were loaded with about 20 mg of powder in their

reservoir (blister or capsule, respectively). The active devices were actuated manually, whereas for the passive one 15 l/min airflow was drawn through it for 2 s (adapted from Colombo et al., 2016).

Figure 6

Gamma camera images taken 2 minutes after delivery using a traditional liquid spray (A) and powder with OptiNose Breath Powered Device (B). Deposition of liquid spray was the greatest in the lower posterior regions of the nose, whereas deposition of the powder was greatest in the upper posterior regions of the nose (adapted from Djupesland et al., 2013).

Table I

Examples of nasal microparticle powders.

Table II

Marketed nasal powder products for local or systemic action.

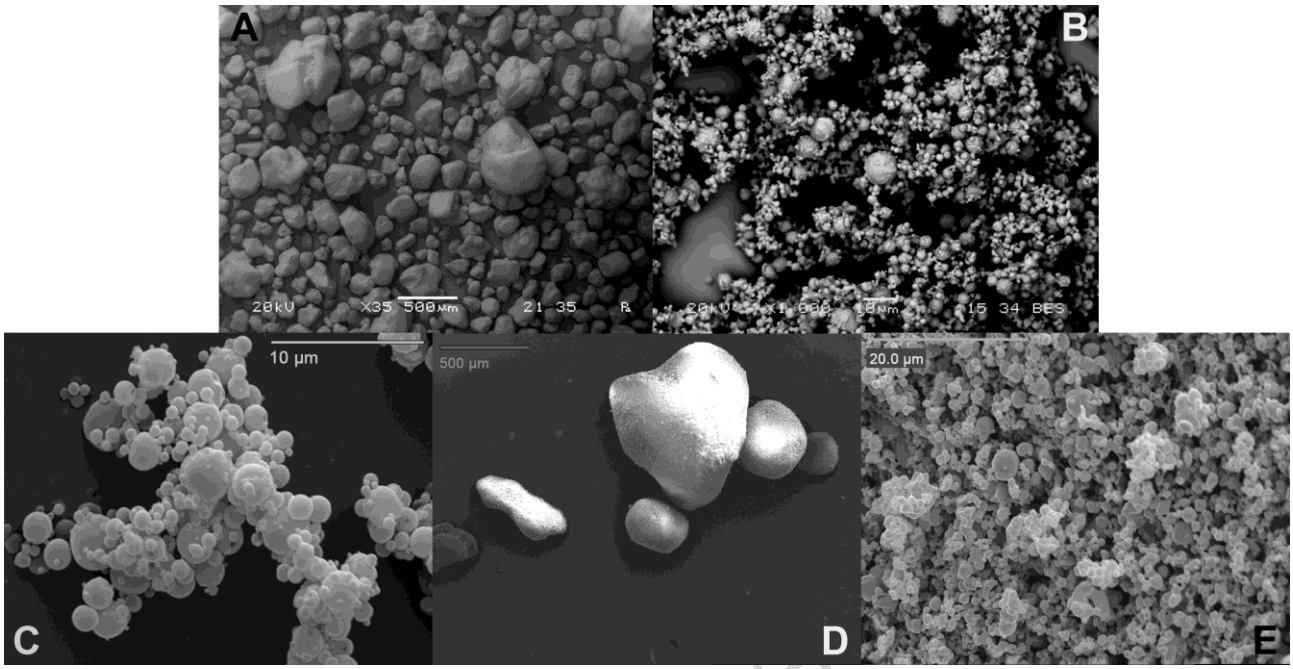


Fig. 1

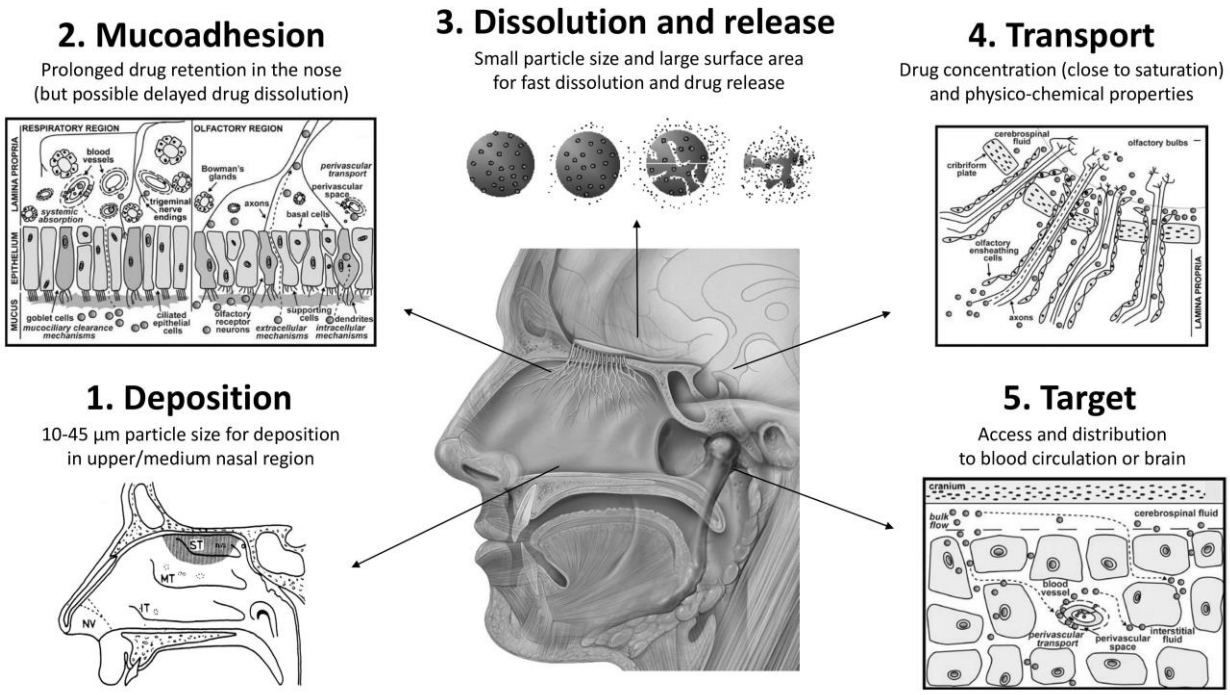


Fig. 2

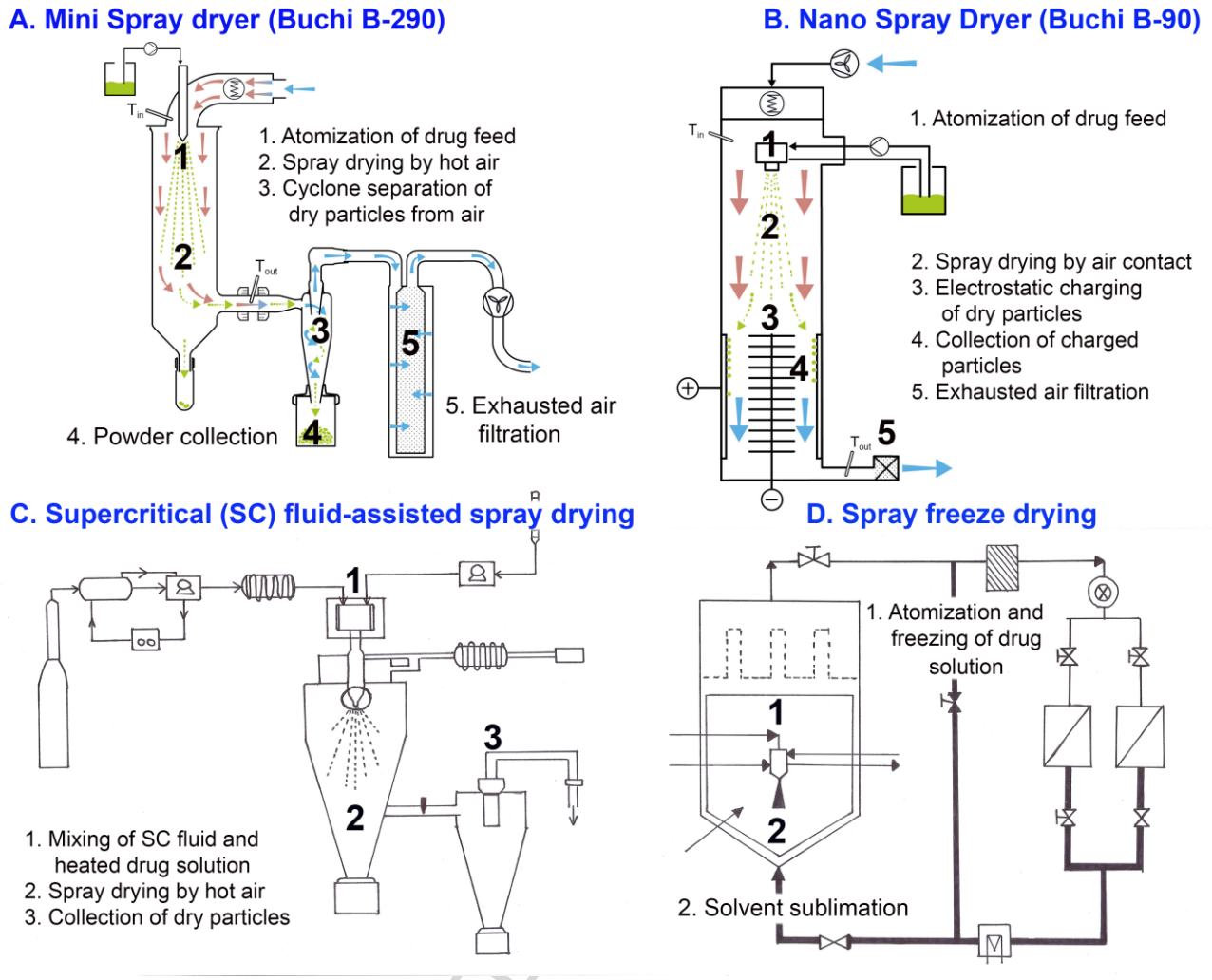


Fig. 3

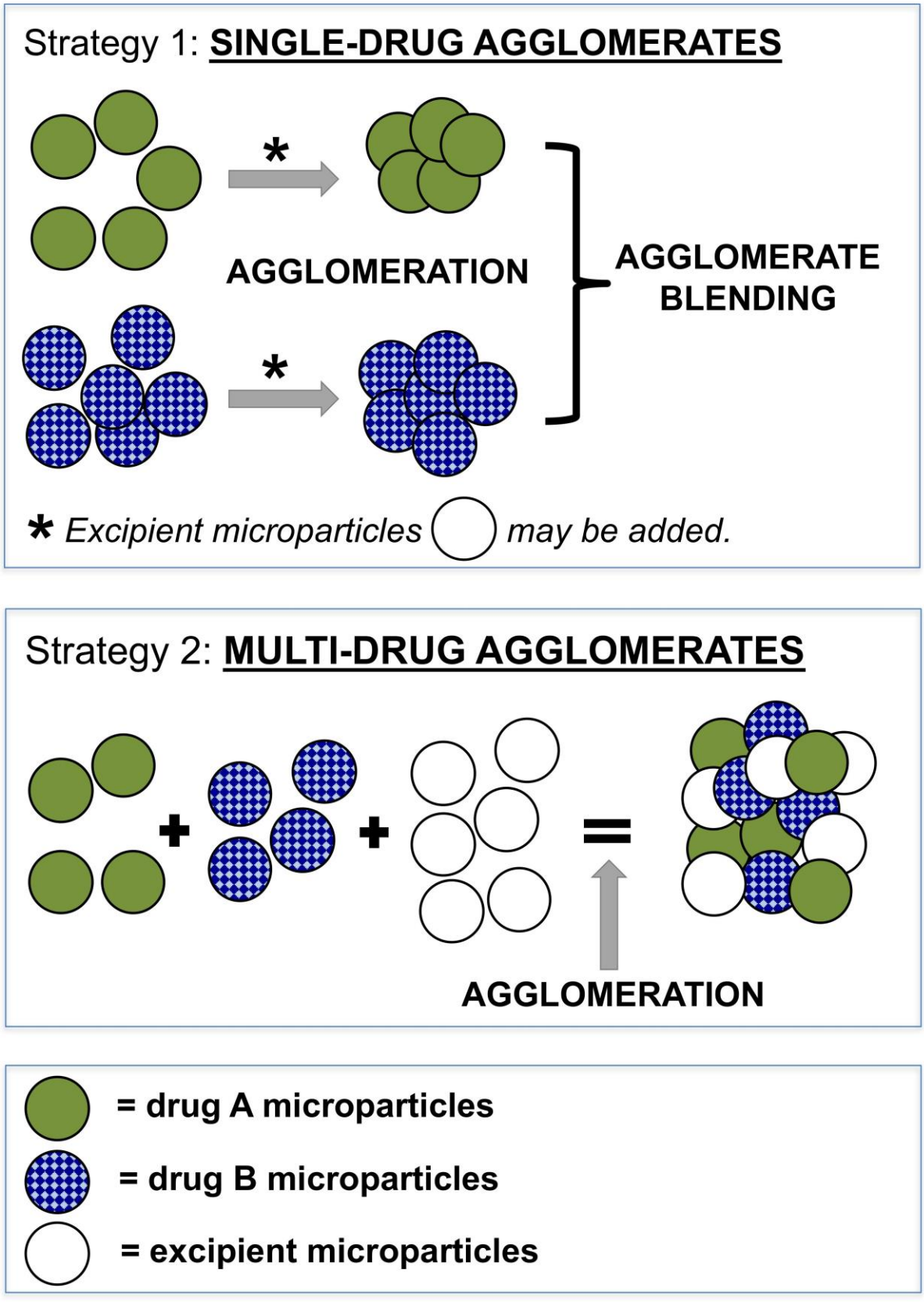


Fig. 4

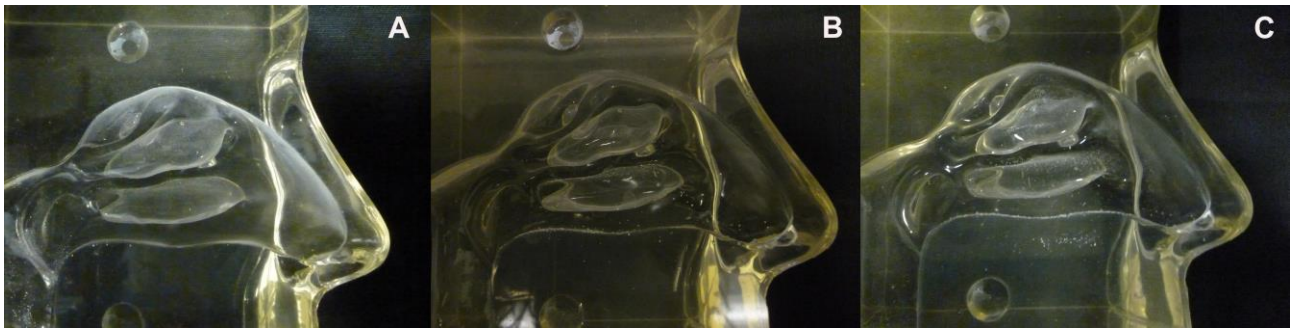


Fig. 5

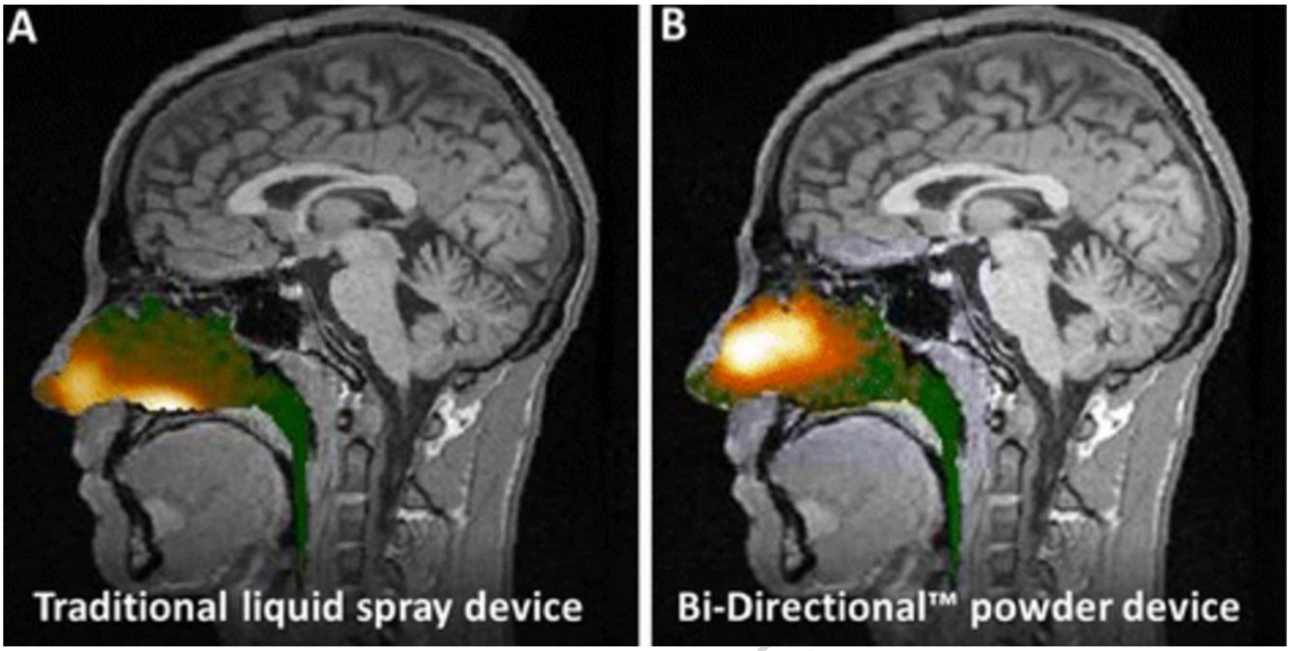
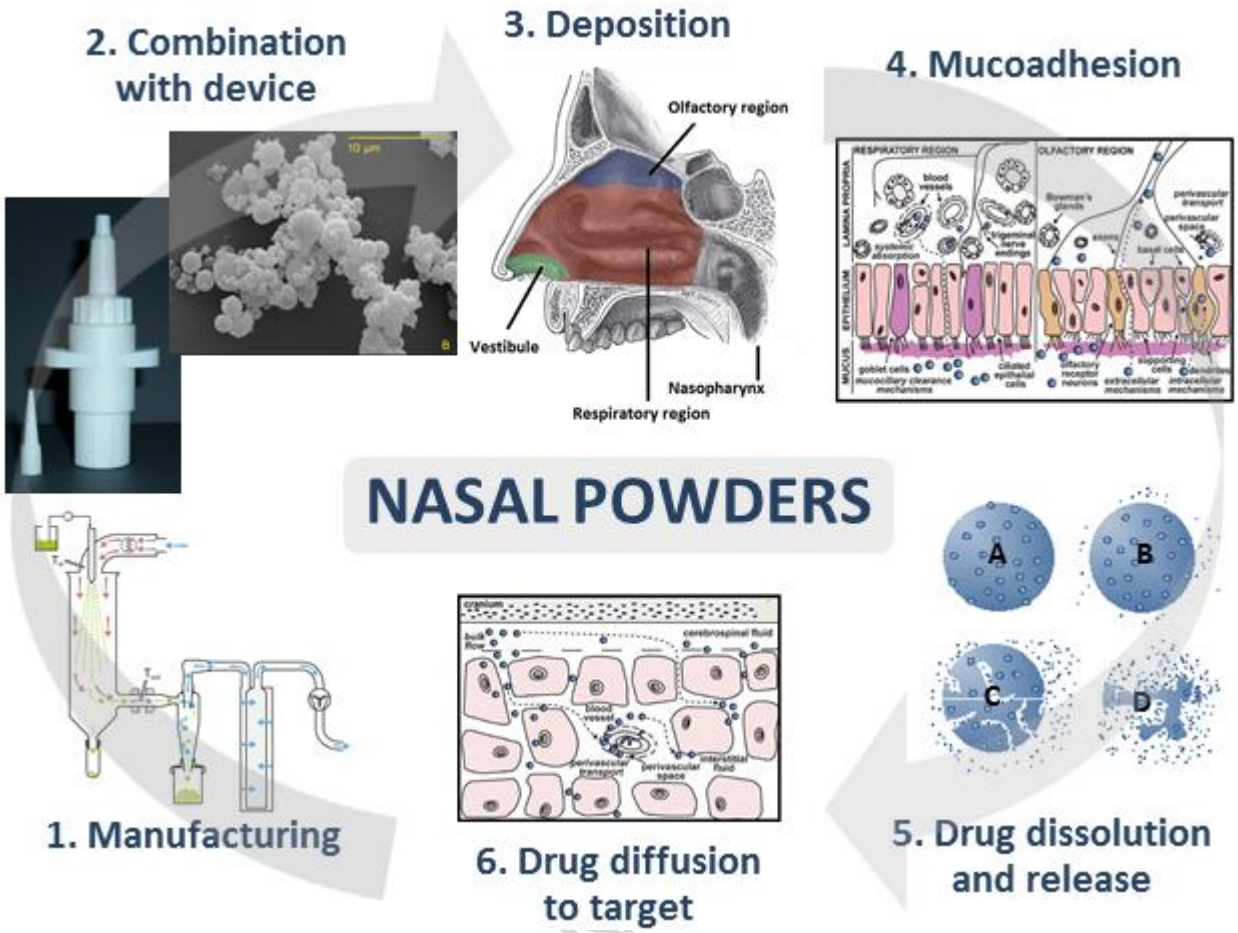


Fig. 6



Graphical abstract