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Spray dried powders for nasal delivery: Process and formulation considerations

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ABSTRACT

Powders for nasal delivery have been recognized as advantageous dosage forms over liquids due to increased stability and residence time on nasal mucosa, with improved bioavailability. They can be manufactured by spray-drying, allowing the optimization of the particle properties that are critical to guarantee nasal deposition, as size and shape. It is also a scalable and flexible method already explored extensively in the pharmaceutical industry. However, it is important to understand how process parameters, particle physical properties and formulation considerations affect the product performance.

Hence, this review aims to provide an overview of nasal powder formulation and processing through spray drying, with an emphasis on the variables that impact on performance. To this purpose, we describe the physical, biological and pharmacological phenomena prior to drug absorption as well as the most relevant powder properties. Formulation considerations including qualitative and quantitative composition are then reviewed, as well as manufacturing considerations including spray drying relevant parameters.

1. Introduction

Nasal drug delivery has been recognized as an attractive route of administration for active pharmaceutical ingredients (API), both small molecules and biomacromolecules [98]. In fact, this route can be a valuable alternative to oral delivery, since the nasal cavity has a large absorption surface area with high vascularization and permeability, leading to a quicker drug absorption and hence a faster onset of action. Furthermore, it is non-invasive, painless and easily auto-administered, favoring patient compliance, relatively to parenteral administration [106,150].

Nasal route is the primary option for the treatment of topical nasal disorders. However, there has been a growing interest in using it for systemic treatments. This is due to fast and direct absorption that circumvent the pre-systemic gastrointestinal and hepatic first-pass metabolism, allowing a quick onset of action and possible reduction of dose [69]. Therefore, systemic delivery is mainly relevant for drugs that need rapid action such as pain management drugs [96]. Additionally, the olfactory epithelium allows unique contact between external environment and central nervous system (CNS), enabling the intranasal drug to directly target the brain, circumventing the blood–brain barrier, commonly referred to as nose-to-brain delivery. The targeted delivery through this pathway avoids side effects related to systemic delivery and improves efficacy of neurotherapeutics [116]. Nasal route has also been studied for the administration of vaccines [127].

Despite the advantages, nasal administration has also some drawbacks that must be addressed during drug product development. First, the low volume of nasal cavity limits the quantity of drug product that can be safely administrated. This is particularly challenging for drugs with poor solubility and/or permeability that may require higher doses. Additionally, physiological and pathological conditions related to nasal mucosa may compromise the extent of nasal drug absorption and therapy efficacy [150,185]. The mucociliary clearance removes the drug from the nasal epithelium by ciliary beating, reducing the time available

Abbreviations: API, Active Pharmaceutical Ingredient; CNS, Central Nervous System; CSF, Cerebrospinal Fluid; DCM, Dichloromethane; DHE, Dihydroergotamine; FDA, Food and Drug Administration; HPMC, Hydroxypropyl Methylcellulose; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IVIVC, In vitro-*in vivo* Correlations; NLC, Nanostructured Lipid Carriers; PEG, Polyethyleneglycol; P-gp, P-glycoprotein; SLM, Solid Lipid Microparticles; SLN, Solid Lipid Nanoparticles.

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for its direct transport of the drug through the nasal mucosa. However, there are strategies to overcome some of these challenges, including formulation modification with excipients, including absorption enhancers and mucoadhesive agents, or using microparticles as nasal drug delivery system [69,135,149,150,190].

Liquid formulations present some drawbacks like challenging chemical and microbiological stability, rapid clearance from the nasal cavity and the need for high volumes to ensure the drug dosage. Solid formulations, represented by powders for nasal delivery, have as advantages their better chemical/microbiological stability, improved residence time on the nasal cavity and enhanced systemic absorption due to an extended contact between powder and mucosa and the higher concentration gradient generated across the mucosa [1], [41,56,113,185]. Powders can also represent a simpler composition in excipients allowing larger quantities of drug to be administered [185]. The final dosage form comprises the combination of the nasal powder formulation and a device for nasal insufflation. The interplay of nasal powder formulation and device is determinant for particle deposition. Devices are determinant on the deposition pattern, and can be designed to target an area like the olfactory region for nose-to-brain delivery [204]. The angle and speed of formulation cloud are critical factors on the deposition pattern related to the device [32,35].

Nasal powders can be manufactured resorting to diverse methodologies including lyophilization[38,60,100,134,155,156], spray drying [1],[73,76,94,105,118,184], supercritical fluid-assisted spray drying [39], spray freeze drying [72,103,202]and agglomeration of micronized powders[16,42,78,163,162,164]. In the literature, spray drying is one of the most often used for nasal powder preparation. It involves the atomization and drying of a feed solution containing the API dissolved or dispersed in a liquid vehicle, which may or may not contain excipients, and collection of the powder. This technology allows a controllable continuous processing and optimization of particle characteristics like size and shape [209], which may impact the drug therapeutic outcome [185].

However, there are still some questions to be answered: how do these particle physical properties affect the final product performance? Which formulation attributes should be evaluated in the product early development? How can all these variables influence the drug product quality and clinical performance?

A few reviews have addressed in detail the anatomy and physiology of the nasal cavity [98,150], formulation and characterization of nasal products [28,31,143,146,149,165,190], in particular Salade et al. [165] et al. reviewed nasal products characterization. Other reviews have addressed specifically nasal powder formulation [63,185], with focus on Fasiolo et al. [185]who reviewed drug formulation and delivery by nasal route. Herein, spray drying process will be focused on together with the formulation parameters that impact the performance of powders for nasal delivery. Some reviews have also addressed immunotherapy and vaccination through dry powders [14,19,50,92,112,186], but given their different mechanisms and characterization, these areas will not be addressed in this review.

1.1. Nasal powders currently on the market and in clinical development

Despite the advantages of powder formulations, there are only two nasal powders approved for systemic action: Onzetra® Xsail®, a sumatriptan product for migraine approved in 2016 by Food and Drug Administration (FDA) [62] and Baqsimi™, a glucagon powder for severe hypoglycemia approved by FDA in 2019 [54]. For topical delivery, there are three nasal powders in the market. A budesonide nasal powder is approved in Europe, while beclomethasone dipropionate and dexamethasone cipecilate nasal powders are available in Japan. These can be used in various therapeutic indications, including for example the treatment of allergic rhinitis [102,185]. Some barriers to the development and approval of more nasal powder products include the shortage of available devices, lack of standardized characterization and performance methodologies and poor understanding of the impact of powders on negative sensory effects. These challenges are further discussed on section 6.

Regarding Onzetra® Xsail®, the nasal administration overcomes the oral associated drawbacks, namely, the high first-pass metabolism and nausea and/or vomiting associated with migraines and the downside of subcutaneous injection-site reactions. The nasal powder shows faster absorption and higher peak plasma concentrations than the correspondent nasal spray, which is important on rapid migraine relief [181]. In fact, most of the dose of nasal spray is swallowed, contrary to the nasal powder product [5].

Baqsimi^{TM} aims to bridge the need of a needle-free treatment for severe hypoglycemia outside the hospital setting [148]. Subcutaneous and intramuscular routes presuppose the preparation of solution and injection by caregivers, which requires training, and often lead to erroneous or delayed administration [153]. Glucagon nasal powder is a portable, ready to use product, with comparable efficacy to injectable glucagon [55]. The formulation includes solubility and absorption enhancers (beta-cyclodextrin and dodecylphosphocholine) and the particle size was designed to prevent lung delivery [137,153–154].

Several drugs for nasal powder administration are being tested in clinical trials, including products for systemic and eventually nose-to-brain delivery, as well as vaccines (Table 1), showing the interest of this delivery system, not only for academical research but also for the pharmaceutical industry.

One example is the dihydroergotamine (DHE) nasal powder, which has completed a Phase 1 safety, tolerability, and comparative bioavailability clinical trial with promising results [6]. This migraine acute treatment product showed favorable DHE tolerability profile and resulted in plasma concentrations comparable to intramuscular administration and higher than the nasal spray. The only not injectable DHE product approved is a liquid nasal spray that presents high variability of the pharmacokinetic profile and prolonged time to full dose administration [6]. This product could bridge the gap between ease of administration and reliable and rapid absorption.

2. Nasal anatomy and physiology

Nasal cavity is involved in breathing, olfaction and external environment protection, and its anatomical and histological characteristics support these functions [150]. Human nasal cavity has a total volume of about 20 mL and a surface area of approximately 150 cm^2 [139]. The small size of the nasal cavity limits the maximum quantity of drug product to be administered to about 100–150 μL in case of liquid formulations [150]or 10–25 mg in case of powder formulations [56,119 119]. Higher quantities can cause nasal mucosa irritation [119]and, in the case of liquids, the excess fluid runs-off, being swallowed and absorbed orally [189].In humans, the middle septum divides the nasal cavity in two symmetrical but not connected parts, each one with four different sections: nasal vestibule, atrium, respiratory region and olfactory region (Fig. 1) [98,150]. The nasal vestibule is the most anterior part of the nasal cavity, covered with stratified, squamous and keratinized cells with sebaceous glands, and features nasal hairs (vibrissae). This area confers resistance against toxic substances, having poor vascularization and low permeability due to its keratinized cells. The atrium is the intermediate region that separates the vestibule and respiratory region, and it is composed of stratified, squamous epithelium anteriorly and pseudostratified columnar epithelium with microvilli posteriorly. Vascularization is low and permeability is reduced given the small surface area and the presence of stratified cells.

Innervated by trigeminal nerves, the respiratory region occupies the largest part of the nasal cavity, and it is divided in the superior, middle and inferior nasal turbinates. The respiratory epithelium contains ciliated and non-ciliated pseudostratified columnar epithelial cells, goblet cells, basal cells and mucous and serous glands. Secretory glands and goblet cells secrete the mucus which is responsible for air humidification

Table 1
Clinical trials of nasal powders for systemic, nose-to-brain or vaccine delivery, registered on clinicaltrials.gov database (accessed on January 2022).

Drug	Condition or disease	Sponsor	Study design	Actual Study Completion Date	National Clinical Trial number
Nasal powders for virus infections					
Norwalk Virus-like Particle Vaccine	Norovirus infection	LigoCyte Pharmaceuticals, Inc.	Phase 1	October 2009	NCT00806962
GelVac™	H5N1 influenza infection	Ology Bioservices	Phase 1	April 2011	NCT01258062
PrEP-001	Influenza A H3N2 infection	Hvivo	Phase 2	February 2016	NCT03220048
	Asthma and human rhinovirus infection	Hvivo	Phase 2	February 2016	NCT03338556
	Viral Upper Respiratory Tract Infection	Hvivo	Phase 2	September 2016	NCT03296917
	Upper Respiratory Tract Infections	Prep Biopharm Limited	Phase 1	May 2017	NCT03198676
FF-3	Influenza A infection	Autoimmune Technologies, LLC	Phase 2	June 2016	NCT02423577
Nasal Powders for Systemic/Nose-to-brain Delivery					
Remimazolam	Procedural Sedation	Paion UK Ltd.	Phase 1	June 2017	NCT03329014
Apomorphine	Parkinson's Disease	Britannia Pharmaceuticals Ltd.	Phase 2 Phase 3	August 2007	NCT00346827
Sumatriptan	Migraine	Optinose US Inc. Avanir Pharmaceuticals	Phase 3	June 2012 March 2014	NCT01462812 NCT01667679
Glucagon	Diabetes Mellitus Hypoglycemia	Eli Lilly and Company	Phase 2 Phase 3 Phase 3 Phase 3 Phase 3 Phase 1	July 2012 January 2015 August 2015 August 2015 August 2018 Not completed	NCT01556594 NCT01994746 NCT02171130 NCT02402933 NCT03421379 NCT04992312
Levodopa	Parkinson's Disease	Impel NeuroPharma Inc.	Phase 2	June 2019	NCT03541356
Olanzapine	Acute Agitation associated with schizophrenia and bipolar I disorder	Impel NeuroPharma Inc.	Phase 1	October 2018	NCT03624322
Dihydro ergotamine	Migraine	Satsuma Pharmaceuticals, Inc.	Phase 1 Phase 3 Phase 3 Phase 3	November 2018 August 2020 Not Completed Not Completed	NCT03874832 NCT03901482 NCT04406649 NCT04940390
Naloxone Hydrochloride	Opioid Overdose	Nasus Pharma	Phase 1	October 2021	NCT04713709
Epinephrine	Anaphylaxis	Nasus Pharma	Phase 1	September 2021	NCT04696822
APH-1105	Dementia, Alzheimer Disease	Aphios	Phase 2	Not Completed	NCT03806478
Sumatriptan	Acute Migraine With or Without Aura	Currax Pharmaceuticals	Phase 3	Not Completed	NCT03338920

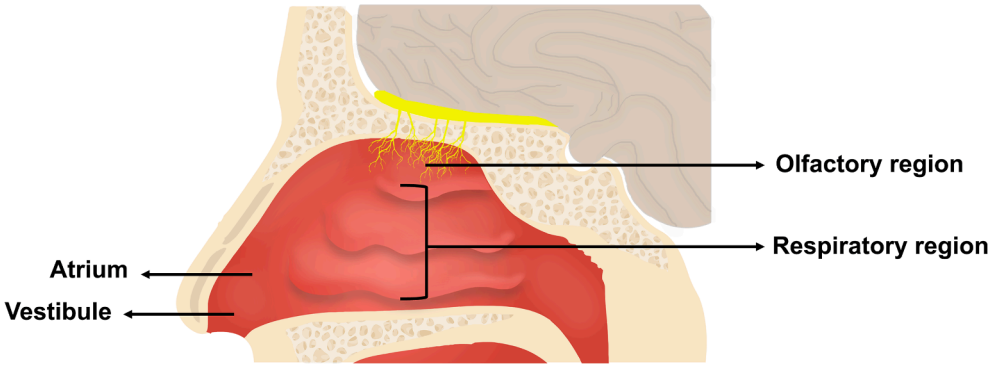

Fig. 1. Anatomy of the human nasal cavity showing the nasal vestibule, atrium, respiratory region (with inferior, middle turbinate and the superior turbinates) and the olfactory region.

and warming as well as physical and enzymatic protection against external agents. Due to the large surface area and high vascularization, the respiratory region is the target for systemic drug delivery [45,80,99,150,190]. The blood supply affects significantly the systemic nasal absorption of drugs. Thus, changes in the blood flow rate impact on nasal drug absorption [80].

Finally, the olfactory region is located in the upper part of the nasal cavity, and its epithelium contains olfactory receptor cells and serous glands, which participate in smell perception. Even though the surface area is small (little contribute to systemic absorption), it enables the direct access to the CNS and it is the target for nose-to-brain delivery [45,80,99,150,190].

The mucus layer has a thickness of 5–15 μm [122] and is composed of 95% water, 2% mucin, 1% salts, 1% of other proteins (as albumin and immunoglobulins), and less than 1% of lipids [190]. To prevent infections, mucus is slightly acid with a physiological pH-value of 5.5–6.5 [20]. To protect the respiratory system from exogenous substances, the nasal mucus is transported towards the nasopharynx and discharged into the gastrointestinal tract, being renewed every 15–20 min [98,135]. This mechanism, named mucociliary clearance, acts also on drug removal from the nasal cavity. For this reason, mucoadhesive components are frequently added on nasal formulations, in order to slow drug clearance and increase the contact time with the mucosa [12,143,190]. Mucin is a polymeric gel-forming glycoprotein and the main responsible component for mucoadhesion [176]. Even if a formulation adheres to the mucosa, the drug has to diffuse through the mucus to reach the nasal epithelial cells [165]. Thus, microparticles need to dissolve so the drug can penetrate the mucus layer, since they are too large to enter the

mucin mesh spaces [110]. Mucopenetrating drug molecules are ideally hydrophilic and neutrally charged at the mucus pH [11].

It is noteworthy that several enzymes, including oxidative and conjugative enzymes, are expressed in the nasal mucosa, despite in lower quantities than in the intestine or liver. Those enzymes are responsible for the degradation of some nasally administered drugs and result in creation of a "pseudo-first-pass effect" [12], hindering the absorption of drugs. Peptide or protein based drugs are particularly sensitive due to the occurring amino peptidases and proteases [120].

As other biological membranes, drugs can permeate across the nasal mucosa through transcellular (across the cell) and paracellular (between cells) mechanisms. Transcellular mechanisms include passive diffusion, endocytic processes, and carrier mediated transport, while paracellular mechanisms include transport through hydrophilic porous and tight junctions. Lipophilic drugs are efficiently and rapidly transported via transcellular pathway and polar drugs are more likely to be transported through the paracellular pathway, which is less efficient and dependent of molecular weight [99,143]. On the other hand, drug delivery to the CNS can occur via the olfactory neuroepithelium, through transcellular, paracellular or neuronal transport [99], or via trigeminal nerves in the respiratory region [45]. However, the olfactory region plays the most important role in the nose-to-brain delivery of drugs to the CNS [133]. Nevertheless, the efflux proteins such as P-glycoprotein (P-gp) can reduce brain uptake after nasal administration and decrease nose-to-brain delivery [79]. The potential efflux of a substrate drug of P-gp can also challenge local and systemic delivery, with reduction of therapeutic success [53]. To address this challenge, specific excipients can be used in the formulation (See Section 3.2.2).

Regarding nasal powders, the anatomy of the nose affects the deposition of powder particles. Before reaching the front surfaces of the nasal turbinates, the airflow passes through a constriction called the nasal valve. These two elements of the nasal cavity are prone to trap air contaminants or drug particles/droplets from nasal devices, especially with larger sizes. For an effective delivery, the drug should penetrate the nasal valve [143]. The main deposition mechanism for particles on the nasal mucosa is inertial impaction [117]. Particles larger than 10 μm are mostly retained in the nose, while particles below 10 μm can be deposited in the tracheobronchial region or the pulmonary region [34].

Considering the anatomy and physiology of the nasal cavity, spray dried powders should be designed with a particular range of particle size to deposit on the nasal mucosa (10–45 μm[185]and should allow adequate residence time, dissolution and permeation to cross the nasal epithelium and reach the target. These features can be optimized through the process and formulation, as described in the next sections.

3. Relevant properties of powder formulation for nasal delivery

Formulation properties such as powder physical characteristics (particle size and morphology, flowability, solid state) and biopharmaceutical profile (mucoadhesion and swelling, drug release and permeation) are critical on the rate and extent of drug absorption [25,185].

In addition to the airstream rate, which is limited by the selected device, particle size and morphology deeply impact on the particle impaction and therefore the aerodynamic profile [117]. Flowability, defined as the ability of particles to move relative to adjacent particles or along walls (as filling equipment walls) [111], is critical for an acceptable and reproducible delivered dose, and successful capsule or device filling. It is determined by the type and extent of interparticle interactions, which are affected by the powder composition, physical properties as particle size and morphology and environmental conditions as relative humidity and temperature [88]. Poor flowability can lead to lower and variable delivered doses through the same nasal device and may also contribute to variable deposition sites in the nasal cavity [90]. Regarding the deposition pattern (where and how the powder is delivered on the airways), which is affected by the powder physical properties, targeting a specific area of the nasal cavity can be necessary to archive enhanced systemic or nose-to-brain delivery [25,63,108,109].

The biopharmaceutical profile related with mucoadhesion, drug release and permeation can be optimized through formulation work, by modifying its components, and particle size and morphology fine-tuning. The solid state greatly impacts on dissolution performance.

3.1. Powder physical characteristics

3.1.1. Particle size

Particle size represents a critical nasal product attribute, given its influence on the steps prior to drug absorption. Reduction of particle size would be preferred to allow faster and complete dissolution during formulation residence time on nasal mucosa. However, small particles have a higher risk of lung deposition, and also present poor flowability [17,25,63]. Too large particles can be trapped by the nasal valve area and the front surfaces of the turbinates, without reaching distal areas of the nasal cavity [143]. Target size for nasal delivery falls in the range of 10 to 45 μm [27,104,107,185]. The larger particle size compared with pulmonary target size (<5 μm), has improved flowability [109].

Even though the nasal device plays a determinant role on the could powder motion and deposition profile, different particle size distributions also have a contribution on the emitted powder aerosol and deposition profile in the nasal cavity.

Deposition profiles are usually assessed either using impactors or nasal casts. Impactors, as the Andersen Cascade Impactor or Next Generation Impactor, coupled with expansion chambers are usually used to provide a global information about the deposition in the respiratory tract and aerodynamic profile. While particle deposition in the expansion chamber represents the nasal fraction, particles in impactor stages represent the fraction reaching the lungs. Nasal casts are artificial nasal cavities that are used to assess particle deposition on the different parts of the nasal cavity. These artificial nasal cavities provide a detailed deposition profile of a nasal product on the different regions of the nasal cavity [32,93,165,206].

The optimal particle size for a specific application should be evaluated, according to the preferred region of absorption of a specific drug, with consideration of the device that is used. However, it should be noted that reduced particle size and span lead to a more uniform and complete covering of the nasal mucosa [25,164]. For nose-to-brain applications, the olfactory region is the target. Yarragudi et al. reported higher olfactory deposition with particles with a mode size of 10 μm than mode size of 2 μm in a human nasal replica cast [206].

Smaller particle size (with increased surface area) leads to enhanced mucoadhesion ability, water uptake and dissolution rate, which may reflect in higher and faster absorption [17,39,76,82,152,167,184]. Therefore, particle size must be optimized to attain optimized mucoadhesion and dissolution properties while maintaining a deposition profile according to the required outcome.

3.1.2. Flowability

Common to powders for pulmonary delivery, a good flowability is also a key attribute of nasal powders, conferring good dispersion through the device and fluidization upon actuation [2]. This property is also critical on the filling process, either into a capsule or directly into the device [109].

Powder flow is related to particle cohesion. Minimal cohesive forces between particles imply good flowability [2,87]. This is highly influenced by particle size and morphology, as well as surface free energy, crystallinity and density [2,7,15].

The interaction between flowability and nasal deposition profile has been little researched. Nonetheless, making use of a nasal cast, Jüptner et al. [108] demonstrated that formulations with better flowability have increased postnasal fraction and lower deposition in the middle and upper turbinates probably due to their low particle cohesion. Higher particle cohesion may lead to the formation of agglomerates that deposit

in the anterior nasal parts.

Several methods can be used to characterize powder flow, as angle of repose, compressibility index or flow rate through an orifice. In a study by Jüptner et al. [109], the flow function coefficient and specific energy measured by FT4 powder rheometer were more suitable and discriminative to assess nasal and pulmonary powder flow comparing with compressibility index, flow through an orifice and angle of repose tests, proposed by Ph. Eur.

Flow measurements can predict the success of filling trials [109]. However, for both formulation discrimination and filling prediction, the method should be chosen carefully.

3.1.3. Particle morphology

Particle morphology affects the interactions and adhesion forces between particles [125,177], with strong interparticulate forces resulting in particle agglomeration and poor powder flow [144,177]. Surface corrugation can increase interparticulate distance and reduce the accessible surface area for particle interaction, decreasing particle interactions [37]. A flat surface promotes large contact areas resulting in increased adhesion forces between particles [177]. Depending on the particle morphology, there is also the possibility of indentations in particles to interlink, leading to worse flow and challenging filling of capsules or nasal devices [109,199]. Porous particles have lower density than non-porous particles, which may increase the respirable fraction given the lower aerodynamic particle diameter [36,85], which is undesirable for nasal delivery. However, this fraction should always be confirmed with aerodynamic profile studies.

Jüptner and collaborators [108] evaluated the influence of particle morphology on nasal cast deposition of model formulations with similar particle sizes. Particles that interlinked led to higher deposition in frontal nasal parts, higher variability and lower deposition in the middle and upper turbinates (zone of interest for systemic or nose to brain delivery). Using an airflow of 15 L/min, wrinkled particles had higher postnasal fraction compared to the fraction at breath hold (0 L/min). In general the study showed that wrinkled morphology can be preferable for higher deposition in targeted zones, as this can be correlated with lower particle cohesion associated with lower deposition on the frontal nasal parts and higher deposition in the middle and upper turbinates. However, this could also lead to a possible lung fraction of formulations with very low particle cohesion [108].

Regarding mucoadhesion and dissolution, high surface area is beneficial [110,185]. For example Dukovski and coworkers attributed the higher mucoadhesion to the larger contact surface area of dexamethasone wrinkled particles comparing to smooth spherical particles [110].

3.1.4. Solid-state form

The solid-state form, which corresponds to the crystalline polymorphic form or amorphous form of the powder formulation components, can affect powder dissolution, stability and bioavailability.

The formation of an amorphous solid dispersion leads to lower long-range order and weak interactions between molecules, promoting faster dissolution and higher drug concentrations dissolved [197]. Dissolved amorphous drug can induce a supersaturated solution in the nasal mucosa, promoting drug permeation and bioavailability, particularly when absorption is limited by drug solubility [46,160,184].

Many reports in the literature supported the improvement of biopharmaceutical performance of amorphous nasal powders. Melatonin [144], carbamazepine [73], lorazepam [105], repaglinide [56] and rokitamycin [74] polymeric spray dried microparticles are examples where drug amorphization led to dissolution enhancement. Physical stability can be a challenge when the drug has tendency to crystallize, especially when the drug is not well dispersed at a molecular level within the polymer, and phase separation occurs [197].

Drugs without solubility challenges can be formulated in their crystalline form. However, the polymorphism can affect dissolution and absorption. This supports the importance of the solid-state characterization of nasal powders, including the evaluation of the polymorphic form of the drug.

3.2. Biopharmaceutical profile

3.2.1. Mucoadhesion and drug release

When particles reach the nasal cavity, they can adhere to the mucosa. Mucoadhesion comprises the intimate contact between a polymeric formulation and the mucosa, due to wetting, gelling and swelling of the polymer, and its diffusion and interpenetration within mucin fibers of mucus (Hitendra Shaligram [130,129,190]. Bonding between polymers and mucins can be covalent or non-covalent as electrostatic forces and hydrogen bonding [11,176]. Electrostatic forces potentiate adhesion and include the interaction between negatively charged mucin at nasal mucosa pH and the positively charged molecules present in the formulation [176].

In the literature, the characterization of formulation-mucus interaction is done resorting to one or more of the following assays:

- Mucoadhesion *in vitro* testing with mucins [40,48,165];
- Mucoadhesion *ex vivo* testing with nasal tissue [47];
- Water intake and swelling *in vitro* testing [46,160,167];
- Zeta potential measurements of microparticles in water or buffer [110,144,166].

Along with the formulation interaction with mucus, the drug needs to be dissolved and released from the microparticle to reach and permeate the nasal epithelium. For polymeric microparticles, this involves water penetration into the formulation matrix and drug dissolution and diffusion out of the matrix [106](Fig. 2). These phenomena can be observed by changes in particle size of microparticles – increase of particle size due to swelling and decrease of particle size due to dissolution. The equilibrium between these processes determines the final drug release performance [76].

Polymer hydration is a critical step, where the polymer–polymer interactions are loosened. The polymer becomes available for interactions with the mucus and the API gets increased mobility within the polymer matrix. Incomplete hydration results in poor swelling and mucoadhesion, while excessive hydration results in high polymer dilution, poor mucoadhesion and lower mean residence time in nasal cavity [144,190]. Drug release rate is controlled by the diffusion of the drug across the swollen and gelled polymer layer and the erosion of the microparticles [29,105]. This balance is determinant to obtain a good degree of mucoadhesion while maintaining drug release, before drug clearance. Even though a fast release is frequently needed to avoid mucociliary clearance and to obtain a fast absorption, viscous gels forming polymers can control and slow drug diffusion [8,29]. This can

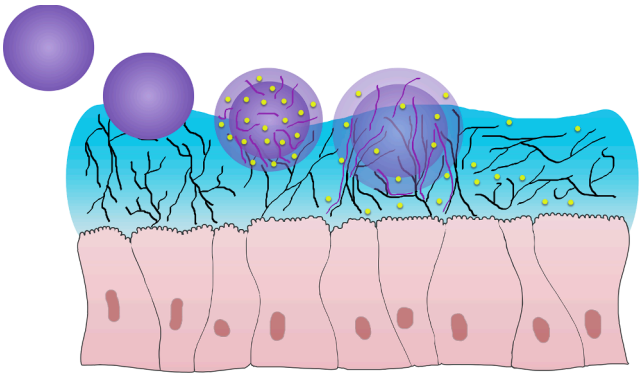

Fig. 2. Schematic representation of polymeric microparticles formulation interacting with mucus and drug release.

be valuable when targeting sustained drug release with highly mucoadhesive formulations.

Drug release and dissolution tests have been carried with compendial (e.g. paddle, flow-through cell and vertical diffusion cell methods) and non-compendial methods (e.g. dialysis bag method) [106]. Most of these methods use large volumes of dissolution medium and require the complete immersion of the particles, conditions that are distinct from the physiologic dissolution conditions of nasal powders in the nasal cavity. Vertical diffusion cells (including the Franz diffusion cell) can be advantageous over other methods, as they allow particles to hydrate and eventually swell slowly, in humid environment conditions similar to those observed in the nasal cavity [131].

3.2.2. Drug permeation

Drug permeation is vital to systemic and nose-to-brain delivery and it is conditioned by the API physicochemical properties and other substances that may reduce or enhance permeation [133,150,185]. Contrary to most lipophilic drugs, hydrophilic drugs and macromolecules may have challenges in permeation. In this case, permeation enhancers can be a valuable addition to the formulation. Permeability enhancers act by altering the structure of the phospholipid bilayer of cells, impairing the tight junctions, removing membrane proteins, inhibiting enzymatic activity or inhibiting efflux transporters [133,185]. Modifying the structure of the phospholipid bilayer may damage the nasal mucosa with protein leaching or stripping off the outer layer of the mucosa [98]. Examples include surfactants, bile salts and fatty acids. Other mechanism involves opening of tight junctions. Chitosan is an example of a permeation enhancer that opens tight junctions transiently, possibly due to its positive charge that interacts with the opening mechanism of tight junctions [51]. Other tight junction modulators as claudin and zonula occludens modulators are very potent in opening tight junctions, but have been mainly tested on intestinal, dermal and blood–brain barriers [77]. Enzymes and efflux transporters (as P-gp) inhibition may be interesting permeation enhancing mechanisms for specific drugs that are either metabolized on the nasal mucosa or are substrates of efflux transporters. The use of P-gp inhibitors (as cyclosporine A and rifampicin) has proven to improve drug permeation and brain uptake [79,170]. Examples of the use of permeation enhancers in nasal powder formulations are further discussed on section 4.1.2. Absorption enhancers for nasal delivery have been reviewed in more detail elsewhere [51].

Increased permeability can be also achieved with wetting and swelling of mucoadhesive particles, which, not only participate in mucoadhesion, but also promote momentaneous mucosal dehydration. This leads to reversible shrinkage of epithelium cells and transient widening of tight junctions, resulting in increased permeability by the paracellular pathway [63].

Blocking permeation may also be of interest considering unwanted nose-to-brain delivery with neurological side-effects. This approach could be relevant for abuse deterrent illicit drugs or vaccines. In the case of vaccines, a more localized drug delivery would avoid potential off-target effects. Some potential strategies include particle and device design to avoid deposition on the olfactory region and inhibition of neuronal cells endocytosis [133]. This last strategy could be useful for drugs that enter the neuronal cells by endocytosis in the olfactory epithelium. Furthermore, certain molecules, such as lidocaine which is known to have a nerve blocking effect [138], could also be used to impair nose-to-brain transport.

4. Formulation composition

A powder formulation for nasal delivery can contain only the API, as the commercially available Onzetra® Xsail®, a sumatriptan nasal powder. If the pure drug has a favorable pharmacokinetic profile and the active dose is high enough for handling and administration, excipients may not be needed, which is advantageous from a safety, manufacturing and regulatory perspective [185]. However, many excipients can be added to address problems such as poor aerodynamic performance, difficult handling/filling or low bioavailability. The impact of the qualitative and quantitative composition of the formulation on its performance will be revised in this section.

4.1. Qualitative composition

4.1.1. Active pharmaceutical Ingredient

The drug properties as molecular weight, lipophilicity, solubility, pKa and stability can affect nasal absorption and bioavailability. The pH of the absorption site and the pKa of the drug affect the quantity of the API uncharged species. At the nasal mucosa, the largest absorption occurs for the nonionized species, given their higher lipophilicity and consequent permeability [150]. Charged drugs may also interact with sialic acid residues of mucins, which have negative charge, hampering mucus penetration and leading to drug mucociliary clearance [11]. Polar drugs have low nasal absorption and it is dependent of molecular weight, since these compounds pass the nasal membrane via a paracellular pathway that is dramatically less efficient than the transcellular route [74,150]. Lipophilic drugs with molecular weight lower than 1 kDa are usually well absorbed exhibiting similar systemic pharmacokinetic profiles to those obtained with intravenous administration. However, lipophilic drugs may present poor solubility in the aqueous environment of the nasal cavity [150]. For example, the low solubility and lipophilic properties of lorazepam decrease the release rate of spray dried lorazepam intended for nasal delivery [105]. For powder formulations, dissolution plays a critical factor since particles need to be dissolved so that the API can permeate the biological membranes. If the drug remains in the undissolved particles, they can be cleared from the nasal cavity by mucociliary clearance before permeation, resulting in reduced nasal absorption [17,150]. In pharmaceutical research, more than three quarters of new drugs are poorly-soluble [89], therefore many strategies have been developed to enhance solubility. Additionally enzymatic metabolism can occur at the nasal cavity environment, which may reduce the dug biological stability [150].

An approach to improve drug stability, regulate protease susceptibility and enhance solubility can be by modifying the drug molecule, for example by generating a pro-drug [24,185]. Once prodrugs are absorbed, conversion to the active drug takes place, releasing it at the intended delivery site [133]. For solubility enhancement, the prodrug would need to have higher hydrophilic character [150]. For instance, to overcome the solubility problem of levodopa, Lee and collaborators modified the molecule introducing levodopa methyl ester hydrochloride for nasal delivery [123]. Another example consisted of producing the sodium salt of flurbiprofen, which had a 10-fold higher solubility than flurbiprofen. The spray dried formulations of the salt presented increased drug release and *ex vivo* permeation [184]. Nevertheless, drug modification has as major drawback - preservation of efficacy and safety must be demonstrated relatively to the original compound [185].

In case of spray drying as the manufacturing technology, API properties also affect the spray dried powder solid state form generated and its stability, as the glass transition temperature, melting temperature and log P [197].

4.1.2. Excipient (s)

The excipients present in FDA-approved nasal powders can be consulted in the FDA inactive ingredients database [66]. In the current update (October 2021), there are only 4 excipients in this list, including hydroxypropyl methylcellulose (HPMC), carrageenan, ink black SW-9008 and potassium chloride. For other nasal dosage forms there are around 60 other excipients included. Even though the number of inactive ingredients for nasal powders is quite limited, in research a wide spectrum of excipients is used with various purposes. They can be included in formulation according to their functions, either to simplify handling or improve bioavailability.

According to their specific roles in formulation, the main excipients used in the literature for nasal powder delivery can be classified in fillers, mucoadhesive agents and absorption enhancers [63,85,185]. Fillers may be added to guarantee accurate dosing and delivery when the drug dose is low, and include for example mannitol and lactose [85,185]. Mucoadhesive agents include polymers like alginate, chitosan or cellulose derivatives [175,176] and are frequently added in order to prolong residence time in the nasal mucosa and resistance to mucociliary clearance [190]. Permeability enhancers are used to improve nasal transport of the drug and include surfactants, fatty acids, phospholipids, bile salts [63,185]. Excipients may also have other purposes as protein protection, namely for biopharmaceutic formulations [33]; agglomeration support, in the case of chimeral agglomerates formulation [162]; mucolytic function for challenging mucus penetrating formulations [136,161] or dispersibility enhancement[33,109]. Regarding agglomeration, lecithin is a key excipient that acts as a binder, conferring adhesive properties and improving the mechanical resistance of agglomerates [16,78]. Its addition can be decisive in agglomerates formation [162]. It is noteworthy that one excipient may have more than one role.

In practice, excipients may have impact on particle properties, formulation interaction with the nasal mucus, drug release, drug permeation and ultimately on drug pharmacokinetics. For example, chitosan, a mucoadhesive and absorption enhancer excipient, was included in nasal carbamazepine formulations, and it increased the drug bioavailability 5.6-fold comparing with the administration of the pure drug as powder [73]. In this section we review how the qualitative composition of excipients affects these parameters – powder physical properties, mucus interaction, drug release and drug permeation.

4.1.2.1. Excipients impact on powder physical properties. Excipients can impact on powder physical properties as particle size and morphology, solid state properties or powder hygroscopicity. Inclusively, it can be of interest to use these excipients do modulate the powder physical properties.

Considering spray drying as the manufacturing method, excipients that confer higher feed solution viscosity usually lead to increased particle size [74,114,178]. This happens for example with higher molecular weight polymers, which are commonly used to increase mucoadhesion, as chitosan [178].

Particle morphology of spray dried nasal powders can also change markedly with different excipients [29,56,78,144,164]. These excipients can be used to alter the particle shape in a specific way [109]. For example, propylene glycol can confer spherical and smooth surface characteristics to particles, contrary to methylcellulose, chitosan and carbopol, which can lead to crumpled particle surface [85]. Importantly, other studies revealed that chitosan can conduct shriveled particles [78] or smooth spherical particles [158,160,201]. These contradictory findings can be explained considering that chitosan has different physicochemical characteristics (molecular weight, degree of deacetylation), and that the morphology is also very much dependent on process parameters. HPMC, a mucoadhesive polymer, and leucine were used as morphology modifiers in a study by Jüptner and collaborators, who revealed that HPMC and high concentrations of leucine induce wrinkled morphology in spray dried nasal powder formulations [108].

Fig. 3a and 3b show an example of different particle sizes and morphologies obtained by spray drying of solutions, varying the polymer, but maintaining the process parameters and drug to excipient ratio [91].

Different excipients can also lead to different solid-state properties of the formulation – in case of amorphous solid dispersions, the glass transition temperature of the excipient (s) will impact on the powder formulation glass transition temperature [33,197]. Moisture content also varies with different excipients, depending on their capacity to absorb atmospheric moisture. Moisture can lead to higher powder cohesion, due to capillary forces, with impact on aerodynamic performance. Leucine is an amino acid frequently used in pulmonary formulations to improve powder dispersion and protect the particle from moisture (anti-hygroscopic effect) by creating a hydrophobic outer shell layer [64,169]. It has also been considered an appropriate shell-forming excipient for nasal formulations to protect against moisture and improve powder dispersibility [203]. Comparing with pulmonary delivery formulations, smaller amounts of leucine are required to form the shell on the larger particles for nasal administration [203]. Elmowafy and collaborators considered leucine to have a positive effect on nasal powder formulations given the low moisture content and good powder flow [57]. Moisture content also plasticizes amorphous solid dispersions,

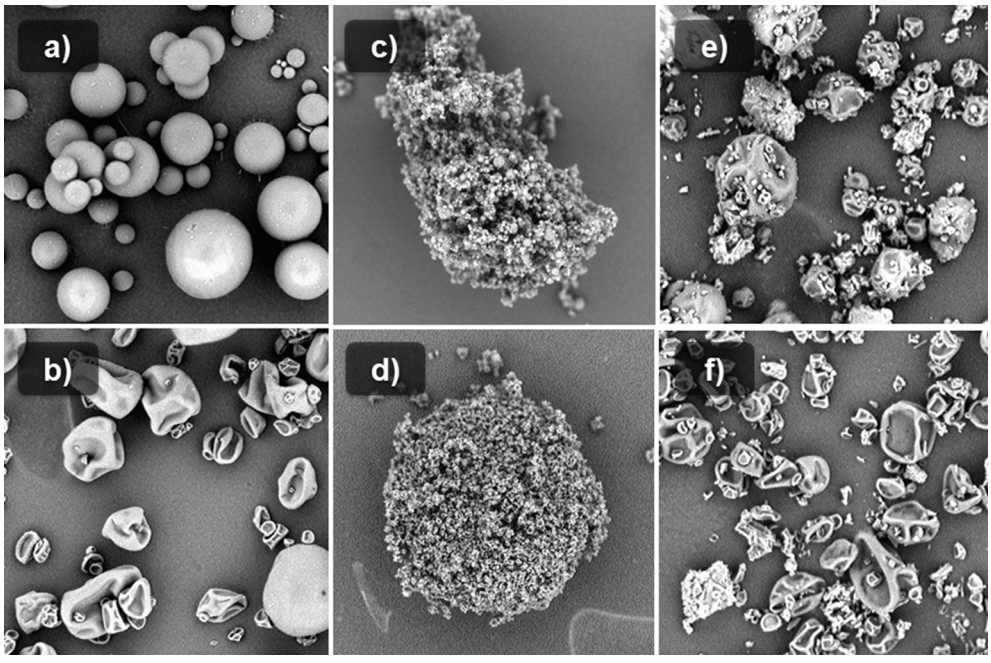

Fig. 3. Scanning electron microscopy images of piroxicam spray dried particles [a) and b)], chimeral agglomerates [c) and d)] and carrier based formulations [e) and f)] [210].

lowering the glass transition temperature [197]. Generally, a lower glass transition temperature indicates higher propensity to drug crystallization [197], which is not desired.

Considering the impact of the excipients on powder physical properties as size and morphology, the aerodynamic performance can be consequently affected and must be assessed.

4.1.2.2. Excipients impact on mucus interaction and drug release. The excipients can greatly affect the interaction between formulation and mucus layer and, consequently, the drug release, which influences the rate and extent of drug absorption. Since mucoadhesion prolongs residence time on the mucosa, mucoadhesive polymers are often included in nasal powder formulations.

Between the different classes of common excipients for nasal powder formulations, polymers have the highest effect on mucoadhesion and drug release. The most common ones include chitosan, cellulose derivatives, alginate, pectin, vinyl polymers [poly (vinyl pyrrolidone) and poly (vinyl alcohol)] and hyaluronic acid [46,56,118,147,152,176,185,205]. Their physicochemical characteristics are critical for the nasal powder performance.

Polymers with higher molecular weight generally promote higher swelling, stronger mucoadhesion and slower drug release. This could be observed for example in studies carried on by Harikarnpakdee et al. [85] and by Nagda et al. [140] where carbopol had higher swelling capacity than chitosan. Moreover, Alhalaweh et al. observed an inverse releationship between wettability and molecular weight [9] and Sun et al. between sustained release profile and molecular weight [178], both regarding chitosan. Sun et al. also observed that low molecular weight had lower bioadhesive profile than medium molecular weight chitosan. However, high molecular weight chitosan showed less adhesive properties, which was explained by the longer chains being entangled and less available for interaction with mucin [178]. Regarding the use of chitosan, it is important to consider other parameters besides its molecular weight: free amino groups, degree of deacetylation and degree of cross-linking, given their influence on the flexibility and conformation of the polymer chains [9,118].

Polymer charge is critical on electrostatic interactions with negatively charged mucin. For example, positively charged chitosan interacts with mucin leading to high mucoadhesion [33,76]. However, even that negatively charged excipients may cause charge repulsion, they may also interact with mucin via hydrogen bonds or Van der Waals, thus having adhesive forces with nasal mucus [76,85,95].

Polymer wettability, related with its hydrophilic character, plays an important role on promoting drug dissolution. In a study by Huh and collaborators, drug release was significantly enhanced when the API was incorporated into hyaluronic acid and polytethyleneglycol (PEG) 6000 microspheres with improved wettability comparing with the API alone [94]. Pomázi and co-workers also obtained more efficient drug release in microparticles with wetting components, including a polymer – polyvinylpyrrolidone K-25 – that improves wettability [152].

To avoid slow drug release rates, the polymer should also have a relatively loose matrix, allowing also water intake and mucoadhesion, promoting rapid drug diffusion and release. Zhao and collaborators attributed to the relative loose polymer matrix the increased release rate compared with the pure API [208]. Interchain crosslinking of polymers tights the polymer matrix, giving it less ability to absorb water, and reduced free chain length for interactions with mucus [190]. This was observed by Katsarov and co-workers, where glutaraldehyde cross-linked chitosan microparticles had reduced swelling, mucoadhesion and extended drug release compared with non-cross-linked microspheres [114].

Other excipients can also influence the interaction with mucus and drug release. For example, mannitol enhanced dissolution rate of N^6-cyclopentyladenosine microparticles in a study [47], as well as dexamethasone release rate from microparticles blended with mannitol in other study [145], which was attributed to the increased powder wetting rate due to the osmotic activity of this excipient. Cyclodextrins increase aqueous solubility of poorly soluble drugs, promoting higher drug dissolution [38,105]. In fact, this excipient has been used as both a solubility enhancer and absorption promoter in nasal drug delivery [137]. Additionally, cyclodextrins may be modified, as thiolated cyclodextrins, to interact with nasal mucus and prolong drug residence time on the mucosa, since thiols groups can form disulfide bonds with proteins, as mucins. For example, Racaniello and collaborators developed budesonide spray-dried microparticles containing thiolated hydroxypropyl-β-cyclodextrin, increasing both drug solubility and mucoadhesion [157]. Cyclodextrins may also interact with other excipients altering the formulation water-uptake and swelling process [105]. Wetting agents (or surfactants) may also play a role drug release, improving dissolution profile, as seen in a study by Pomázi and collaborators [152].

4.1.2.3. Excipients impact on drug permeation. In addition to the influence of the API physicochemical characteristics, excipients may also impact on drug permeation. Assessment of drug permeation is usually performed with *in vitro* cell models (e.g. RPMI 2650 cell line and Calu-3 cell line) or *ex vivo* models (e.g. using sheep, rabbit or pig nasal tissue) [165].

For highly permeable drugs, the diffusion rate through membranes is primarily dependent of the drug release profile from the formulation. In these cases, a correlation between drug release and permeation profiles has been observed. For instance, propranolol spray dried mucoadhesive microspheres presented drug permeation corresponding to drug release profiles, depending on the polymer used as excipient [85]. The same was observed by Dalpiaz and co-workers, with *ex vivo* permeation having correlation with drug release studies [47]. Additionally, Dukovski et al. concluded that dexamethasone permeation was determined by its dissolution rate considering suspensions of the API and of spray dried API and pectin microspheres [110].

For poorly permeable drugs, absorption enhancers are advisable. Chitosan is a biocompatible polysaccharide that interacts with nasal mucus and affects permeability of the epithelium by transiently opening the tight junctions. Hence, it prolongs mucoadhesion and enhances transport across the membrane [28]. Several authors have related higher drug permeability values with chitosan [76,113,167]. Bile salts like sodium taurocholate and phospholipids like dipalmitoylphospatidylcholine have also shown to increase the permeation rates of spray dried nasal powders [94,113]. The phospholipid dodecylphosphocholine is present in a nasal powder commercial product (Baqsimi^{TM}), which highlights the value of these excipients. Nonetheless, the use of permeation enhancers should be considered with caution given that some of these agents such as surfactants, bile salts and fatty acids may damage the nasal mucosa due to alteration of cell membrane structure [13,24,99]. Thus, histological and toxicological evaluation are mandatory.

4.2. Quantitative composition

In addition to the qualitative composition, the quantitative composition is an important factor to consider. It represents the drug and excipient (s) ratio on the formulation and drug load, and it influences the particle properties, mucoadhesion, dissolution and permeation.

The maximum quantity of powder recommended to be nasally administered (10–25 mg per nostril) may limit the drug load [185]. For example, if the active dose of an API is 20 mg per nostril, very low quantities of excipient can be added. In opposition, if the active dose is 1 mg, excipients are necessary to ease handling and filling. If an amorphous dispersion is required, the drug load may also be conditioned, since a minimum quantity of polymer may be needed to stabilize the amorphous form of the product during its shelf life [197]. Therefore, in

order to select the drug load, it is important to bear in mind the dose that must be administered as well as the solid state properties.

Considering manufacturing by spray drying, the quantities of drug and excipient may alter the characteristics of the feed solution, namely its viscosity, which can determine solid mobility and consequently lead to different particle size and morphology [8,18,46,56,95,140,145,195]. As aforementioned, higher feed solution viscosity typically leads to increased particle size. If there is an excipient that promotes increased feed solution viscosity, and it is used in higher quantity, increased particle size is expected to be obtained. Additionally, some excipients may induce a specific particle morphology. However, their quantity may be determinant to attain the target morphological characteristics. For example, Jüptner and collaborators [108] demonstrated that leucine concentration used in spray dried nasal powder formulations is critical on the particle morphology. Accordingly, while lower concentrations of 10% leucine did not alter the spherical morphology considerably, higher concentrations of 18% leucine led to wrinkled morphology [108].

When using a mucoadhesive polymer, it is expected that lower drug to polymer ratio leads to higher mucoadhesion and slower drug diffusion from the polymer matrix. Higher amounts of polymer result in higher gel polymer network viscosity and swelling, hampering drug diffusion through the viscous gel layer and increasing the diffusion path length through which the API has to transverse [140]. Many examples in the literature demonstrate this relation, with different polymers including chitosan, gellan gum and HPMC and different drug loads [1], [18,57,56,75,86,95,118], Hitendra S. [130,129]; Hitendra Shaligram [130,129,140,147,178,179].

Higher quantities of permeation enhancers can also lead to increased permeability, as seen by Huh and collaborators where the permeation rate and permeated amount after 4 h increased 5.7 and 4.8 fold respectively, when the bile salt permeation enhancer was duplicated [94].

4.3. Pre-clinical in vivo evidence

In the literature, it is common to evaluate the pharmacokinetics of nasal powder formulations in rodents, sheep and rabbits. For nasal administration, devices for human use can be adapted for the animal model or specific devices for animal administration can be used [56,160,165,208].

Huh and collaborators compared the bioavailability of fexofenadine hydrochloride solution and powder formulations with a mucoadhesive agent after nasal administration to rabbits. Absolute bioavailability increased from 3.1% with the solution to 28.5% with the microspheres formulation and attained the value of 47.6% when a permeation enhancer was also present in the powder formulation. Both mucoadhesion and permeation enhancing effects contributed to increase drug bioavailability [94].

Rassu and co-workers formulated a model polar drug of low molecular weight into chitosan and/or methyl-β-cyclodextrin spray dried microparticles and compared their blood and cerebrospinal fluid (CSF) drug concentrations over time after nasal administration to rats. The drug was not significantly detected in the blood or CSF after administration of aqueous suspension. However, all powder formulations originated detectable blood and CSF drug concentrations, with higher values for formulations with cyclodextrins. The authors attributed the higher bioavailability and higher permeation in the CSF to the morphology and structural composition of microparticles imposed by cyclodextrin. Nonetheless, the chitosan formulation had a higher area under the curve ratio between CSF and bloodstream, proving to be more selective for nose-to-brain delivery. The authors concluded that while chitosan should be more selective in increasing paracellular transport through the olfactory epithelium, methyl-β-cyclodextrin should be more effective in increasing both paracellular and transcellular transports through respiratory and olfactory epithelium [158].

In a study by Elmowafy and collaborators, microparticles of repaglinide and mucoadhesive agents (pectin, gellan gum and dextran) were nasally administrated to diabetic rats, and the blood glucose levels were assessed. All formulations decreased blood glucose levels more significantly than the intranasal solution or intravenous drug. Gellan gum microspheres response was faster and earlier, which was justified by the faster drug release seen *in vitro* as well as by its mucoadhesive properties [56].

The bioavailability of spray dried formulations for nasal delivery is summarized on Table 2. Their values reflect not only the drug related properties, but also particle and formulation characteristics that influence nasal deposition, mucoadhesion, drug release and permeation phenomena [71].

5. Manufacturing and filling processes considerations

The most important factor to consider on nasal powder manufacturing is ensuring particle size suitability, to guarantee deposition on the nasal cavity. Formulation strategies include: engineered microparticles of the appropriate size [API-only or API and excipient (s)], powder blends and chimeral agglomerates (Table 3) [16,168,185,188].

Engineered microparticles (Fig. 3a and 3b) without any additional manufacturing steps are the most common nasal powder formulations studied in the literature [185]. Many particle engineering technologies allow the generation of powders within the target size (10–45 μm) [185]. They can be divided in top-down and bottom-up approaches. Bottom-up approaches include spray drying, freeze-drying, spray freeze drying and supercritical fluid-assisted spray drying, and may allow higher control of the particle properties, since these are formed from the molecular level. Top-down approaches involve the application of mechanical energy to physically break particles to finer ones and include milling. Hammer milling could be suitable for powder production within the nasal size range, since typically it can generate particles ranging from 15 to 50 μm [10]. However, this process has not been exploited in the literature for nasal powder production. Milling is only applicable when raw materials have particle size higher than target.

Chimeral agglomerates (Fig. 3c and 3d) are obtained by tumbling or vibrating microparticles (1 to 50 μm, preferably having a median diameter-volume between 4 and 6 μm [42]that can be prepared through another process and sieving the intended size range fraction (106 to 1000 μm [42]. Although small particles lead to rapid dissolution, a powder with a significant fraction of particles with diameter below 10 μm have the risk of lung inhalation and, often, poor flowability [25,185]. In order to overcome these challenges while maintaining rapid dissolution, an extra processing step can be added to small particles to form chimeral agglomerates. Weak attraction forces hold the primary particles together to form larger agglomerates, which break into fragments with a larger size than the primary microparticles during administration, outside the respirable size range. Such agglomerates have been defined as “chimeral” as their size is transient, being reduced during insufflation. This process leads to improved flowability and packing comparing with primary particles [42,78,162]. The formation and yield of the process depends on the composition of the microparticles [16,42,162].

By adding a larger carrier, powder blends (Fig. 3e and 3f) can be useful to improve bulk powder properties or allow too small API particles to deposit on the nasal cavity [168]. It can also be the option for sensitive drugs that cannot be subjected to the stress caused by the manufacturing strategies used to obtain engineered particles, for example thermolabile drugs that cannot undergo spray-drying. This carrier can be composed of engineered microparticles with the adequate particle size for nasal deposition which can be manufactured, for example, by spray-drying. Blends of API and a filler may be also useful when the drug dose is low. Carrier-based formulations, common in dry powder lung delivery formulations, are prepared by blending of particles (for example API raw material or spray dried particles of API and

Table 2
Bioavailability and area under the curve (AUC) ratio of CSF to blood of spray dried powders for nasal delivery.

Drug	Excipient (s)	Absolute bioavailability (%)	Relative bioavailability to nasal solution* (%)	AUC Ratio CSF/ Blood	Animal model	Reference
Cyanocobalamin	Microcrystalline cellulose	25.1	–	–	Rabbit	[71]
	Dextran	6.9	–	–		
	Crospovidone	14.6	–	–		
N^6-cyclopentyladenosine	Mannitol-lecithin	1.9	–	4.3	Male Wistar Rat	[47]
	Chitosan hydrochloride	1.4	–	57.5		
Metoprolol tartrate	Amioca and Carbopol	10.8	–	–	New Zealand white rabbits	[44]
Fexofenadine hydrochloride	Hyaluronic acid and PEG 6000	28.5	913.8	–	New Zealand white Rabbits	[94]
	Hyaluronic acid, PEG 6000 and sodium taurocholate	47.6	1526.4	–		
Rokitamycin	Chitosan glutamate	32.5	–	1.2	Male Wistar rats	[74]
Verapamil hydrochloride	Chitosan	58.57	122.43	–	Male New Zealand white rabbits	[1]
Deferoxamine mesylate	Chitosan chloride	6.15	–	–	Male Wistar rats	[160]
	Methyl-β-cyclodextrin	10.26	–	–		
Salmon calcitonin	Inulin, Chitosan	–	275.12	–	Male	[39]
	Inulin, Sodium taurocholate	–	190.47	–	Sprague-Dawley rats	
	Inulin, Beta-cyclodextrin	–	235.39	–		
N^6-cyclopentyladenosine	Chitosan	1.85	–	47	Male Wistar rats	[158]
	Chitosan and methyl-β-cyclodextrin	12.8	–	8.2		
	Methyl-β-cyclodextrin	36.0	–	3.9		

* Relative bioavailability in percentage was calculated as the AUC for nasal powder divided by AUC for nasal solution, multiplied by 100, for the same dose administered, using the data from the cited articles.

excipient) [144,188]. Contrary to lung delivery, the carrier needs to deposit together with the API in the delivery site, and a low separation during dispersion is required to avoid lung deposition. This strategy seems promissory for vaccine delivery, using small size API particles (<5 μm) blended with larger carriers, since particles smaller than 5 μm are suitable for immune cells uptake, and the carrier would allow nasal deposition and improved flow properties [188]. However, a strong limitation is the low API to excipient ratio that is required [107].

5.1. Evidence of the advantages of spray dried microparticles

The literature reports advantages of powder over liquid formulations, and spray dried powders over powders manufactured differently.

As other solid formulations, long-term stability, especially in terms of microbiological requirements, is more easily achieved in powders, without the need to add preservatives which can cause adverse effects [23,185]. For example, spray dried microspheres composed only of a small molecule API and a mucoadhesive polymer have shown to be stable under accelerated conditions, namely tramadol [18], valsartan [147] and diltiazem [118] microspheres for nasal delivery. This is particularly relevant for biopharmaceutics, as preservatives are avoided as well as a cold chain for storage/transport or accidental slow freezing that compromises their potency or/and efficacy [182,202]. In a study comparing spray dried and liquid formulation of ghrelin, only 2.67 ± 0.57% of the peptide in powder formulation was degraded comparing with 95.64 ± 0.85% in the liquid formulation at 25 °C for 4 weeks [166]. Spray drying of ghrelin nanocomplexes into microparticles can also overcome the challenging stability and interparticle adhesion and aggregation related with these colloidal systems, improving their handling and portability [57].

Improved residence time on the nasal cavity due to higher mucoadhesion is also a reported advantage of solid formulations, namely spray dried powders [33,166], which can be reflected into higher extent of absorption [1]. Interestingly, higher mucoadhesion conferred by powders is relevant for nose-to-brain delivery since the contact time with the olfactory epithelium is increased. Zidovudine prodrug powder formulation is an example where detectable amounts were found in the cerebrospinal fluid in opposition to the correspondent aqueous suspension [46].

Powders also allow the administration of higher drug doses, especially for poorly soluble drugs in aqueous medium. Drugs can reach higher concentrations and potentially saturate in the small nasal fluid volume, enhancing their permeation [16,184]. They can also intake water from the nasal mucosa, which dehydrates the epithelium and opens tight junctions [33].

It is noteworthy that spray dried powders have advantages comparing with other powder formulations. Studies have demonstrated that spray dried microparticles have more potential for nasal administration than the correspondent physical mixture [46,152]. In fact, this process allows a precise control over particle size and morphology, and often leads to drug amorphization, resulting in more efficient dissolution and increased bioavailability. Dalpiaz and co-workers attributed higher

Table 3
Formulation strategies and corresponding manufacturing processes for nasal powders.

Formulation	Manufacturing process	Strengths	Weaknesses	References
Engineered microparticles	Spray drying	• Tight control of particle properties • Scalability • Continuous process	• Possible degradation of thermolabile drugs	[171,198,200]
	Freeze drying	• Suitable for thermolabile products • Controlled residual water content	• Need of a secondary dispersive force • Very time-consuming • Poor control over the particle properties • Not easily scalable	[198]
	Spray freeze drying	• Suitable for thermolabile products • Produces porous particles with enhanced flowability • Control of particle size	• Stress induced through the freezing and dehydration • Time consuming • Expensive	[171,198,200]
	Supercritical fluid-assisted spray drying	• The use of the flammable and toxic solvents is avoided • Control of particle size • Mild process conditions • Scalability	• Prolonged processing time due to slow feeding rate • Complexity of the set-up • High costs	[171,180,198,200]
	Hammer milling	• Reasonable energy requirements	• Not suitable for products with low melting temperature • Dependent of raw material particle size • May not suitable for biologics	[10]
Powder blends	Blending	• Easy and cheap process • Potential for vaccine delivery (carrier-based formulations)	• Low API to excipient ratio required (carrier-based formulations) • Lung deposition possible if separation of carrier and API during dispersion (carrier-based formulations) • Raw materials may not have the desired particle properties	[188]
Chimeral agglomerates	Tumbling or vibrating microparticles	• Rapid dissolution • Better flowability than primary microparticles	• Agglomeration support excipients may be necessary • Lung deposition possible if there is high separation during dispersion	[16,42]

dissolution rates of spray dried particles to their high porosity and amorphization of the drug in the polymer matrix, compared with physical mixture [46]. These spray dried microparticles increased 1.8, 3.2 and 18.6 times the uptake of the drug to the cerebrospinal fluid of rats compared with its physical mixture, the dispersion of solid lipid microparticles (SLM) in the presence of chitosan and SLM in solid form, respectively [46].

Spray drying has shown higher drug entrapment efficiency compared with other production methods as coacervation precipitation method [1]. It also leads to regular spherical particle morphology contrary to precipitation or freeze drying method [1],[167], which can be decisive in particle deposition on the nasal mucosa [108].

Due to their physical characteristics, spray dried microparticles can also be more suitable for nose-to-brain delivery than other formulations such as chimeral agglomerates. In a recent study [183], flurbiprofen spray-dried microparticles enabled higher drug direct transport to the brain than flurbiprofen-mannitol/lecithin agglomerates, probably due to their physical characteristics, as particle size, that allowed a suitable emitted plume for higher olfactory deposition.

5.2. Particle engineering by spray drying

Spray drying is a well-established technology for the preparation of dry powder drug delivery systems. It is a scalable method explored extensively in the pharmaceutical industry given its flexibility, reproducibility and control of particle properties, as size and morphology [118,144]. With spray drying, it is possible to optimize formulation and process variables in order to obtain the required outcome, by designing and controlling the composition of liquid feed and drying conditions [164,195–196].

Spray drying involves 4 steps: liquid feed preparation, liquid atomization, drying and powder collection. The liquid feed preparation depends on the liquid system required (e.g. solution, suspension, emulsion). The liquid feed is pumped into a drying chamber through a nozzle that atomizes the liquid into small droplets, which are rapidly dried by a hot drying gas. The particles are then separated from the gas by a cyclone or a bag filter and collected. The spray drying apparatus may differ in the nozzle used (two-fluid, ultrasonic, pressure, etc.), drying chamber size and geometry, or gas type and flow direction. Process parameters may also vary, as inlet and outlet temperature and drying gas velocity. These features affect the final particle properties, as size and morphology, due to different mechanisms of droplet formation and drying kinetics. The powder collection system and design may also impact on size distribution of the collected powder [49,195,197].

Spray drying can be performed either in closed or open loop, depending on the drying gas recirculation. Fig. 4 shows a schematic representation of spray drying in closed-loop mode.

5.2.1. Liquid feed preparation

Liquid feed can be a solution, a suspension or a colloidal system. Solution feed is the simplest one, and its preparation comprises the mixing of the components in the solvent system. It precludes lack of homogenization that may happen with two-phase systems, and allows for example the generation of single-phase systems, as amorphous solid dispersions when a polymer is present [194,197]. It is important to consider that some of the API and excipients raw material properties are mitigated by the dissolution process, such as raw material particle size and solid state. In addition to solutions, spray drying has been used to dry emulsions [84,132], liposomes [33,126], solid lipid nanoparticles (SLN) [70], nanostructured lipid carriers (NLC) [207], suspensions [71] and polymeric nanoparticles [81](Fig. 5).

These suspension or colloidal feeds can be necessary when the API or excipient (s) have solubility limitations, or when special properties of these systems are important to transfer to the resulting microparticles [194]. However, the right choice of solvent system may mitigate difficulties in solubilizing API and excipient (s) [209]. Lipid based systems can be used to overcome solubility limitations of an API on the nasal mucosa. It is important to assess the drug properties (as melting point and lipophilicity) before choosing this strategy, since that depending on the API, amorphous solid dispersions may be a better option for solubility enhancement, and their preparation (spray drying of a solution containing one or more polymers) is less complex and time-consuming than lipid based systems (as liposomes, SLN or NLC) [197].

Transferring properties to the final dry particles can be greatly

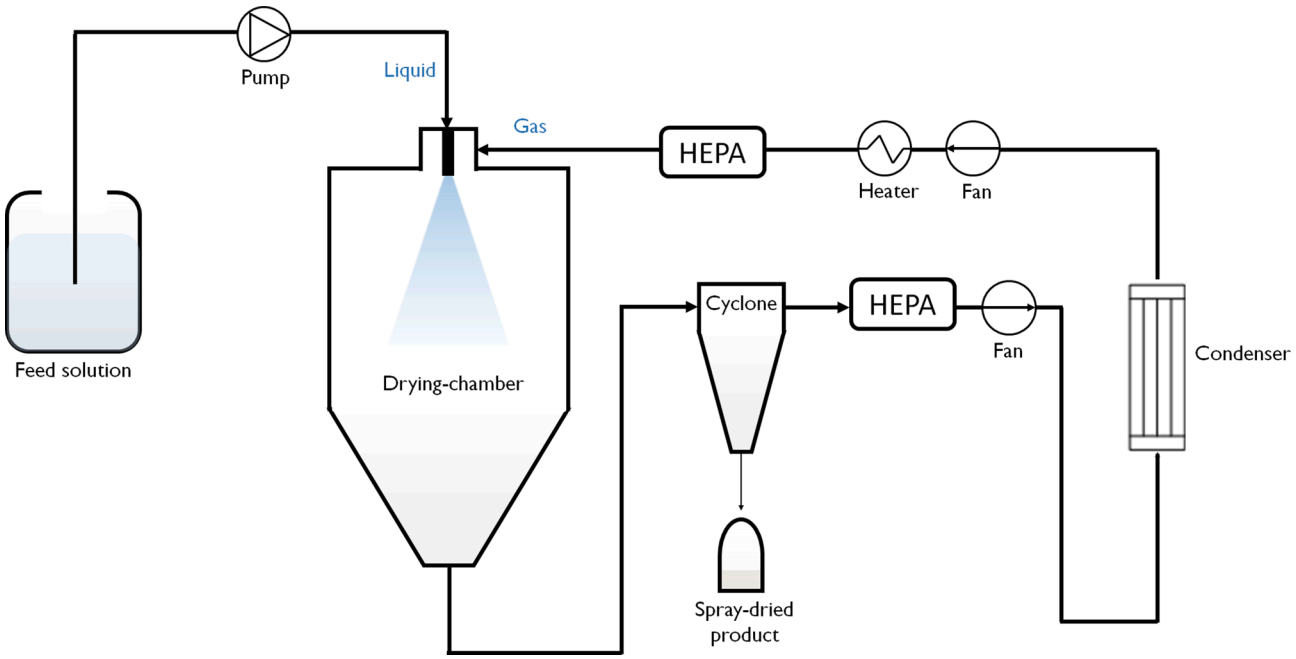

Fig. 4. Schematic representation of spray drying process in closed-loop mode.

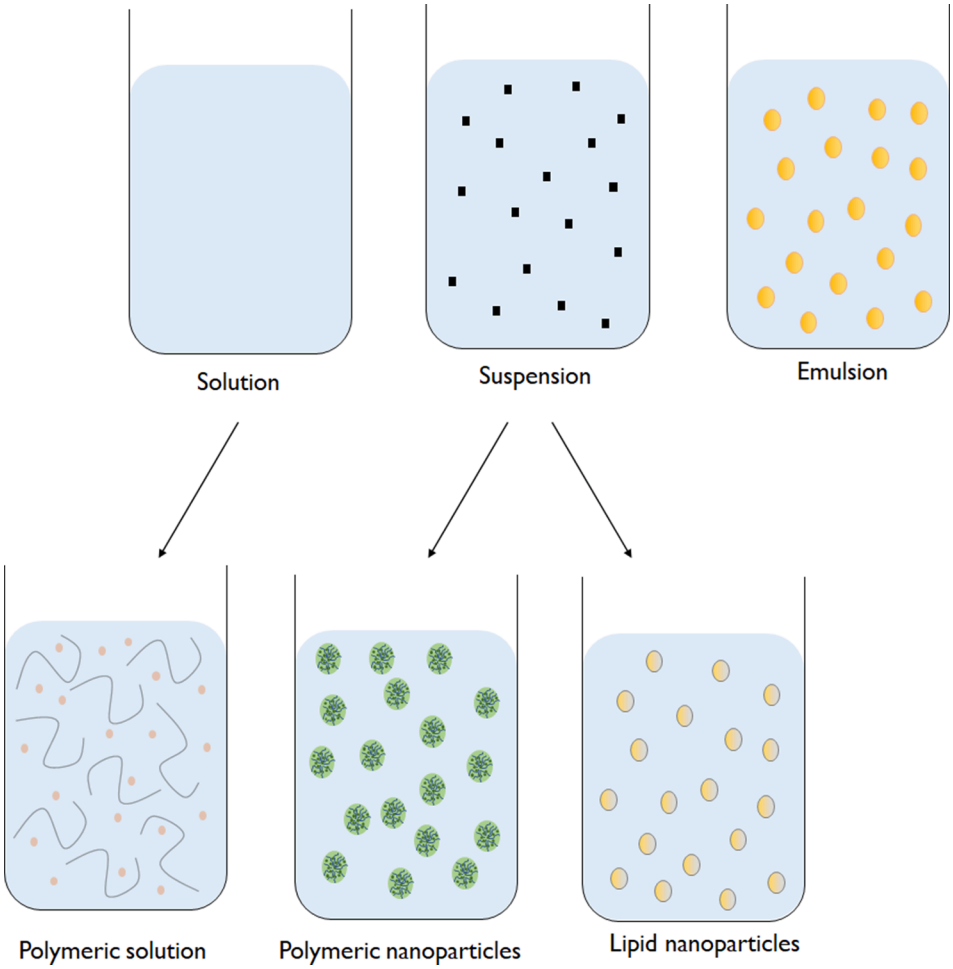

Fig. 5. Examples of possible liquid feed systems.

valuable. One example is using nanosystems that may confer surface functionalization and increased permeation. These properties can result in enhanced brain targeting and/or bioavailability [3,151]. Some of the disadvantages of the resulting nanoparticles (agglomeration, poor flowability, lung deposition) can be mitigated by including them in a microparticle in the nasal size range [151,194]. Despite of these features, suspensions or colloidal systems bring an extra complexity and require an extra production step, which can be undesirable in an industrial environment.

Chen et al. explored spray dried liposomes of a protein coated with mucoadhesive polymers for nasal delivery, taking advantage of the protective effect and permeation enhancement of liposomes and the prolonged contact with the nasal mucosa and better storage stability by drying the liquid system and adding a mucoadhesive agent [33]. Elmowafy et al. studied spray dried polymeric nanoparticles of repaglinide for nasal delivery, joining the advantages of the nanocomplexes – prolonged contact with the mucosa, mucosal uptake of nanosized particles, avoidance of reticuloendothelial system clearance, permeability enhancement – with higher stability and ease of handling promoted by spray drying. These nanocomplexes become agglomerated in dry microparticles, suitable for nasal delivery [57].

It is important to note that the type of liquid feed system has impact on the particle size, as reported by Martinac et al. (solution vs. emulsion and suspension) [132] and Hafner et al. (solution vs. double emulsion) [84].

The solids concentration may also affect the particle properties. Particle size increases substantially with higher solids concentration in dilute solutions of 1 to 5% w/w, given the higher solution viscosity and less liquid to evaporate [74,84,115,159]. Gavini and co-workers used different feed solution concentrations (0.25% or 1% w/v) to prepare microspheres for nasal delivery and reported an increase of particle size as the feed solution concentration increased [74]. The same happened in another study by Gavini and collaborators when the concentration was increased from 0.3% to 1% w/v (particle size increased from 3 to 5 μm to 11 μm) [76]. Katsarov and colleagues also verified increase of particle size when solids concentration was increased from 1% to 2% w/v, which could minimize the fine particle fraction (<5 μm) that could cause undesired lung deposition [115]. The degree of API entrapment is not affected by higher concentrations of feed solution [74,159]. However, if the viscosity is too high there is a risk of filament formation, leading to inadequate atomization [197]. For example, high viscosity of the feed and the presence of gelling masses led to low yields on another work by Gavini and collaborators [76].

During droplet drying in spray-drying process, particles are formed when the solids concentration reaches a specific critical level at the droplet surface [195]. Therefore, increased solids concentrations in concentrated solutions (more than 5% w/w) have little impact on particle size. In an optimized spray dying process with high throughput (in most industrial applications concentrations are higher than 10% w/w [195], this parameter is typically not a critical factor to consider. The solids concentrations should only be carefully evaluated when working with dilute solutions, which is more common during research and development.

5.2.2. Solvent

Considering a solution as the liquid feed, the solvent should be selected according to some criteria including: solubility of drug and excipients in the solvent (preferably greater than 50 mg/ml), low toxicity and environmental hazards, solution viscosity and high volatility for fast evaporation [209]. For example, García-Arieta and collaborators decided not to use water as the solvent due to lack of solubility of the excipients, which could form two populations of particles – API-only and API-excipient particles – thus implying different particle sizes and shapes with impact on deposition pattern on the nasal cavity [71].

The solvent is removed during the spray drying process and, hence, only residual amounts are present on the final product. Solvent properties, such as boiling point, vapor pressure and enthalpy of vaporization, determine the process parameters required to efficiently remove the solvent during spray drying [197]. Different evaporation rates and surface tension can lead to different final properties of the particle, like size, morphology and radial distribution of the components [197,209].

Gungor and co-workers prepared microspheres through spray drying of an emulsion with two different organic solvent systems: dichloromethane (DCM) or a mixture of DCM with ethyl acetate. Drug loading efficiency increased twice when only DCM was used. This can be due to its low boiling temperature that allowed accelerated solvent removal resulting in increased drug loading efficiency. The mixture of DCM with ethyl acetate led to smaller particles, probably because of the lower density of ethyl acetate [83].

5.2.3. Spray drying apparatus

Differences in spray drying apparatus have impact on the yields, particle size and residual moisture. For research purposes, laboratory scale spray driers of small dimensions are frequently used. However, it can be challenging to obtain particles suitable for nasal delivery in laboratory scale equipment. On one hand the small size of the drying chamber does not allow drying of large droplets (impaction of droplets on the glass walls before drying) [166]. On the other hand, coarse particles can concentrate on the bottom of the drying chamber [71].

The nozzle used has also great impact over the particle properties. At laboratory scale, two-fluid and ultrasonic nozzles are frequently used, while pressure nozzles are mostly used in large-scale spray dryers [4]. Two-fluid nozzles are mainly used to produce small particles within the range of 1–30 μm, while ultrasonic and pressure nozzles generate larger droplets. For two-fluid nozzles, particle size is mostly controlled by the atomization gas flow rate, while for ultrasonic nozzles particle size depends on the frequency of vibration – the higher the frequency, the smaller the particle size. Silva and co-workers produced particles in the nasal size range (10–45 μm) with two-fluid nozzle and 45 kHz ultrasonic nozzle, but not with 25 kHz ultrasonic nozzle (particles larger than 45 μm). Even though ultrasonic nozzles presented lower yields, the particle size distribution span was considerably lower compared with two-fluid nozzle, which can be critical to minimize the fraction of powder with potential to reach the deep lungs [172,173]. Jüptner and Scherließ were also able to generate particles with size suitable for nasal delivery by using a 60 kHz ultrasonic nozzle [109]. Contrary to the previously mentioned study by Silva and co-workers, in this study, the two-fluid nozzle allowed generation of smaller particles, useful for pulmonary delivery (<5 μm) [109], as different materials and process parameters were used, with a large contribution of the higher atomizing flow rate.

Large scale spray dryers are much more efficient in producing large particles due to higher residence times and increased drying capacity in the drying chamber [4].

5.2.4. Spray drying process parameters

Parameters such as atomization gas flow rate, feed rate and drying temperature are determinant on the final powder properties.

Particle size is one of the powder properties more influenced by spray drying process parameters. Low ratio between atomization gas flow rate and feed rate lead to higher particle sizes [115,118,172,184,206]. However, when it is too low, it leads to lower yields, due to inefficient drying and consequent loss of wet material on the equipment walls of small spray dryers [115,145,147,166]. Therefore, it may be challenging to obtain high yields aiming to produce particles with size adequate for nasal deposition, at the range of 10–45 μm, with laboratory scale equipment. An optimum balance between feed flow rate and atomization gas flow rate needs to be determined for each process, so that the target particle size is obtained while maintaining reasonable process yield. This challenge tends to be resolved at pilot and commercial scales. The drying and atomization gas usually used in the literature is compressed air, but in some cases nitrogen and other inert gases are used

when the product is oxygen-sensitive or when flammable solvents are present [26].

Other property greatly affected by process parameters is particle morphology. Particles tend to be spherical with short drying times and high evaporation rates and shriveled at slower drying conditions [195]. Manipulating drying temperature and droplet size can result in particles with very different morphologies [184,195].

Spray drying process parameters also influence residual amount of solvent. Reduced residual quantities of solvents are obtained with more efficient drying process, which is achieved with lower feed rates, higher atomization gas flow rate and higher temperatures [166,179].

5.2.5. Secondary drying

The solvent used in the liquid feed remains in the resulting powder in small quantities, typically less than 2–10% by weight [142]. For organic solvents, the ICH stipulates maximum acceptable quantities [97], due to toxicological concerns. If the solvent used is water, residual moisture will remain present in spray dried powders and its quantity is crucial for the powder flowability, aerodynamic behavior and stability. High water content (>2–5%) may lead to formation of agglomerates due to particle cohesion and potential for microorganisms growth, and low content (<1%) may increase electrostatic charges, and both phenomena negatively affect flowability [166]. Low moisture content also is also associated with higher long-term stability [166].

Water activity, a measure of available water that can support the growth of microorganisms, should also be low to prevent microbial proliferation. Dry solid dosage forms, as nasal powders, are expected to have low water activities. Therefore, spore germination or microbial growth is not expected. For these formulations, reduced microbial limit testing can be an option for product release and stability evaluation [192].

Secondary drying is used to either adjust the moisture or comply with the limits for residual organic solvents [97,174,194]. The most commonly used secondary dryers are tray, agitated vacuum, fluid bed and biconical rotating vacuum dryers [142].

5.3. Nasal delivery devices and powder filling

Delivery devices can be active or passive, where the difference is based on the mechanism of aerosolization and the way of use. In the first case, the device has a mechanism to aerosolize the powder, as mechanically actuated insufflators. One example is the Impel NeuroPharma Precision Olfactory Delivery (POD®) device, which was developed to delivery liquids or powders using a pressurized gas to emit the dose, after mechanical actuation. This device was developed to target the upper nasal space [204]. Passive devices require the patient inhalation force to allow powder delivery [25]. A device can also be either single or multi-dose, and the powder may be contained directly in the device, in a blister or in a capsule. For example in the Aptar single shot nasal unidose the formulation is filled directly into the device, while for the Optinose Bi-Directional Breath Powered device and Miat nasal insufflator a capsule is previously filled with the powder [52,144,191]. Examples of multi-dose devices are the Astrazeneca powder inhaler device (Rhinocort turbuhaler product) for budesonide nasal delivery [52], a passive device, and IDC Multi-Dose Dry Powder Drug Delivery device developed to deliver powder accurately and in a user-friendly way [101]. Nasal devices characteristics and performance have been reviewed by Djupesland [52].

Precision filling equipment is necessary to automatically fill the capsules or device compartments with drug product, and the process affects the precision of filled weight and aerodynamic performance of the nasal powder [141]. The filling process must guarantee dose uniformity, which can be challenging given the low amounts of powder adequate for nasal administration [61]. Several low-dose systems are available for capsule filling, that work by volumetric (as drum and dosator filler systems) or gravimetric methods [61]. Flowability is critical on the filling process. The flow function coefficient and specific energy measured with a powder rheometer have shown to discriminate flow behavior and can predict the filling success for a drum system [109]. The filling process may have influence the aerodynamic performance and emitted dose since the powder plug generated in the filling process could hinder powder dispersion from the device [109]. Therefore, changes in the filling process should be accompanied by aerodynamic performance studies.

6. Opportunities and challenges

Spray dried powders for nasal delivery represent an opportunity for drugs that require fast onset of action, systemic or nose-to-brain delivery, or high mucoadhesion for a prolonged absorption. Amorphous dispersions may represent an extra opportunity for poorly soluble drugs, even though amorphization has not been completely exploited for nasal delivery. From a manufacturing point of view, spray drying allows a fast, well controlled and scalable production, which are appreciated in the industry.

Despite the current knowledge on nasal powder formulation, manufacturing and characterization, there are still many questions to answer. A challenge that can be found is the lack of translation between different *in vitro* methods and lack of correlations between *in vitro* and *in vivo* results [71,78]. This is particularly critical during formulation screening, where biorelevant *in vitro* methodologies would be helpful to choose the most promising drug product. In vitro-*in vivo* correlations (IVIVC) and physiologically based pharmacokinetic modelling for nasal powder delivery would be valuable for predicting the pharmacokinetics and nose-to-brain delivery of new nasal powder products and reduce pre-clinical and clinical trials. However, this can be challenging due to nasal delivery complexity and lack of standardized *in vitro* release testing methodologies [106]. For IVIVC, the challenge is the development of a reliable predictive drug release method that simulates the *in vivo* environment [106]. Standardized characterization methods, not only for drug release but also aerodynamic performance, mucoadhesion and permeation, would also allow to integrate and compare results from different authors, which currently is difficult due to the very different methodologies used. Guidelines from European and American regulators lack recommendations on advanced performance characterization, namely regarding drug release, mucoadhesion and permeation. FDA guidance documents (Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action [65] and Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products–Chemistry, Manufacturing, and Controls Documentation: Guidance for Industry [67]) do not address nasal powders, focusing only on liquid formulations. The Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products [58] from the European Medicines Agency recommends tests to characterize nasal powders, as particle size distribution and delivered dose uniformity. Additionally, some performance quality tests for nasal powders can be found on the United States Pharmacopeia [193], but, once again, little tests are recommended, being only based on delivered dose uniformity and particle size measurements. Even though these tests are essential to assure nasal powder quality, they are not useful to assess the behavior of formulations in the nasal cavity, where drug release, mucoadhesion and permeation mechanisms play an *major* role. Regulatory recommendations on nasal powder advanced characterization would be an important step towards standardization of methods, while assisting the industry in developing new nasal products.

Other challenge is the choice of the animal model to use in preclinical *in vivo* trials. Rodents are frequently used in nasal delivery research, due to lower cost and easier access than other species [43]. However, there are significant anatomical differences between these laboratory animals and humans. For instance, rodents have higher levels of olfactory function with a large olfactory mucosa area of approximately 45–50% of the nasal surface. On the contrary, humans use the

nose predominantly for breathing and only approximately 3% of the nasal mucosa accounts for olfactory mucosa [30]. This difference can be critical on nose-to-brain delivery studies, where rodents may overestimate the direct brain delivery that would happen in humans. While for toxicity studies rats and mice could be suitable models, for pharmacokinetic and pharmacodynamics studies larger animals such as rabbits and dogs are preferred [43]. Monkeys are more similar to humans in anatomy and percentage of olfactory mucosa, which makes them a better animal model choice for nose-to-brain studies. However, the use of non-human primates in scientific research is limited due to ethical and practical challenges [59]. Different animal models also represent distinct nasal architecture and morphology with different airflow characteristics and breathing patterns, which are determinant on particle deposition [30,99]. Therefore, nasal deposition profile and pulmonary fraction can be different between species, which influences the *in vivo* performance.

A different challenge concerns sensory effects of nasal powder formulations, which are still poorly understood. Liquid formulations may drip down the throat and cause bad taste whereas powders are more likely to cause greater sensory irritation, as well as itching, sneezing or pain, after powder contact with the highly sensitive nasal mucosa [68,187]. These negative sensory effects can lead to patient compliance issues [168]. However, masking unpleasant taste, odor and sensation has not been exploited in nasal delivery research yet [68]. Additionally, sensory effects are difficult to assess by *in vitro* methodologies and *in vivo* pre-clinical studies [187]. Lenoir et al. [124]applied the Slug Mucosal Irritation assay to evaluate and predict nasal discomfort of nasal liquid formulations, and demonstrated a correlation between higher mucus production in slugs and increased incidence of stinging, itching, and burning sensations in humans. This assay was further applied to powder formulations [187], where lower particle size and excipient charge were associated with nasal discomfort.

Regarding clinical efficacy, patients may present certain nasal conditions that limit nasal drug absorption. Nasal polyps, septal deviation and turbinates engorgement are examples where the surface area to volume ratio and airflow are disturbed, affecting particle deposition [121]. Protein expression may also be affected by certain pathological conditions. For example, P-gp expression is relatively upregulated in patients with chronic rhinosinusitis [21], which may challenge local treatment of this condition and nasal absorption of drugs for systemic action [22].

Finally, regarding devices, there is still only a limited selection available for nasal powder delivery, and they have not been investigated as thoroughly as devices for liquid forms. This is a major challenge in product development, as the device design and mechanism play an important role on powder deposition profile [128]. The combination of the formulation with the device should be optimized, which can be another challenge given the little information available on this subject.

Having a device from the first phases of formulation development is beneficial, as it allows the adjustment of powder properties that are more adequate for that specific device. However, this may be challenging as there is a shortage of devices available. More device development and availability would be beneficial for both academical research and pharmaceutical industry, increasing knowledge on the interplay of formulation and device and expediting product development.

7. Conclusions

The nasal route is of great interest for the administration of drugs that require fast systemic absorption or direct brain delivery. It is also an alternative for other delivery routes when these are associated with limitations, such as pre-systemic hepatic metabolism in oral route or impossibility of self-administration in intravenous route. Powder dosage forms present significant advantages relative to liquid formulations, namely better stability, increased mucoadhesion and the possibility of administration of higher drug doses. Spray drying allows for control of particle properties critical for powder performance, and it is a scalable and flexible technology suitable for nasal powder manufacturing.

In the early development of a new nasal powder product, scientists should determine the product characteristics that are necessary to meet the therapeutic need as well as the formulation and process parameters that affect those characteristics. For formulation development, the API properties, the target delivery and dose requirements are important factors to consider in an early stage. Several process and formulation variables have high impact on the final powder properties, which affects drug absorption. To understand why, it is important to know the physical, biological and pharmacological phenomena that happen on the nasal mucosa, namely particle deposition, mucoadhesion, drug release and permeation, and their interaction.

Liquid formulations are still the primary choice in nasal product development by the industry, with a much larger number of products approved. Even though the production of liquid dosage forms may be easier and cheaper, and more accepted by patients, an investment in research should open more possibilities with nasal powder products. There are still many challenges in this area, but further research on nasal powder delivery is expected to bring new advantageous alternatives to current drug products. It could also enable new drug formulations approval that may not be successful through other administration routes. Nasal powders for systemic and nose-to-brain delivery are especially promising, both for biologic and chemical APIs, and their development could bring new treatments and solutions to different patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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