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1. Introduction

Intranasal drug administration has a long tradition and was and is still used for medical as well as recreational purposes. The most common use is for treatment of local symptoms e.g. nasal congestion in the course of a common rhinitis or inflammation linked to allergic rhinitis. The medications intended for local activity are well established and can be found across the globe in every pharmacy and drug store. Examples for topical treatment of rhinitis are decongestants (oxymetazoline, xylometazoline, naphazoline), anti-histamines (azelastine, levocabastine, olopatadine) and glucocorticoids (e.g. mometasone, budesonide, fluticasone). For this particular indication, drugs should act fast and only locally while systemic absorption should be as low as possible; this to avoid systemic side effects which are linked with typical oral formulations of comparable drug substances.

As described earlier [1] intranasal administration has much more potential. The nasal mucosa can be used for non-invasive systemic administration of drugs. The surface of the nasal mucosa in humans is around 150 cm², a tissue which is well supplied by blood vessels. This ensures a rapid absorption of most drugs, can generate high systemic blood levels and avoids the first pass metabolism which needs to be taken into account following oral administration. This bypassing of the gastrointestinal system even enables the delivery of peptide hormones [1]. Calcitonin and desmopressin are on the market for years now; insulin and glucagon were under clinical development for this administration route [2].

The rapid absorption of drugs via the nasal mucosa is also utilized for pain medications (e.g. fentanyl nasal sprays), rescue medications like naloxone for opioid overdosing or midazolam for seizures in children. An important aspect for such medications is that intranasal adminis-
tration is considered a non-invasive administration route and easy to do for self-administration or for care-givers. It has a low potential for injuries or disease transmission (hepatitis B, HIV). This is of special importance if fast relief from severe symptoms is required and patient’s ability to deal with injections is impaired. Intranasal triptanes for migraine treatment, fentanyl to stop cancer breakthrough pain and ondansetron to relieve nausea are examples for this trend. For these indications, single dose systems or multi-dose pumps with counting or lock-out mechanisms are available to reduce the risk of unintended overdosing or misuse [1].

Vaccines may also benefit from the intranasal route. Existing vaccines commonly utilize the intramuscular and oral administration route. While the respiratory and gastrointestinal tract is very immune competent and fights with microbes permanently, the muscle is not the first choice. Intramuscular vaccination primarily induces systemic immune response, mainly via formation of vaccine-strain specific circulating antibodies. Injections of vaccines were done since the early days and they are indeed effective. So for most people today vaccination is equal to getting an intramuscular injection which is linked to pain. For the health care professional it is linked to fears of needle stick injuries, risk of disease transmission and dangerous medical waste.

![Figure 1](image1.png)

**Figure 1.** Multi-dose spray pumps can be fitted onto the bottles using a crimp ferrule, screwed-on or simply snapped on (from left to the right). In the forefront different types of nasal spray actuators.

Intranasal vaccination provides a promising non-invasive and gentle alternative. The nasal mucosa is continuously exposed to dust and microbes and therefore extremely immune
Intranasal Drug Administration — An Attractive Delivery Route for Some Drugs

Intranasal administration is an attractive route for a wide range of drugs and indications. With this review we will try to provide some insight into this technology and some considerations for a successful development of such drugs.

2. Evolution of multi-dose spray pumps

Multi-dose spray pumps represent the highest share of delivery systems for intranasal administration. This type of pumps was developed some 50 years ago and ousted step by step droppers and pipettes. These multi-dose spray pumps now dominate the market because they are very cost effective and convenient. The technical solution is quite simple: drug formulation is filled into multi-dose bottles made of glass or different plastic materials, which are closed by attaching the nasal spray pump including a dip tube. Nasal spray pumps are displacement pumps and when actuating the pump by pressing the actuator towards the bottle, a piston moves downward in the metering chamber. A valve mechanism at the bottom of the metering chamber will prevent backflow into the dip tube. So the downward movement of the piston will create pressure within the metering chamber which forces the air (before priming) or the liquid outwards through the actuator and generates the spray. When the actuation pressure is removed, a spring will force the piston and actuator to return to its initial position. This creates an underpressure in the metering chamber which pulls the liquid from the container by lifting up the ball from the ball seat above the dip tube at the bottom of the metering chamber [1]. The metering chamber ensures the right dosing and an open swirling chamber in the tip of the actuator will aerosolize the metered dose. In these pumps systems no measures are taken to prevent microbial contamination when in use, thus the formulation must contain preservatives, in most cases benzalkonium chloride (BAC). To date, most of the medications administered nasally contain a preservative to support long storage times and proper in-use stability. For some years now, most manufacturers of delivery systems offer so called “preservative free systems” (PFS) which are designed in such a way that no preservatives have to be added. At least in Europe, authorities support the use of preservative-free nasalia and request it for children and adolescents [4]. A switch from preserved to unpreserved medications is also often used as a life-cycle management measure and the products are clearly labeled as “without preservatives” or “does not contain preservatives”. Today, preservative free systems are most widely used to moisturize the nasal mucosa using saline solutions or for nasal decongestants.
In December 2012, the US Consumer Product Safety Commission (CPSC) issued a rule to require child resistant (CR) packaging for any over the counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline [5]. This class of drugs is widely used as decongestant for cough & cold medications. The reason for this request was the high number of accidental uptake of such medications by children and resulting serious health risks. The commission estimated that approximately 39 million units of nasal products containing imidazolines are sold annually in the US. A great proportion of the nasal products are presented with metering nasal spray pumps. In a comment [5] the CPSC stated that nasal spray pumps even when crimped onto the bottle are not considered CR and that either the pump action or the over cap must be child resistant. This forced the pharmaceutical industry to introduce child resistant features for nasal decongestants intended for the US market.

3. A short introduction on intranasal administration

Nasal sprays or drops are widely used and therefore easy-to-use and cost-effective solutions are already available for liquid or for dry powder formulated drug products. Also the basic requirements for the development of nasal sprays are well known. An important point when a development for nasal administration is considered: the product should have no unpleasant smell and should not be irritating or influence the sense of smell. There should be also no safety concern, if a dose is unintentionally shot into the eyes.

For most nasal spray pumps the dispensed volume per actuation is set between 50 and 140 µl, and an administered volume of 100 µl per nostril is optimum in adults. Higher volumes are prone to drip out immediately. So the anticipated dose should fit into a volume of roughly 100-200 µl when both nostrils are sprayed. Standard spray pumps will deposit most of the sprayed dose into the anterior region of the nasal cavity (see Fig. 3) [6]. Surface tension of the droplets and mucus layer will cause the immediate spread of the spray. Afterwards mucociliary clearance will distribute the liquid layer within the nasal cavity. Since the nasal mucus...
layer is continuously renewed and discarded into the throat, the nasal residence time of the administered drug depends on how fast it dissolves within the mucus layer and penetrates into the mucosa [7].

If a nasal spray is considered, authorities will require a lot of data to describe the nasal spray pump and its performance as part of the container closure system [8, 9]. Most of these required parameters are used for quality control purposes. For nasal deposition efficiency, the spray plume angle and administration angle are critical factors, while many other spray parameters, including droplet particle size, have relatively minor influences on deposition within the nasal cavity [10].

The nose is a very effective filter and most particles and droplets will be caught within the nasal cavity. Only particles less than 10 µm median aerodynamic diameter, so called fine particles, can reach the lower airways during nasal breathing [11]. Most spray pumps will generate an aerosol with a mean particle size from 40-100 µm during the fully developed phase which is recognized as fine mist. Such an aerosol will deposit well in the nasal cavity.

To date, nearly all drugs for intranasal administration are liquids and just some recreational drugs are used as powders. Of course dry powder preparations can be used without the need for reconstitution to a liquid. The particle size should be in the same range as droplets from a nasal spray and fine particles should be minimized to avoid pulmonary deposition. The size and structure of the particles must be a compromise between safe administration (no fine particles, good deposition) and fast speed of dissolution of the particles within the mucus layer [3]. Powders for nasal administration will most likely need protection from moisture uptake though the moisture sensitivity may be formulation-dependent. Long term use of powder
formulations may result in mucosal irritation and chronic use should be considered with caution, but single administration should be of much lower risk.

4. Which technology is on the market?

For intranasal administration of drugs a lot of delivery systems are available, simple and low cost as well as highly sophisticated. It ranges from droppers, to sprayers to be attached to a syringe, to so called unit- and bi-dose systems as well as multi-dose solutions for liquids. This wide range of available systems opens the door to tailored packaging.

There are some considerations to choose the right solution in a competitive environment. Convenient and safe use and cost of goods need to be balanced. Also the availability of high speed filling and packaging equipment for the selected presentation should be evaluated. There are of course some other considerations for the different types of systems which should be discussed here.

**Droppers** are the simplest and -just looking on packaging costs- the cheapest way to deliver medication into the nose. The blow-fill-seal (BFS) technology is widely used. The BFS droppers made of polyethylene or polypropylene are cheap but require special filling equipment. Also the material for the dropper (e.g. adhesion profile, evaporation rate) as well as processing temperatures during the BFS process may set some limitations. Splitting half doses from one single container may be a challenge and so for each nostril (if the medication requires this) one dropper needs to be considered. To deliver the right dose, some substantial overfilling is required which can be neglected for cheap formulations but may be important for expensive drugs.

Droppers for multi-dose presentations are still on the market but can be considered to be obsolete. A preserved formulation for multi-dose presentations is mandatory but preservatives will not solve all hygienic jaundices. Precise dosing is also close to impossible so that only drugs with a wide safety margin can be used with such systems. Intranasal administration using droppers is not very convenient. To get a good nasal deposition, the recipient should lie down or bend the head backwards to improve deposition.

For some rescue medications like naloxone or midazolam or some intranasal vaccines **spray tips** (see Fig. 4) attached to standard Luer-syringes are used to deliver the drug. The handling is somehow inconvenient, because in most cases the drug must be transferred from a vial into the syringe. Then the spray tip is attached and the system is ready for administration. The generated spray and the quality of the nasal deposition depend much on the characteristics of the spray tip and the smooth displacement movement of the plunger of the syringe. If no mechanical aid is employed (e.g. removable clips to split 2 half doses), it is difficult to separate doses for each nostril. Also, depending on the handling procedure, a dead volume of 70-130 µl for the spray tip + syringe combination must be considered. A concern for such kits may be a possible confusion of the administration route. The used syringes are easily fitted with a needle and there is some risk in real life, that the drug intended for intranasal administration is injected. Most of these disadvantages can be avoided if prefilled systems are used.
So called unit/bidose systems (see Fig. 5) for liquid formulations are state of the art for the intranasal administration of drugs requiring exact dosing. They have been on the market for more than 10 years for intranasal breakthrough pain and migraine management. The systems contain one or two separated half doses ready for administration. They are optimized for easy intuitive and safe handling. These systems will also ensure an optimal nasal deposition of the drug. These advantages are linked to a somehow higher price. The filling is similar to the procedure used for prefilled syringes and requires appropriate equipment.

**Figure 4.** Spray tips for syringes which are used for the intranasal administration of naloxone, midazolam or some influenza vaccines.

**Figure 5.** Examples of unit/bidose systems for liquids on the left with a glass vial which contains the one or two doses of the drug product and dry powder devices on the right.
Dry powder systems: In the near future, some drugs and vaccines will probably focus on dry powder formulations to take advantage of improved storage conditions. It may be a challenging task to generate a powder with the right particle size. As mentioned before, the particles must be designed for safe administration (no fine particle fraction), good deposition and fast dissolution within the mucus layer. For dry powders, electrostatic charge and moisture ingress must be considered. Systems which actively drive out the powder, using compressed air generated by a pump-like mechanism, seem to be better accepted than passive ones, where the powder is taken up by the nasal air flow. Dealing with dry powder needs of course different manufacturing and filling technologies, which are already available for other medications.

Multi-dose solutions are by far the most widely used package solution. In Asia, simple squeeze bottles are on the market which can be considered obsolete because exact dosing is not possible and during use mucus may be sucked back into the bottle. The current standard multi-dose solutions are metering nasal spray pumps attached to bottles containing 10-30 ml of a liquid formulation. For this reason we would like to provide a closer insight into the technology of spray pump systems. As mentioned earlier the manufacturer fills the drug formulation into multi-dose bottles made of glass or Pharma-grade plastic materials. These are then closed by attaching the spray pump including a dip tube. The pump may be fixed by a screw closure, crimped on or simply snapped onto the bottle [1]. Now the system should be tight and no leakage should be observed during subsequent handling. This filling process is done on high-speed lines which can easily fill and close 60-200 bottles per minute.

Before the system can be used, the pump must be primed. This is normally done by the patient just before first use. A number of priming strokes is required to purge the air off the system and dip tube and to deliver the product at the intended dose volume. Spray pumps are displacement pumps. When actuating the pump, a piston moves downward inside the metering chamber. A valve mechanism with a ball sealing the metering chamber against dip tube and container at the bottom of the metering chamber will prevent backflow into the dip tube. So the downward movement of the piston will create pressure within the metering chamber which forces the air (before priming) or the liquid outwards through the actuator and generates the spray. When the actuation pressure is removed, a spring will force the piston and the connected actuator to return to its initial position. This creates an underpressure in the metering chamber which pulls the liquid from the container by lifting up the ball from the ball seat above the dip tube at the bottom of the metering chamber [1]. For a proper repeated function the spray pump should be held in upright positions to ensure that the end of the dip tube is always submerged in the formulation.

4.1. Bottles

Bottles or containers are an integral part of multi-dose container closure systems and will also influence the general appearance of the final product. Special shapes may be used to differentiate a product from competitors. Glass bottles are less prone to cause interactions and will give good protection to the formulation even for long storage intervals. Sometimes the glass can influence the stability of the formulation (change in pH, release of trace metals). This depends of course on the quality of the glass which is described by its hydrolytic class (classes
I-III are normally used for pharmaceutical products). The disadvantages which glass bottles may have are the higher weight and the risk to breakage when dropped [1].

Bottles are also made of plastic material (e.g. polyethylene, polypropylene, polyethylene terephthalate). A pump supplier will most likely not manufacture these bottles because a complete different technology is used. Parts for spray pumps are quite exclusively made by injection moulding which gives high precision. Bottle manufacturers use a process referred to as blow-moulding. The general principle is to make a hollow raw part and then blowing up the material to the final dimensions. The most important disadvantage for all bottles made of plastic material is evaporation/weight loss during storage. Plastic materials are not a perfect barrier for gas or water evaporation. This problem can be tackled using laminated materials but these are more expensive. Another potential risk has to be considered: inks and adhesives from labels may migrate through the bottle wall and leach into the formulation [1].

Pure mechanics but critical for all types of bottles: the bottle opening must fit the pump exactly. It needs to be tested and dimensions need to be controlled because variations may cause leakages or damage the housing of the pump during final assembly. To avoid any issues, consultation of the pump system supplier is highly recommended as these companies are experienced in managing this interface. The pump supplier should be able to recommend a range of suited bottles from suppliers which provide reliable quality. Before switching to another bottle or bottle supplier, the compatibility with the pump system should be checked in advance [1].

5. First steps to identify the right delivery system

One of the first steps in approaching the development of an intranasal drug administration project is to select the appropriate system for delivering the drug formulation. The selection of the delivery system is strongly governed by the type of formulation envisaged for delivery. Most likely the formulation will be liquid (solution or suspension), but also powder or gel formulations are possible. Of course the dosing frequency as well as legal restrictions (e.g. for controlled substances) will influence the decision for a single or multi-dose presentation. Once the basic type of system has been selected, it is then prudent to do some basic compatibility investigation or studies in order to avoid any obvious incompatibilities between the components and the proposed active pharmaceutical ingredient (API) and any known excipients before moving on to the formulation development stage.

The materials used for the systems are selected by the manufacturer to warrant proper mechanical function and low likelihood of chemical interactions. In practice potential interactions between the formulation and parts of the spray pumps due to sorption or swelling should be excluded. Typical tests that could be considered at this stage include immersion tests of the functional parts of the pump in the formulation to detect swelling or discoloration. First tests with assembled pumps from this immersion test will provide data on potential effects on mechanical function (e.g. friction, metering).
A simple test for spray performance will assure that the formulation can be aerosolized by the considered pump and the delivered particle size is appropriate for effective nasal deposition. As mentioned earlier, the particle size should be in the range from at least 10 to a maximum of 150 µm. Particle sizes above 10 µm assure that no product passes into the lungs and impact in the nasal cavity. Droplets greater than 150 µl should be avoided as they are prone to run out of the nasal cavity immediately. It is not unwise to perform such preliminary compatibility tests with a certain range of different pumps to get an impression which may provide the best performance.

Table 1. Typical classes of materials used for nasal spray systems

<table>
<thead>
<tr>
<th>Material</th>
<th>Typical functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene (PE)</td>
<td>Functional parts of the pump, actuator and fixtures, dip tube, bottles</td>
</tr>
<tr>
<td>Polypropylene (PP)</td>
<td>Functional parts of the pump, actuator and fixtures, dip tube, bottles</td>
</tr>
<tr>
<td>Polyoxymethylene (POM)</td>
<td>Functional parts (may release formaldehyde!)</td>
</tr>
<tr>
<td>Rubber or elastomers</td>
<td>Gaskets, seals, stopper</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>Springs, balls for valve mechanism</td>
</tr>
<tr>
<td>Aluminum</td>
<td>Ferrules for crimped connections</td>
</tr>
<tr>
<td>Glass</td>
<td>Bottles, vials, balls for valve mechanisms</td>
</tr>
</tbody>
</table>

Table 2. General information on the container closure system related to materials of construction which should be provided by the supplier of the system
At the end of the whole development process the requirements from authorities are straightforward: “For the final product (=formulation in combination with the whole container closure system) the suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the system when presented as part of the drug product)” [12].

6. Formulation development

Nasal drug formulations are broadly categorized into several types including solutions, suspensions, powders or gels. A key factor in selecting the type of nasal formulation to be developed is whether the therapy is intended for local or systemic application. Depending on the application, factors such drug absorption rate from the nasal mucosa into the systemic blood circulation and residence time in the nasal cavity become key elements in the formulation development process.

Taking as examples spray solutions and suspension type formulations, the following factors should be considered during nasal formulation development:

**Drug, particles:** consideration should be given to the desired therapeutic concentration for each dose, keeping in mind whether the total dose to the nasal cavity will be one (single nostril delivery) or two (one delivery into each nostril). For aqueous solutions and suspensions the typical dosing volume ranges are 50-140µl and for solution or suspension in pressurized metered dose inhalers (pMDIs) the typical delivery volumes are in the range of 25µl. The primary particle size of the API in suspension formulations also needs to be considered with regard to the droplet size delivered during dosing and any impact it may have on the dissolution of the particles once deposited in the nasal cavity.

**pH/buffers:** the pH inside the nasal cavity can influence the rate and extent of absorption of ionizable drugs. The average baseline human nasal pH is reported to be around 6.3 [13] and the pH of several commercially available nasal spray products are in the range of 3.5 to 7.0, and the optimal range for pH of these nasal formulations is suggested to be 4.5 to 6.5 [14]. The pH of the formulation can also affect the stability of the drug product during its shelf life so this also needs to be considered during development.

**Osmolality:** Studies have shown that hypotonic nasal spray formulations improve drug permeability through the nasal mucosa [15] and some marketed products report osmolality in the range 300-700mOsmol/K.

**Viscosity/surface tension:** the majority of commercially marketed products contain agents that modify the viscosity and surface tension of the formulations, they are included in order to manage factors such as thinning and thixotropic behavior and are key elements in the
performance of the dispensed product such as drop particle size, spray angles and also influence the residence time of the product once delivered, in the nasal cavity.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>IIG limit for nasal route, %w/w</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol, 200 proof</td>
<td>2</td>
<td>Co-solvent</td>
</tr>
<tr>
<td>Anhydrous dextrose</td>
<td>0.5</td>
<td>tonicity</td>
</tr>
<tr>
<td>Anhydrous trisodiumcitrate</td>
<td>0.0006</td>
<td>buffer</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>0.0366</td>
<td>preservative</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>0.119</td>
<td>preservative</td>
</tr>
<tr>
<td>Butylated hydroxyaniolose</td>
<td>0.002</td>
<td>antioxidant</td>
</tr>
<tr>
<td>Cellulose microcrystalline</td>
<td>2</td>
<td>Suspending agent, stabilizer</td>
</tr>
<tr>
<td>Chlorobutanol</td>
<td>0.5</td>
<td>preservative</td>
</tr>
<tr>
<td>Carboxymethyl cellulose Na</td>
<td>0.15</td>
<td>Suspending agent</td>
</tr>
<tr>
<td>Edetate disodium</td>
<td>0.5</td>
<td>Chelator, antioxidant</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Not reported</td>
<td>pH adjustment</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.7</td>
<td>preservative</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>0.132</td>
<td>Penetration enhancer</td>
</tr>
<tr>
<td>PEG400</td>
<td>20</td>
<td>Surfactant, co-solvent</td>
</tr>
<tr>
<td>PEG3500</td>
<td>1.5</td>
<td>surfactant</td>
</tr>
<tr>
<td>Phenylethyl alcohol</td>
<td>0.254</td>
<td>Preservative, masking agent</td>
</tr>
<tr>
<td>Polyoxyl 400 stearate</td>
<td>15</td>
<td>surfactant</td>
</tr>
<tr>
<td>Polysorbate 20</td>
<td>2.5</td>
<td>surfactant</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>10</td>
<td>surfactant</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>20</td>
<td>Co-solvent</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>0.3</td>
<td>Preservative</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>1.9</td>
<td>tonicity</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>0.004</td>
<td>pH adjustment</td>
</tr>
<tr>
<td>Sulfuric acid</td>
<td>0.4</td>
<td>pH adjustment</td>
</tr>
</tbody>
</table>

Table 3. Examples of key nasal formulation excipients and their inactive ingredient guidance (IIG) dosing levels

Other excipients: in addition to buffer salts several types of excipients may be required in order to develop a stable nasal spray formulation. These include solvents and co-solvents to keep the active pharmaceutical ingredient (API) in the dissolved or suspended state, as well as preservatives for non-sterile products. If the formulation is a suspension or emulsion, surfactants and/or emulsifying agents, stabilizers and suitable oil-phase components may be
required. Although there are numerous surfactants, emulsifying agents, solvents, co-solvents, oils and preservatives available, only a limited number of excipients are listed in the US FDA inactive ingredient guide (IIG) for nasal products. Table 3 lists some key excipients and their IIG dosage levels, as reported in the FDA IIG database for nasal spray formulations [16].

**Controlling residence time in the nasal cavity:** increasing the residence time of the drug, once delivered on the nasal mucosa, can be beneficial especially for local applications and can aid drug absorption through the nasal mucosa. One approach is too increase the viscosity of the formulation but this should be balanced against any impact on droplet size distribution during delivery into the nasal cavity [17].

**Penetration enhancers:** these agents increase the penetration of drugs through the nasal mucosa. Typical penetration enhancing agents are solvents, co-solvents, ionic and some non-ionic surfactants, selected fatty acids, including oleic acid and certain lipids and cyclodextrin [18, 19].

**Powder and gel nasal formulations:** in formulating nasal powders the key elements to manage are controlling the primary particle size of the API as well as the excipients to get efficient nasal deposition, and selecting a system that provides acceptable protection of the powder during storage and efficient delivery to the nasal cavity during dosing. For nasal gel applications the formulations can be relatively simple and key elements will be stability and shelf-life and the selection of the dispensing system used to deliver the gel to the nasal cavity.

### 7. Performance parameters

Nasal drug product performance characterization is driven by regulatory requirements which allow for successful approval and marketing of these products. The most stringent regulatory standards for nasal drug products are issued in the USA [20] and in Europe [21]. During the development process information has to be documented on many factors in order to construct a regulatory dossier. Typical expectations for development characterizations in the US and Europe are detailed in Table 4.

Once approved and marketed these products have to be routinely controlled in order to assure ongoing performance and quality and the typical regulatory expectations for marketed nasal product specifications and testing are detailed in Table 5. The rationale behind these performance characterization tests are related to factors such as dosing accuracy, shelf life, product robustness and user safety, the key ones being as follows:

**Priming, re-priming:** most nasal spray pumps need to be primed in order to fill the dosing chambers before use and to assure full dosing of the product. In addition, some pumps do not retain the dose in the metering chamber when stored for longer periods, i.e. 7 days, 1 month etc. and may need to be re-primed before use after a specified period of non-use which will be defined in the patient leaflet.
Table 4. Examples of product characterization test during development of nasal spray products.

<table>
<thead>
<tr>
<th>Characterization test</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability / shelf life</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Temp. cycle testing</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Priming re-priming</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Micro/bioburden</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Extractables</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Leachables</td>
<td>√</td>
<td>N/A</td>
</tr>
<tr>
<td>USP tests, 601, 87, 88, 661, 381...</td>
<td>√</td>
<td>N/A</td>
</tr>
<tr>
<td>Drop testing, vibration, shipping, air transport tests</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Effect of orientation</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Plume geometry</td>
<td>√</td>
<td>N/A</td>
</tr>
<tr>
<td>Profiling near exhaustion</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Performance in the hands of different users</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Particulates</td>
<td>√</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 5. Examples of routine control testing for nasal spray products.

<table>
<thead>
<tr>
<th>Control test</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priming, re-priming</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Dose weight (through life)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Leakage</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Dimensional, metrology</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Droplet/particle size distribution</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Spray pattern</td>
<td>√</td>
<td>N/A</td>
</tr>
<tr>
<td>Extractables</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>√</td>
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**Dose weight through life**: this test assures that the pump delivers the prescribed dose consistently throughout the use-life of the product, usually beginning middle and end of use. Regulatory requirements exist in most markets for limits on dosing accuracy and these can be found by referring to each country specific regulatory dosing limit specifications for nasal products.

**Leakage**: this assures that the product integrity is maintained throughout its proposed shelf life and that the contents are not lost during storage at various environmental conditions. The ICH stability test conditions [22] are the key reference with regard to stability testing.

**Dimensional/metrology measurements**: these assure that the spray pump meets specified critical quality dimensions in order to assure that the nasal product functions efficiently and meets the key performance tests assuring consistent quality.
Particle size distribution: this can refer to the primary particle size specification of the API itself in suspensions or to the droplet (liquid solution) or particle (powder) size distribution of the delivered spray. Specifications need to be put in place for this key parameter and the justified limits registered in the regulatory submissions as it is closely related to nasal deposition efficiency.

![Image](image1.png)

**Figure 6.** Typical display from a spray pattern test using laser imaging, which can give information about the ovality of the emitted spray.

Spray pattern: this is another test to assure consistent quality of the delivered nasal spray and characterizes parameters such as angle and plume shape, see Figures 6 and 7.

![Image](image2.png)

**Figure 7.** Typical display from a spray angle test using laser imaging, which can give information about the angle of the emitted spray.
**Extractables/leachables:** this test assures the safety of the product and specifically measures and controls the potential chemical contaminants which may come from the packaging or container closure system into the formulation and therefore be potentially toxic for the patients, if ingested. The PQRI [23] have issued detailed guidance documents on this subject in conjunction with the FDA which outline how to tackle this specific parameter.

**Particulates:** this test characterizes the contamination of the nasal formulation by any foreign particulates and is related to the overall safety of the product.

**Microbial limits:** specification and tests exist to measure and characterize this parameter, for preserved nasal formulations this will usually mean measuring the levels of preservatives, e.g. benzalkonium chloride in the product and during its proposed shelf life. The units of measurement are usually colony forming units (CFU’s). For non-preserved nasal products the characterization tests are somewhat more complicated and include challenge testing with contaminated bacterial environments to assure the integrity of the system for protection against microbial contamination. Special drug delivery systems are needed in order to use non-preserved nasal formulations.

**Robustness:** here a number of different test are applied including dropping the whole packaging, exposure to vibration, simulation of shipping and transportation. These characterization tests are meant to assess the robustness of the product to normal transport and day to day use.

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**Table 6.** General information on the container closure system which should be provided by the supplier [8,9].

**User studies:** these tests look at the ergonomic and human factor aspects of the systems and include investigation and data generation on potential issues such as orientation, patient handling (young, old, comprised dexterity etc.), actuation forces and many other factors.
Regulatory Guidance’s have appeared in the last few years outlining how to tackle these ‘human factor’ issues [24].

As can be seen from the above list of tests, the development process for a nasal drug product can be quite long, intensive, and costly and depending on the complexity of the product can take upwards of 18 months keeping in mind that suitable real time stability data also need to be generated for regulatory submissions.

8. Trends for nasal drug administration

8.1. Use of preservatives in multi-dose products

For some years now, so called “preservative-free multi-dose” systems (“PFMD”) are on the market and gain share. Such systems are certainly appreciated by the growing number of patients who experienced discomfort with preserved formulations. The issue of significance for the patient and consumer, however, is the high incidence of local side effects attributed to preservatives. The discussion is controversial, and published preclinical and clinical studies are not always consistent. It seems to be clear that short-term use of preparations containing preservatives at low concentrations is well tolerated, but preservatives can cause serious inflammatory effects with long-term use [25]. The responses may include chemical irritation, hyperreactivity and true allergies [26]. The German Authorities (BfArM) addressed the use of benzalkonium chloride for nasal sprays in 2003 [27] which encouraged the preservative free systems for this administration route. Today a range of technical solutions is available to overcome this issue. The highest risk of contamination obviously comes from the orifice of the nasal spray system, because it may come in contact with skin and mucosa as well as with infected mucus in the nose. Some marketed systems use the oligodynamic activity of a silver wire in the tip of the actuator, a silver coated spring and ball [28]. Such systems are able to keep microorganisms down between long dosing intervals, even when the tip is immersed into bacterial contaminated fluid [29].

The most recent preservative free systems follow a purely mechanical approach to minimize interactions between parts of the device and the formulation. One technical solution to prevent contamination via the orifice is referred to as “tip seal technology” [25]. A spring loaded valve is located directly below the opening of the tip orifice and does not allow any microbes to migrate from any surfaces or contacted liquids into the system, the orifice is “sealed” under resting conditions. The tip seal keeps the system closed until a defined pressure (for nasal sprays it is more than 3 bar) is reached by pressing down the actuator. Then the system will open and the formulation is forced through the orifice with a higher pressure than needed to open the valve. When the pressure drops at the end of the actuation the tip seal will immediately close the orifice with an outward movement. So no backflow of potentially contaminated medication or other liquid is possible. Depending on the pump system, the fluid path may even be “metal-free”, which means the springs needed for the device operation do not come in contact with the formulation [25].
To avoid contamination of the formulation via venting air different technical solutions are used. The simplest way is sterile filtration of the venting air using separate filters or filter gaskets. For oxygen-sensitive formulations, so called collapsing bags or depressed systems are used. The formulation is filled in a special, microbial tight bag which is protected by a surrounding bottle. When dispensing the product, the bag collapses with the content not coming in contact with the ambient air. Some pumps are constructed in such a way, that the whole system is air-tight and during use some vacuum (up to -300 mbar) is generated within the bottle. Those systems allow even a purging with inert gases to reduce oxygen content in the container head space [25]. These described technical solutions to make the use of preservatives obsolete are well established and mature technologies.

8.2. Non-aqueous nasal formulations

The majority of prescription nasal spray products on the market are aqueous formulations. Just recently some so called “dry mist” nasal sprays (e.g. QNASL®, ZETONNA™) were introduced. For these products the technology of the pressurized metered dose inhalers (pMDI’s) is utilized which are well established for the treatment of asthma bronchiale and chronic obstructive pulmonary disease. The active ingredient is dissolved or suspended into hydrofluoroalkane (HFA) propellant and typical delivery volumes are in the range of 25µl. Non-aqueous nasal spray formulations are suspected to have increased levels of safety risks due to the fact that they use excipient such as propylene glycol, isopropyl alcohol and PEG400, which are known to cause local irritation particularly for chronic use [30]. Nasal steroids such as beclomethasone and ciclesonide are formulated in such non-aqueous HFA propellants and in this case it is the same formulation approach as is used for inhalation suspension products using pressurized metered dose inhalers (pMDI’s).

8.3. Side actuated spray pumps

An innovative development in nasal spray pumps are side actuated nasal spray devices designed to help improve patient compliance due to their reduced dependence on patient actuation force or speed. These devices are intended to be compact, ergonomic with intuitive design and have short and motionless nasal nozzles where the fingers are no longer in contact with the nostrils. They have softer actuation and are suitable for a wide range of applications including pediatrics and elderly patients who may have compromised dexterity.

8.4. Unit- and bi-dose sprayer

Unit dose devices can also be considered attractive options for certain types of therapy, especially for all kinds of rescue medications. The ready to use packaging will reduce stress (e.g. no fear for injuries, disease transmission) and handling errors which may happen in such situations. Such kind of packaging also limits the amount of drug which needs to be handled which is important for controlled substances.
9. Conclusion

Intranasal drug administration is a technology with an interesting past and a fascinating future. In only a few fields cooperation between developers of novel pharmaceutical remedies on one side and manufacturers of sophisticated delivery systems on the other side is equally essential. Precise metered dosing, maximum flexibility, product protection and, last not least, patient adherence are the key areas to work on. The increasing use of unpreserved formulations in both prescription and OTC (over the counter) products establishes additional challenges. Patients and consumers appreciate the convenient and intuitive handling of modern nasal delivery systems, properties which are important for further and sustainable success of nasal administration in general. However, with regulatory demands increasing, professional guidance is needed and should be provided by manufacturers of nasal drug delivery systems to support pharmaceutical companies in finding the optimum configuration. Even though such support can not exempt marketers form performing proper due diligence on the finished product, it is obvious that time to market can be reduced substantially if available resources are utilized in a proper cooperation mode.

Figure 8. Example of a side actuated multi-dose spray pump

a. Pain management, e.g. migraine or cancer breakthrough pain episodes, here the molecules are often potent and the amount of dose should be limited in order to avoid any undesirable side-effects or risks of diversion or misuse.

b. Vaccines are often one-off treatments and they can be formulated in powder forms so as to avoid the cold chain logistics difficulties associated with liquid vaccines and can easily be used out the hospital environment, such as field vaccination stations.

By using such unit dose or single throw away devices, one can avoid many of the issues outlined above for pain or vaccination therapies.
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