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Nasal delivery systems and their effect on deposition and absorption

H. Kublik^{a,*}, M.T. Vidgren^{b,c}^a*Astra GmbH, D-22876 Wedel, Germany*^b*Department of Pharmaceutics, University of Kuopio, P.O. Box 1627, FI-70211 Kuopio, Finland*^c*Astra Draco AB, P.O. Box 34, S-22100 Lund, Sweden*

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Abstract

Due to nasal anatomy and physiology, with a non-ciliated area in the anterior part of the nasal cavity and a ciliated region in the more posterior part of the nose, the site of deposition is of importance for the nasal mucociliary clearance and retainment of a formulation in the nose. Many drug delivery devices for nasal application of liquid, semisolid and solid formulations were investigated in respect to their deposition in the nasal cavity. The site of deposition and the deposition area depend on several parameters which are related to the delivery device, such as mode of administration, particle size of the formulation and velocity of the delivered particles. Several in vitro and in vivo methods have been used to study distribution and clearance of intranasally delivered therapeutics. The relationship between deposition, absorption and related bioavailability of the nasally applied formulation has been shown. © 1998 Elsevier Science B.V.

Keywords: Nasal drug delivery; Device; Administration mode; Formulation; Deposition; Distribution; Clearance; Absorption

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*Corresponding author.

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1. Introduction

For many years drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions, and has resulted in a variety of different medications including corticoids, antihistamines, anticholinergics and vasoconstrictors. In recent years, increasing investigations of the nasal route have focussed especially on nasal application for systemic drug delivery.

It has been estimated that the total sales for nasal products in 1996 was about 5 billion US\$. A remarkable increase of the market for nasal drug therapy is expected if the nasal route is successful in superseding parenteral application for peptide delivery.

Optimization of inhalation medication requires consideration of the strong interactions between formulation, device, mode of administration and patient. The evaluation of each part has to be seen in connection with the other influencing factors.

Regardless of the required means of action—local or systemic—there are several factors that should be taken into account to optimize nasal administration. Having an adequately designed and developed drug delivery system and formulation in respect to deposition, clearance and absorption the therapeutic effectiveness can be improved and adverse events minimized.

The deposition site for nasally applied drugs within the nasal cavity depends upon the type of delivery system and the technique of administration used. It determines the subsequent translocation of the deposited preparation by mucociliary clearance and has an influence on absorption and hence

effectiveness of the medication. In several studies the relationship between initial deposition pattern and mucociliary clearance, which results in a secondary deposition of the administered drug, has been investigated. Only a few investigations relate these results to pharmacokinetic and pharmacodynamic data to highlight the relationship between deposition, clearance, absorption and effect of the medication.

Only a few nasal delivery systems used in experimental studies are currently on the market to deliver therapeutics into the nasal cavities, i.e. nasal drops as multiple or single-dose formulation, aqueous nasal sprays, a nasal gel pump, pressurized MDIs and dry powder inhalers.

2. Anatomy and physiology of the nose in relation to deposition and clearance

Nasal anatomy and physiology greatly influence primary deposition and mucociliary clearance of administered drug substances and are, therefore, important for nasal absorption. Gizurarson and Bechgaard [1] listed several factors which have an effect on nasal absorption. Some of the anatomical factors, such as nasal length, the bend from the nostrils into the cavity and structure of the turbinates, can directly be related to deposition in the nasal cavity. Passing the nostrils the nasal passage extends from the nasal vestibule to the nasopharynx at a length of about 12 cm. It is separated by the nasal septum into two cavities and further divided by the folds of the superior, middle and inferior turbinate, considered to be the main nasal passages. The main nasal passages with a length of approximately 6 cm end behind the turbinates at the arch of the nasal septum.

At the end of the nostrils the airways are con-

stricted in the region of the nasal ostium, which results in an acceleration of the inhaled air. In the preturbinate region (atrium) because of the construction, with a wider cross-sectional area, the air flow is decreased and has to change direction to enter the main nasal passages of the turbinates. This results in higher air flow resistance and increased turbulence. Due to nasal anatomy there are two major deposition areas. One near the ostium internum where a high degree of turbulence occurs because of the constriction, and another one in the anterior region of the middle turbinate due to the change of the airflow direction from vertical to horizontal flow. The vestibule, atrium and the beginning of the turbinates are covered by non-ciliated surfaces. Mucus flow in this anterior third of the nasal cavity is only 1–2 mm/h and occurs mainly by traction of the mucous layer due to ciliary movement of posteriorly located cilia [2]. The main nasal passages are highly vascularized and ciliated. Here the rate of mucus flow is 8–100 mm/min. It is assumed that in this region, with increased surface area, highest air flow resistance and ciliated cells, the main drug absorption takes place [3]. If particles are deposited just posterior to the ostium internum, they are moving in an anterior direction until the nasal area ends and then are blown out [2,4].

Nasal deposition depends on the size and shape of the nose [5,6]. It can also be correlated to body length and weight and increases with decreasing age for a given particle size and flow rate [7]. Zhang and Yu [8] could reduce interspecies differences by including the total bend angle in the nasopharynx as an additional variable in the calculations for the prediction of nasal deposition. Cheng et al. [6] considered that nasal geometry is a main factor affecting aerosol deposition. They measured the nasal morphometry of four male adults by a magnetic resonance imaging technique. The coronal sections of the nasal airways at different distances from the nostrils were illustrated. In the main nasal passage, which is located 3–8 cm behind the beginning of the nostrils, the most complicated and asymmetrical profile, due to the folds of the turbinates, is seen at a distance of approximately 5–7 cm from the nostrils. Hence the surface area of the nasal passages from the nostril to the nasopharynx shows its maximum at this distance: 11–14 cm² depending on the individual morphology. The cross-sectional

area had local maxima and minima and increased from the anterior vestibule to the turbinate region with its maximum in the nasopharynx. The geometric parameter was calculated for each individual area, dividing the total surface area (180–240 cm²) by the mean cross-sectional area (2.0–3.8 cm²). The nasal deposition efficiency increased with increasing geometric factor, i.e. with increasing surface area or decreasing cross-sectional area.

3. Deposition and absorption of inhaled particles

Inhaled particles are deposited by five mechanisms [9]: interception, impaction, sedimentation, diffusion and electrostatic precipitation. Only three of these mechanisms have importance for nasal deposition: inertial impaction, gravitational sedimentation and Brownian diffusion [10–12].

Deposition by interception only occurs to fibrous particles, when the trajectory of the particle brings it close to the surface and the edge contacts the surface. Usually fibrous particles are orientated parallel to the air flow streamlines [13]. Small particles which are highly charged and have a high electric mobility are deposited by inducing image charges on the surface of the airways. However, deposition due to these mechanisms is usually of minor importance.

Inertial impaction may occur whenever the airstream carrying the particles changes its direction. If the particles are heavy, large or moving fast, they may be unable to follow the airstream as it changes direction. Instead, they fly off tangentially and strike the airway wall [11]. The probability of impaction in a bent airway is:

$$Ud^2 \sin \theta / R \quad (1)$$

where: θ , angle of the bend; U , airstream velocity; d , particle aerodynamic diameter; R , airway radius.

It can be derived from Eq. (1), that the airway geometry, the size of the inhaled particle and the inhalation flow have a major influence on deposition due to inertial impaction. Considering the nasal delivery device, the aerodynamic diameter of the delivered particles can be varied. In addition, the technical construction of the device has an influence on airstream velocity, and thus it is possible to

influence deposition. Impaction is the major deposition mechanism for particles larger than 0.5–1 μm in the nose and the oropharynx. Deposition in these regions is further increased with obstruction and high inspiratory flow rates, when turbulent air flows are created [14].

In the small conducting airways, deposition occurs mainly by gravitational sedimentation [15]. A particle settling under gravity accelerates to a steady terminal settling velocity, at which gravitational force is balanced by the resistance of the air through which the particle falls [16]. The rate of settling is proportional to the square of the particle diameter according to the Stokes equation [17]. The smaller the particle the more slowly it sediments. The terminal settling velocity is described by:

$$(\rho - \sigma)gd^2/\gamma \quad (2)$$

where: ρ , density of the particle; d , diameter of the particle; σ , density of the air; γ , viscosity of the air; g , gravitational acceleration.

Deposition by gravitational sedimentation can only be influenced by the variation of the particle size. The density is already fixed by the character of the drug substance.

The third deposition mechanism, Brownian diffusion, is restricted to particles whose diameter is less than 0.5 μm . Particles of this size can be pushed towards a surface by the random collision of gas molecules. Higher deposition is predicted with an increasing diffusion coefficient and decreasing flow rate [6].

Usually this mechanism can be ignored for the administration of nasal delivery systems, since the diameter of drug particles in nasal dosage forms are seldom 0.5 μm or less.

Aerodynamic particle size is the key factor of nasal deposition. Correlation of aerodynamic particle diameter and nasal deposition efficiency at a given flow rate shows a minimum deposition of particles of approximately 0.5–1 μm [18]. Above this particle size deposition increases due to inertial forces, below it increases due to turbulent diffusion. Inertial impaction, dominant for particles above 0.5 μm , is the main deposition mechanism in the nose. For particles larger than 0.5 μm inspiratory nasal deposition increases with increasing particle diameter and with increasing inhalation flow rate. Although the nose

filters particles more efficiently during expiration than during inspiration, in the investigations of Heyder and Rudolf [19] expiratory deposition was lower than inspiratory nasal deposition due to particle deposition in the lungs. At low flow rates particle deposition in the lungs is higher, with increasing flow rates the deposition in the nose increases. The main deposition mechanism for particles smaller than 0.2 μm is diffusion. With this mechanism nasal deposition increased with decreasing particle size and with decreasing flow rate.

Absorption by the nasal route is facilitated by a highly vascularized epithelial layer with a good blood flow, the rich lymphatic plexus and a relatively thin and porous endothelial membrane. The absorption routes via the nose include transcellular and paracellular passive absorption, carrier-mediated transport and absorption by transcytosis [20]. The main mechanism is transcellular passive diffusion. Therefore the solubility, the partition coefficient and the molecular weight of the drug are of major importance [21]. However, the absorption rate with regard to the nasal deposition site has not yet been elucidated.

4. Description of nasal delivery systems

Depending on the physico-chemical properties of the drug, the therapeutic aims, the basic compliance of the patients and marketing issues, the most suitable delivery system and formulation strategy have to be chosen. A lot of nasal devices, especially for systemic medication, have only been used for experimental studies [22]. Four basic formulations must be considered, i.e. solution, suspension, emulsion and dry powder systems. Liquid preparations often contain aqueous formulations, but also alcohol, oils or other organic solvents. Compatibility with additional excipients and the solvent have to be considered in choosing the delivery device.

If accurate dosing is required the most widely used delivery devices are mechanical pumps and pressured aerosol systems. Su and Campanale [23] discussed five different areas regarding the consideration of the requirements for an aerosol or pump system, including formulation aspects, valve, container and actuator requirements and quality control issues. With regard to formulation, physico-

chemical compatibility, solubility, chemical, microbiological and physical stability of the active ingredient, and necessary additives, determine their own specific requirements for a delivery system.

4.1. Liquid nasal formulations

Liquid preparations are the most widely used dosage forms for nasal administration. They are mainly based on aqueous formulations. Their humidifying effect is convenient and useful, since many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. One major drawback of water-based dosage forms is their microbiological stability, because the required preservatives impair mucociliary function [24,25]. Especially in long-term nasal treatment, preservatives can be the major cause of irritation and allergic rhinitis [26]. Besides microbiological stability, the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major disadvantages of liquid formulations [27,28]. The site of deposition and deposition pattern of nasally applied liquid formulations is dependent on the delivery device, the mode of administration and the physico-chemical characteristics of the formulation. Usually a wide distribution of the preparation in the nasal cavity is desired whether the drug substance is administered for local or for systemic application.

Other requirements such as patient compliance, cost effectiveness and risk assessment result in a variety of different dosage forms for liquid nasal formulations.

4.1.1. Instillation and rhinyle catheter

An easy way to deliver drops to a defined region in the nasal cavity is the use of a catheter. The combination of an instillation catheter to a Hamilton threaded plunger syringe was used by Hughes et al. [29] in order to compare the deposition of drops, nebulizers and sprays in rhesus monkeys. In a study by Harris et al. [30], 0.2 ml of the formulation were placed in a tube. One end of the tube was positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth. Dosing of catheters is determined by the filling prior to administration and accuracy of the system. Nasal deposition and distribution of catheter-

applied solutions depend strongly on the means of administration. This system is only used for experimental studies.

4.1.2. Drops

Nasal application devices are often associated with drops, one of the oldest delivery systems for nasal administration of liquids. They are low-cost devices and easy to manufacture. Their disadvantages are related to the use of liquid formulations, such as microbiological and chemical stability. In addition, the mode of administration is of great importance for the efficacy of the medication. Correct administration of drops requires complex manouvers [31]. The delivered volume cannot be clearly controlled and the formulation can be easily contaminated by the pipette. Depending on the position of the head, the delivery of a relatively large volume often results in fast clearance down the laryngopharynx.

4.1.3. Unit-dose containers

The major advantage of disposable unit-dose containers compared to other water-based formulations is the avoidance of preservatives. Due to their portability and small size they improve the patients comfort. In contrast to multi-dose nasal drops the volume is determined by the filling volume of the unit-dose. The dose accuracy results from filling accuracy and use of the device. There are two different devices currently available. The best known form is the bottlepack package, which delivers the formulation in the form of a drop pressed out of the unit-dose pipette. The deposition of the preparation is the result of the administration technique.

The dose accuracy determined by the filling volume is higher compared to multiple-dose drops, but still lower than the accuracy of metered-dose nasal sprays. This fact is due to the lack of a pressure point or any other guiding mechanism during action. A further increase in dose accuracy can be achieved by a second form of unit-dose containers, which operates with an actuator with a nasal adaptor and has a small chamber with a piston. The liquid formulation is kept in a plastic container (Fig. 1a). A similar device (Fig. 1b) divides the dose, so that half of the total dose is administered in each nostril. Depending on the mode of administration a residual volume of 10–30% of the formulation can remain in these devices after actuation.

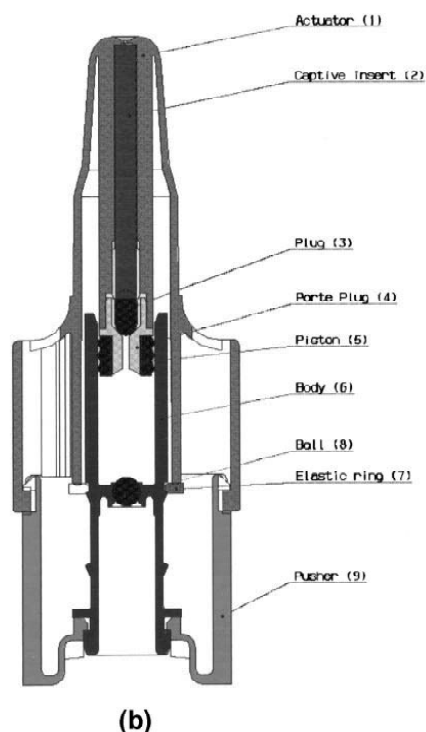
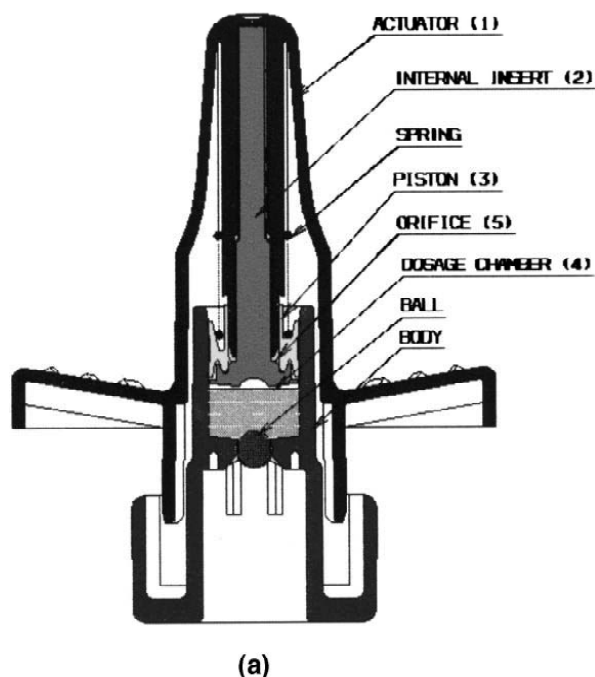


Fig. 1. (a) Nasal unit dose system (Monospray®, Valois S.A., Le Neubourg, France). (b) Nasal two-dose system (Bidose®, Valois S.A., Le Neubourg, France).

The reduction or withdrawal of preservatives achieved with these devices requires an aseptic filling of the device, which is only suitable for cost extensive and sensitive drug substances. The containers of other unit-dose or bi-dose-systems are comprised of a small glass ampoule (Fig. 2), which has the advantage of a better compatibility to the drug formulation, and that autoclaving of the preparation is possible. Compared to the bottlepack container, a better distribution of the dose, a more controlled and user-friendly application mode and a higher dose accuracy can be achieved due to the pressure point. Usually, the particle size distribution and the spray angle are dependent on the mode of actuation. A system based on a pressure point uses the inertia of the actuation finger and is therefore more independent of an individual manual actuation.

The increasing use of water-based metered sprays can be explained by their simplicity and hygiene. The disadvantages of nasal sprays are similar to nasal drops mainly due to the requirement of preservatives. Nasal spray devices include the squeezed bottle, the metered-dose pump spray, and new devices known as airless or preservative-free spray pumps.

4.1.4. Squeezed bottle

Squeezed nasal bottles are mainly used as delivery device for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly dependent on the mode of administration. Differences between vigorously and smoothly pressed application influence the dose as well as the droplet size [32]. Thus the dose is hard to control. Therefore squeezed bottles with vasoconstrictors are not recommended to be used by children.

4.1.5. Metered-dose pump sprays

Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays.

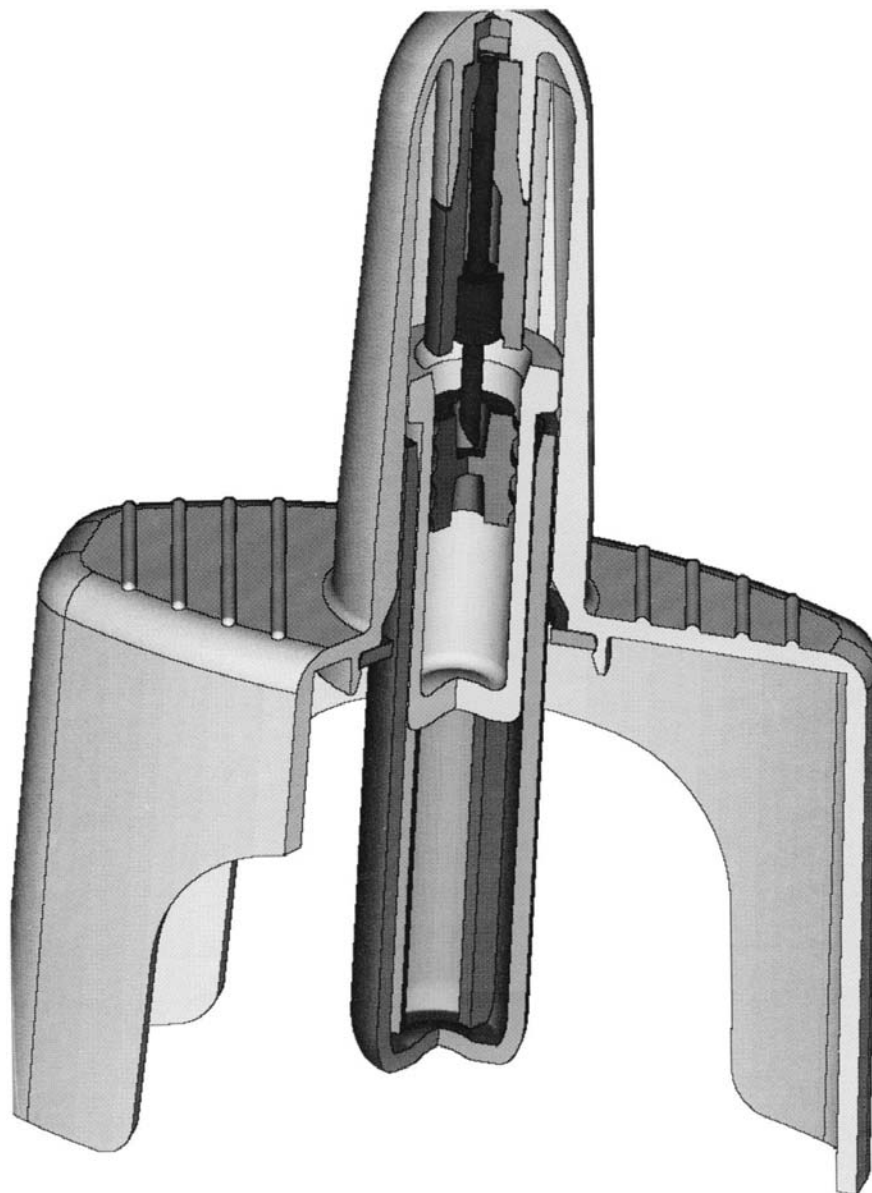


Fig. 2. Nasal unit-dose system with glass container (Pfeiffer, Radolfzell, Germany).

Compared to squeezed bottles and continuous valve sprays, they allow the application of a defined dose with a high dosing accuracy and a typical spray pattern. Dose volumes between 25 and 200 μl are available as standard. Spray characteristics vary according to the precompression mechanism, the type of the selected pump and valve and the physical properties of the product. Viscosity, thixotropic behavior, elasticity and surface tension of the liquid determine the spray pattern, the particle size of the

drops, the dose and the dosing accuracy. Metered-dose pump sprays include the container, the pump with the valve and the actuator. The form of the actuator has to be adapted to the required use. For correct dosing the tip should avoid the collection of residual drops. The length of the actuator has an influence on deposition of the application into the nose. Special adaptors for children are available on the market. For safety reasons a captive insert is fitted into the actuator in order to avoid risks of

liquid ejection without actuation, to decrease the dead volume in the actuator and to reduce contamination.

Dependent on the product delivered, especially with respect to its rheological behavior, surface tension and required spray characteristics, the geometry and dimensions of the pump mechanism can be adapted to fulfil these demands.

Special geometries of the orifice determine the spray pattern and distribution. The cone angle varies between 35 and 90°. A small cone angle results in a more posterior deposition, while the wider angle shows a broad distribution in the anterior part of the nasal cavity [33]. A multiple-channel system in the orifice of the nasal adapter, by which the solution is sprayed in several different directions, additionally ensures a good distribution. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are on the market.

4.1.6. Airless and preservative-free sprays

In order to minimize the use of preservatives and to increase the stability of products which are very sensitive to oxidation, several suppliers have developed pumps which prevent the entry of air back into the device during dispensing. So far three main principles for airless pumps have been realized: the collapsible bag, the sliding piston system and a system which works against a vacuum.

The pump prevents air entering the package. The vacuum created after dispensing is compensated by reduction of the container volume, which can be done by deformation of a collapsible plastic container (Fig. 3a) or dragging of a sliding piston within a glass or plastic bottle (Fig. 3b).

Some devices function under the low pressure of a compressed gas, such as nitrogen or carbon dioxide, in order to offset the volumes of product expelled outside the bottle.

Working against a vacuum requires a larger container, which is only partly filled because the drop of the pressure in the container under about 500 mbar reduces the performance, especially the dose volume.

Besides the reduction of preservatives and anti-oxidants a major advantage of airless pumps is their use in any position with unchanged dose accuracy,

which is useful especially for children or bedridden patients. However, both systems require an absolutely tight packaging, as leakage of air into the device is a major problem leading to increased control procedures.

A different preservative-free system compensates the volume of the dispensed dose by an air flow through an aseptic filter into the container (Fig. 4). The nasal adapter is protected from contamination by a pure mechanical sealing system. An advantage is that the microbiological sealing system mechanism is directly integrated in the very end of the tip, so that not only the content of the bottle, but also the content of the pump and the nasal adapter up to the orifice is protected.

4.1.7. Compressed air nebulizers

An often used compressed air nebulizer in nasal deposition studies is the Devilbiss Sprayer. Hughes et al. [29] carried out deposition studies in rhesus monkeys delivering a dose of 70 µl with a compressed air pressure of 30 p.s.i. for 0.5 s with an automatically timed pump. The resulting mass medium aerodynamic diameter (MMAD) was 1.5 µm (geometric standard deviation (GSD)=1.5) measured with an aerodynamic particle sizer (APS 3310, TSI, Inc., St. Paul, MN). This delivery device offers a variety of parameters such as different volumes, different particle sizes by pressure variation or different duration of the administration. This allows the adaptation of the compressed air nebulizers especially for study purposes. At the same time this device is not suitable for systemic drug delivery by the patient himself due to the variety of parameters and the complicated design with compressed air supply.

4.2. Powder dosage forms

Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a prolonged contact with the nasal mucosa. It has been shown by Illum et al. [34] that small volumes of liquid and powder particles have almost the same clearance rate. The addition of bioadhesive excipients results in a decreased clearance rate. Using

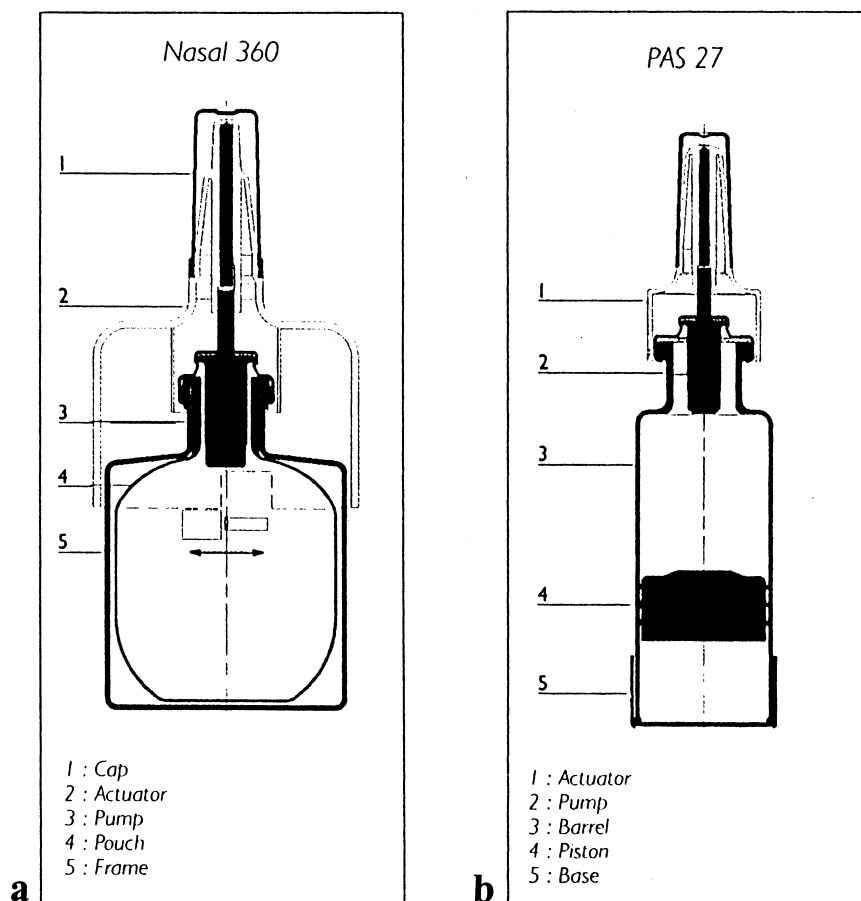


Fig. 3. (a) Airless nasal device with collapsible bag (Nasal 360®, Valois S.A., Le Neubourg, France). (b) Airless nasal device with sliding piston (PAS 27®, Valois S.A., Le Neubourg, France).

dimethyl- β -cyclodextrin as nasal enhancer Schipper et al. [35] showed that the use of a powder formulation results in a higher bioavailability of insulin compared to a solution formulation.

Large volumes of liquid preparations are more easily cleared to the nasopharynx and oropharynx from where they enter the posterior part of the tongue. Therefore administration of nasal powders may increase patient compliance, especially for children if the smell and taste of the delivered drug is unacceptable. The powder allows the delivery of the highest mass of active ingredient without the necessity of a vehicle. However, the suitability of powder formulations compared to liquid preparations is highly dependent on the solubility of the active drug substance, its absorption rate, particle size and potential irritability. Aerodynamic properties of the powder determine the deposition pattern in the nose.

Furthermore, powder properties such as particle size and shape, density and flow characteristics have an influence on the distribution in the nose.

4.2.1. Insufflators

For study purposes, an insufflator can be constructed using a straw or tube which contains the drug substance for inhalation [36]. Sometimes this was combined with a syringe in order to blow the mixture into the nostril [29]. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient deaggregation of the particles and results in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules. The use of a gelatin capsule enables the filling and application of differ-

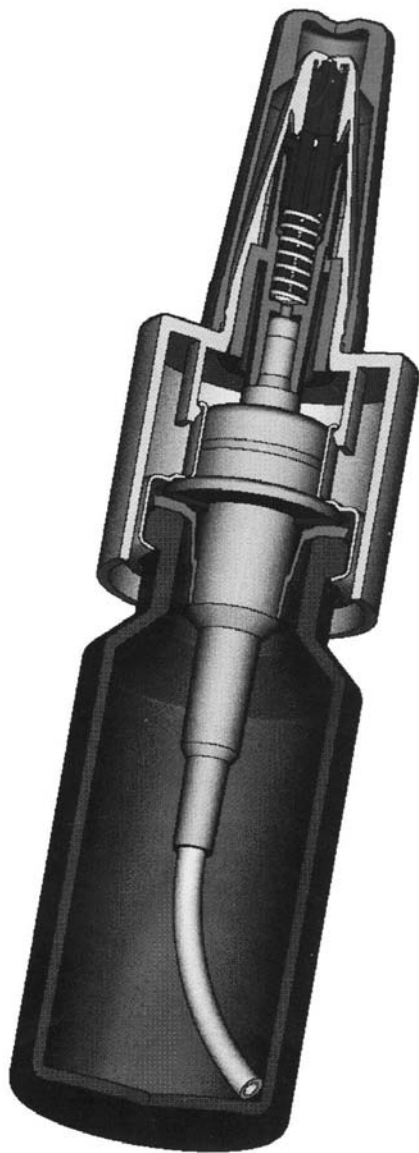


Fig. 4. Preservative free pump with air filter (Pfeiffer, Radolfzell, Germany).

ent amounts of powder. Previously the Rynachrom® insufflator was marketed by Fisons.

De Ascentiis et al. [37] standardized the powder delivery of a MIAT nasal insufflator device (MIAT S.p.A. Milan, Italy) by connecting it to a pressurized air reservoir and applying a pressure of 0.3 bar with an impulsion time of 0.2 s to investigate the influence of the carrier particle size on the emitted dose. It could be shown that the percentage of emitted dose for three different carriers increased

with particle size until it became constant between 100 and 300 μm . The recorded picture of the spray pattern of the powder also revealed the influence of particle size on insufflation behaviour.

4.2.2. Mono-dose powder inhaler

To ensure a high dose accuracy for intranasally applied powders the application by a mono-dose device, similar to a small unit-dose syringe, is possible. The particle size of the administered powder results from the drug particle size and the quality of deaggregation of the powder, which is determined by the mode of actuation.

With this device, a new development enables the application of freeze-dried powder, which can be lyophilized directly in the device (Fig. 5). Pushing a piston results in a precompression of the air in an internal chamber. Finally the piston pierces a membrane which separates the chamber from the lyophilized drug and the expanding air expels the substance into the nostril. The particle size of the administered powder and deposition in the nose is influenced by the physical characteristics of the freeze-dried powder due to the conditions during lyophilization and the force used to compress the device.

4.2.3. Multi-dose dry powder systems

To achieve a higher patient compliance with the nasal powder applicator some novel multiple-dose nasal powder delivery systems have been developed. The first commercially available multiple-dose nasal powder inhaler delivering the topical corticosteroid budesonide has been tested in a clinical trial by Malmberg et al. [38] (Fig. 6). In addition, a second multiple-dose powder device (Easyhaler®, Orion, Finland) has been introduced.

4.3. Pressurized MDIs

MDIs were primary used in pulmonary drug delivery and adapted to nasal use by changing the shape of the application device outlet. They are manufactured by suspending micronized drug particles in liquid propellants with the aid of surfactants.

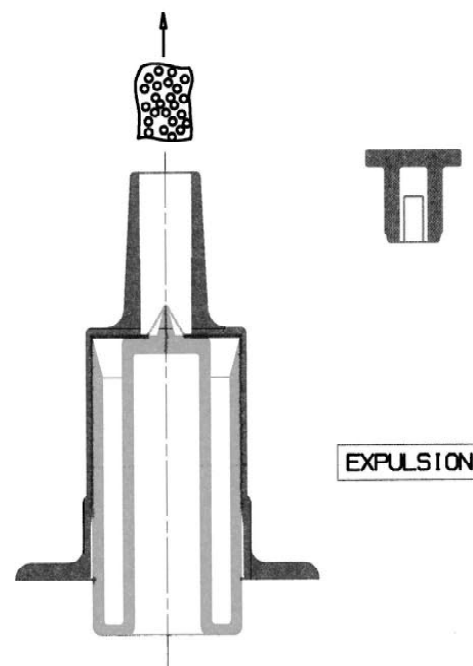
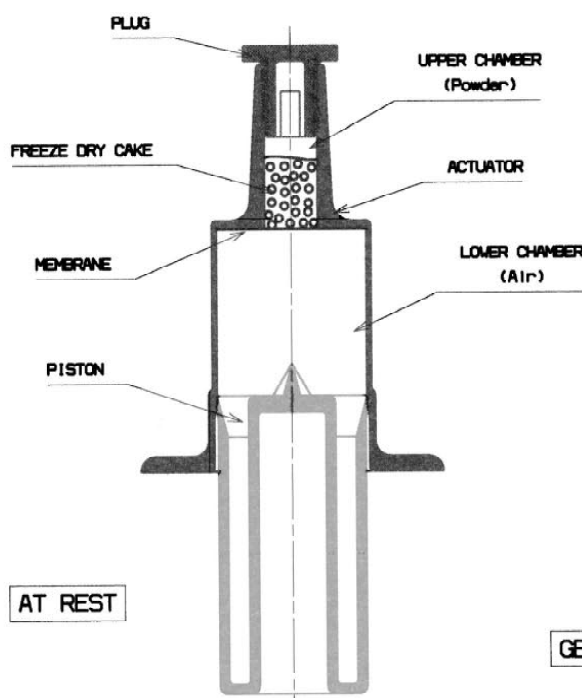
The physicochemical compatibility of the active ingredient and dispersing agents with the propellant must carefully be evaluated. The combination of different propellants will affect the vapor pressure



VALOIS
Division Pharmacie

LYPHODOSE

DESCRIPTION



GENERAL SKETCH FOR PRESENTATION ONLY

Fig. 5. Nasal mono-dose system for lyophilized powder (Lymphodose®, Valois S.A., Le Neuborg, France).

and the physical stability of the aerosol system. Phase separation, precipitation, crystal growth, polymorphism, dispersibility and adsorption properties of suspended drug particles have an influence on drug particle size, dose distribution and deposition pattern. They have to be investigated for each specific formulation.

The advantages of MDIs are their portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use [39]. The generation of aerosol from the pressurized MDI is independent of inhalation and can be delivered directionally. The disadvantages of MDIs include possible irritation by propellants and surfactants and malfunctioning in cold air. Propellants used in MDIs can irritate and dry mucous membranes [38,40]. In addition, propellants and

surfactants, such as sorbitan trioleate, have a decreasing effect on ciliary activity [41]. The irritating effect of a pressurized aerosol can also be due to a 'cold freon effect' as the spray is delivered to the nose from a short distance by a relatively high pressure, which leads to collision of aerosol droplets onto a narrow area of the mucosal layer [32].

The major drawback of these delivery devices is the depletion of the ozone layer by halogenated propellants (CFCs). CFCs contribute to the depletion of the earth's ozone layer. Therefore, in 1987 an international committee restricted their use and in the future CFCs have to be eliminated entirely. The replacement candidates for CFC propellants are hydrofluoroalkanes (HFA). However, the change to these propellants poses a lot of technological challenges and requires modifications as well as toxicological and clinical data.



Fig. 6. Multiple-dose dry powder inhaler (Turbohaler®, Astra Draco, Sweden).

4.4. Nasal gels

The use of nasal gels as carriers for systemically applied drugs has been investigated in order to prolong the contact time of the formulation on the nasal mucosa [42]. For experimental tests, formulations have been administered by means of a syringe [43]. In respect of the viscosity of the gel, pre-compression pumps, allowing accurate dosing, have been developed. Use for nasal administration requires a specially designed nasal adapter as an actuator.

The deposition of the gel in the nasal cavity depends on the mode of administration, because due to its viscosity the formulation has poor spreading abilities. Without special application techniques it only occupies a narrow distribution area in the nasal cavity, where it is placed directly. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market.

5. Characterization of nasal delivery devices

5.1. Determination of particle size distribution

Since the particle size of the applied or inhaled preparation has a major impact on nasal deposition of the formulation, the characterization of this parameter is important for the design and evaluation of the delivery device. Particle size distribution of active ingredients or the entire formulation can be determined before filling of the device, or after actuation as entire formulation. The results of the latter method are affected by the device and its deaggregation properties.

Particle size measurements can be carried out with commonly used methods such as sieving techniques [37], microscopy [44], Coulter counter measurements [34] or laser light-scattering systems.

The use of laser light-scattering systems based on Fraunhofer diffraction allows the measurement of the droplet size at the point where the formulation is sprayed out of the nozzle. Due to their aerodynamic size the particles vary their position in the expelled cloud, hence the distance from the tip of the nozzle to the laser beam has a major influence on the result of the measurement. Distances of 3–10 cm have been used with various delivery devices [33,45,46].

However, because the aerodynamic behaviour of inhaled particles depends not only on size but also on mass, additional measuring and determination methods based on inertial separation techniques should be used. These methods have mainly been carried out for the evaluation of pressurized MDIs and powder inhalers for pulmonary use. Different cascade impingers (Twin impinger, Multistage liquid impinger) or cascade impactors (Andersen impactor) can be chosen to determine the fine particle fraction of the delivered drug dose. Although the required particle size for nasal deposition varies with pulmonary demands, impactors are also useful in evaluating nasal dosage forms; instead of fine particles, it can be focused on particle sizes above 6 μm . The first three stages of the Andersen sampler collects particles in this size range, therefore this method has been used for the evaluation of a nasal powder inhaler [47]. Minor changes of available impactor constructions facilitate a more precise distribution. Yu et al. [48] used an impactor with cut-off diameters at 0.5, 1, 2, 4, 8 and 16 μm to differentiate

particle fractions of a metered-dose nasal spray. They included an additional glass chamber to classify a fraction $>16\text{ }\mu\text{m}$. The results have been compared to a measurement by laser holography and showed no significant difference. Hughes et al. [29] used an aerodynamic particle sizer (APS 3310, TSI, Inc., St. Paul, MN) to determine the mass medium aerodynamic diameter and the geometric standard deviations of a compressed air nebulizer, a nasal pump spray and a dry powder insufflator.

5.2. Methods to study deposition

Several studies have been carried out to measure the deposition in the nose and to evaluate the influence of different parameters. These investigations have gained importance not only for pharmacological applications but also for the assessment of environmental toxicology. There are two main issues investigated in deposition studies; the amount of deposited particles and the location of the deposition in the nose. With respect to these questions different methods have been applied.

5.2.1. Amount of deposition

In order to study the amount of deposition the difference between inhaled and exhaled particles has been determined using casts or *in vivo* studies.

The nasal deposition of ultrafine particles in the range of 0.005 to 0.2 μm has been investigated in casts from adults and children. Particles of monodisperse radiolabelled aerosols penetrating through the cast were collected in a membrane filter, in which radioactivity was determined [49]. A filter to catch silver and polystyrene latex particles before and after passage through the cast was also used by Cheng et al. [7,50]. Casts of human noses have been prepared on the basis of three-dimensional tomographic pictures [13] or post mortem [18,32]. The latter method often results in different airway geometries due to the post mortem shrinkage.

Compared to *in vivo* results, cast experiments quantitatively often underestimate deposition efficiency [51]. It has been assumed that natural surface irregularities, flow rate variations, intersubject differences or bioadhesion phenomena are possible explanations for this discrepancy. Therefore, the relation between the amounts of inhaled and exhaled particles have also been investigated in

humans by means of different filter techniques [19,52,53]. Recently Cheng et al. [6] have used pre- and postexposure measurement of polystyrene latex and silver particles by an ultrafine condensation particle counter. Larger particles in the range of 0.5–15 μm were counted by an aerodynamic particle sizer measuring the aerodynamic diameter and the particle number concentration [54].

The information given by these experiments facilitates an estimation of the deposited amount.

5.2.2. Location of deposition

Using casts as models provides information on the location of the deposition. In order to subsequently evaluate clearance mechanisms, additional noninvasive radiolabelling techniques have been applied. The use of gamma-scintigraphy is well known in medicinal and pharmaceutical studies. The location of radiolabelled material or drug substances in the body is followed by gamma-camera pictures. Only very seldomly can the drug substance itself be chemically radiolabelled. Usually the radionuclide technetium ($^{99\text{m}}\text{Tc}$) in combination with diethylenetriaminepentaacetic acid (DTPA), human serum albumin (HSA), teflon particles, sulfur colloid particles or as pertechnetate (TcO_4^-), is added as plain material or in combination with drug substances to administered preparations (Table 1).

Provided that the radionuclide is homogeneously distributed in the formulation and has no influence on particle size distribution of the preparation, the deposition and clearance of the drug substance and formulation is equated with the location of the followed radionuclide. In order to ensure these prerequisites Thorsson et al. [47] determined the aerodynamic particle size distribution of a reference powder and the radiolabelled preparation emitted from the powder inhalator by measurements with an Andersen sampler and a multi-stage liquid impinger. For liquid formulations the preparation of radiolabelled material mainly includes the addition of a $^{99\text{m}}\text{Tc}$ -compound in aqueous solution. Powder formulations require a different preparation technique. The radiolabelling method used by Illum et al. [34], Thorsson et al. [47] and Ridley et al. [55] included a freeze-drying step to eliminate the water in which $^{99\text{m}}\text{Tc}$ was added to the powder. Vidgren et al. [36] used a double-labelling technique to compare the clearance rates of plain drug particles labelled

Table 1
Nasal deposition studies with regard to different delivery devices

Ref.	Device	Method	Investigated parameter
Aoki and Crawley, 1976 [58]	Drops–pipette spray	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance: concentration, 3/30% HSA; application volume, 0.1–0.75 ml
Mygind and Vesterhauge, 1978 [32]	Squeezed bottle; pump spray; drop bottle; nebulizer	Plastic cast with dye (toluidine blue)	Deposition: application mode, inhalation air-flow (25, 50–70 l/min)
Unno et al., 1983 [63]	pMDI (pressurized metered-dose inhaler); capsule powder; insufflator	Plastic cast with moistened filter paper: analysis of drug content	Deposition: nasal geometry, inhalation air-flow (0.5–2 l/min)
Yu et al., 1983 [70]	Pump spray	Impaction spray pattern on TLC plate	Spray pattern, dose delivery
Lee et al., 1984 [59]	Pump spray	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance: pathology
McLean et al., 1984 [57]	Nebulizer squeeze bottle spray bottle pipette	Gamma-scintigraphy with pertechnetate	Deposition, clearance: application mode
Bond et al., 1985 [45]	Pump spray	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance: volume 0.05/0.1 ml; cone angle 30/60°
Hardy et al., 1985 [28]	Pump spray drops	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance: volume, 1/3 drops
Hallworth and Padfield, 1986 [64]	pMDI pump spray	Glass cast: analysis of drug content and amaranth dye	Deposition: inhalation air-flow (0/10 l/min)
Harris et al., 1986 [30]	Pump spray	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance, absorption: application mode
Illum et al., 1987 [34]	Pump spray; capsule; powder insufflator	Gamma-scintigraphy with ^{99}mTc -DTPA	Deposition, clearance: bioadhesive influence
Newman et al., 1987 [33]	Pump spray	Gamma-scintigraphy ^{99}mTc -teflon particles	Deposition, clearance: volume 0.05/0.1 ml cone angle 35/60°
Newman et al., 1987 [59]	Pump spray	Gamma-scintigraphy ^{99}mTc -teflon particles	Deposition, clearance: application mode
Newman et al., 1987 [66]	pMDI	Gamma-scintigraphy ^{99}mTc -teflon particles	deposition, clearance: application technique–inhaler position
Harris et al., 1988 [46]	Pump spray	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance: viscosity
Morén et al., 1988 [67]	Drops–pipette	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance: application technique
Pennington et al., 1988 [59]	Pump spray	Gamma-scintigraphy with ^{99}mTc -DTPA	Deposition, clearance: viscosity
Vidgren et al., 1991 [56]	pMDI capsule powder insufflator	Gamma-scintigraphy ^{99}mTc -DNCG	Deposition, clearance: application mode
Hughes et al., 1993 [29]	Nebulizer; pump spray; drops; powder insufflator	Gamma-scintigraphy with ^{99}mTc -sulfur colloid particles	Deposition, clearance: rhesus monkeys, application mode
Thorsson et al., 1993 [47]	Powder inhaler	Gamma-scintigraphy with ^{99}mTc	Deposition, clearance: inhalation air-flow (29.9/46.3 l/min)
Newman et al., 1994 [65]	Pump spray	Gamma-scintigraphy with ^{99}mTc -HSA	Deposition, clearance: volume 80–160 μl , inhalation air-flow (gentle/ vigorous)
Newman et al., 1995 [71]	pMDI pump spray	Gamma-scintigraphy with ^{99}mTc	Deposition, clearance: application mode
Ridley et al., 1995 [55]	Pump spray rhinyle catheter	Gamma-scintigraphy with ^{99}mTc -DTPA, ^{99}mTc -pertechnetate	Deposition, clearance: application mode bioadhesive influence

with ^{99m}Tc and bioadhesive microspheres labelled with ^{111}In . The formulations were prepared by spray drying of aqueous solutions of the drug mixed with the radionuclides.

6. Deposition and clearance

Pharmacological treatment for local or systemic action by the nasal route requires the knowledge of the formulation deposition in order to improve the efficiency of nasal medication. Several parameters in respect to the device or application technique have been investigated using different delivery devices (Table 2).

6.1. The relationship between clearance, deposition and delivery device

When evaluating the distribution of the formulation in the nasal cavity two different modes of deposition have to be considered: the initial deposition area directly after application and a secondary total deposition area due to the distribution by mucociliary clearance. While the initial deposition area determines the rate of mucociliary clearance, the total deposition area affects absorption rate by the covered mucosal surface.

The evaluation of a device by results of initial deposition may vary due to the subsequent distribution by the clearance mechanism. Hughes et al. [29] found nasal deposition rates of ^{99m}Tc –sulfur colloid particles in six rhesus monkeys by measurement of radioactivity. The coefficient of variation for the deposition values of each of the four different devices varies with regard to the time of the measurement (Table 2).

The comparison of a nasally applied dry powder inhaler (DPI) and a pressurized metered-dose inhaler (MDI) by Vidgren et al. [56] showed a tendency for

larger initial deposition after application of the DPI, but without significant difference. Due to more extensive spreading of the DPI-formulation after 15 min, the covered area of the DPI was significantly different.

Many studies reveal the influence of mucociliary clearance on secondary deposition area. However, the initial site of deposition has a major influence on clearance rates. Three different clearance phases following nasal delivery have to be distinguished [57]. The first phase within the first minute after application, mainly applicable for liquid formulations and large application volumes, is a very rapid clearance due to swallowing or run-through of the formulation into the pharynx. The following second phase occurring 15–30 min after application results from progressive clearance of the material deposited in the ciliated area of the main nasal passages. The part of the dose distributed in the non-ciliated far anterior part of the nose disappears very slowly, this clearance phase lasts over several hours. The second and third phases are responsible for the biphasic clearance pattern, observed in nearly every nasal deposition study. Depending on the initial partitioning of the formulation between the anterior non-ciliated and the posterior ciliated areas, the clearance rate and retained amount of the nasal dose can be determined.

The overall clearance of liquid formulations in healthy patients is approximately 30 min [28,33,58–60], with a relatively high variability due to deposition sites, physiological and environmental influences. Values in the range of 5–90 min have been measured by Aoki and Crawley [58]. Considering the biphasic clearance pattern the initial clearance rate is about 6–10 min while the secondary slower phase takes 75–580 min depending on the delivery device used. It was clearly evident that the clearance of sprays is much lower than the clearance of nasal drops [28,30,58,59]. While Hardy et al. [28] could

Table 2
Coefficient of variation (C.V.) for deposition values in rhesus monkeys ($n=6$)

Delivery device	C.V. initial deposition value (%)	C.V. deposition value after 30 min (%)
Instillation catheter	11	15
Compressed air nebulizer	17	29
Nasal pump spray	43	22
Dry powder insufflator	57	23

From Hughes et al., 1993 [29].

differentiate between spray and drops by the prolonged last clearance phase, Harris et al. [30] distinguished both delivery devices by the initial fast phase. The reason for this difference may be the site of deposition due to the administration techniques of the drop application in a sitting or in a supine position.

Several investigations have been carried out to prolong the contact time between the formulation and nasal mucosa by thickening nasally applied solutions with different polymers such as methylhydroxypropylcellulose, methylcellulose or gellan gum [46,61,62]. A tendency to decreased clearance rates with increasing concentrations of methylcellulose was seen after application of nasal sprays. However, there is an optimum concentration of methylcellulose after which a further increase of viscosity again results in a lower nasal retention time of the formulation [46]. It was assumed that the different clearance behaviour of the formulations may be due to the particle size of the sprayed viscous solutions which results in different deposition sites. The direct interrelationship between formulation, device and deposition is clearly evident in this investigation.

A more effective trial to lower the clearance rate was the nasal application of bioadhesive excipients. A comparison of three different sodium cromoglycate formulations distinguished between a clearance rate of 15 min for plain particles from a capsule powder insufflator as well as for a nasal solution used as a spray and a clearance rate of several hours for material applied in form of bioadhesive microspheres[34].

6.2. Influence of nasal air-flow

The influence of inhalation air-flow with regard to various nasal delivery devices has been investigated by cast and human experiments. A slow air-flow of 25 l/min and a sniff-like air-flow of 50–70 l/min have been applied by suction in a plastic cast to investigate the deposition of toluidine blue from various nasal delivery devices. Mygind and Vesterhauge [32] reported that deposition of the dye from pressurized MDIs was independent of the air-flow, while deposition of nebulizers differed with respect to various flow rates. Already deposited particles from a nebulizer could be moved far posteriorly by a

sniff-like suction. However, this phenomenon is highly dependent on the surface characteristics of the cast and may not be relevant in *in vivo* situations.

Other cast experiments with pMDIs confirm the independence of this delivery device of inhalation air-flow [63,64]. For a nasal pump spray a trend was seen that the formulation deposited more posteriorly if an air-flow of 10 l/min was applied. The particles from the pump spray achieved 370 cm/s [64], while particles expelled from pMDIs had a velocity of 5200 cm/s at a distant of 2 cm from the actuator tip [52]. Comparing the air-velocities of different devices, and taking into account that impaction is the main deposition mechanism in the nose, the different deposition behaviour becomes evident. However, in *in vivo* experiments deposition of a nasal pump spray was independent of inhalation flow-rate [65]. This discrepancy may be explained by different particle velocities achieved with the applied spray pumps, different administration modes and deviating nasal geometries.

Aiming for a maximal inspiratory flow, the mean nasal peak inspiratory flow-rate (PIF) of healthy humans is approximately 48 l/min with a wide interindividual variation of 20–85 l/min [47]. Deposition of a radiolabelled powder formulation delivered with a multi-dose dry powder inhaler was investigated in healthy subjects at two different inspiratory flow-rates (PIF 46.3 ± 6.8 l/min, duration 0.9 ± 0.1 s and PIF 29.9 ± 2.5 l/min, duration 1.6 ± 0.2 s). Total nasal deposition and deposition area after inhalation at these flow rates were not significantly different. There was a tendency to larger deposition areas at the maximal flow rate. However, the total nasal deposition in % of the dose was slightly higher for the lower air-flow [47]. Nuutinen et al. [40] reported a dose independence of a nasal multiple-dose powder inhaler above a very low air-flow of 5–10 l/min. In general the investigations show a very low inhalation air-flow dependence for the deposition of material from various devices which confirms the effective filter properties of the nose.

6.3. Influence of administration techniques

For some devices the direction during administration is of high importance. Mygind and Vesterhauge [32] noted that it is preferable to use the tested

nebulizer in two different directions to achieve a good distribution. McLean et al. [57] used the same device and emphasized that changing the direction in a 30° angle not only resulted in a different deposition, but also showed a 30% reduction of the emitted dose due to the technical construction of the device. Although Mygind and Vesterhauge [32] suggested that devices which result in a concentrated deposition of a single localized area, such as pMDIs, should be administered in two different directions this behaviour could not be confirmed in *in vivo* studies. Changing the holding angle of a pMDI by 30° does not result in a different deposition and clearance pattern compared to the double dose in a single position [64].

Especially in the application of nose drops, the mode of administration has a remarkable influence. The delivery of drops in a supine position with hyperextended head simply results in a rapid drainage of the formulation into the pharynx [31]. Mygind [31] gave an impressive illustration of correct and incorrect use of nasal drops. In order to ensure a good distribution he suggested to administer nasal drops in a supine position with the head tilted back. After application the head should be turned to the right side, the left side and again to the original position before the normal sitting position is assumed again. Each position should be held for 30 s. Following administration by this technique a good distribution through the whole nasal cavity was achieved [28]. Morén et al. [67] compared the procedure with another one in which the drops were administered with the head tilted back followed by two rapid inhalations. A significantly better distribution of the drops was seen with the first technique, although the total distribution in nasal cavity and pharynx was similar. But since the deposition especially in the anterior part of the nasal cavity contributes to the nasal absorption [30] the complicated technique must be preferred. The dependence of deposition and distribution of nasal drops on administration technique clearly demonstrates the advantage of spray devices especially for systemic treatment.

Also for microsphere formulations, the patient's position during and after application has an influence on clearance. The clearance rate for starch microspheres was lower when the subjects were in a supine posture compared to an upright position [55].

6.4. Influence of application volume and cone angle

The spray cone angle of the nasal adaptor determines the width of the spray pattern and hence the deposition area in the nasal cavity. Changing the cone angle from 60 to 35 or 30° resulted in a larger more posterior deposition area and a faster clearance rate of the formulation due to the higher deposition in the ciliated area [33,45]. Depending on the therapeutic aim the cone angle of the device should be chosen with regard to the deposition area. Aoki and Crawley [58] studied deposition and clearance of drop volumes between 0.1 and 0.75 ml. Surprisingly the application volume of the drops had no effect on the distribution and retention of the material. It must be assumed that volumes above 0.1 ml are too large to be retained on the nasal mucosa and excess solution is rapidly cleared after extensive coverage of the nasal cavity.

Newman et al. [33] compared 1×100 and 2×50 µl of a nasal spray administered in one nostril. The 100-µl volume resulted in a larger deposition area and its retention in the nasal cavity was lower due to the higher deposition rate in the more posterior ciliated zone. Application of 2×80 µl distributed in two nostrils covered a similar area to 140 µl in one dose [65]. Harris et al. [68] have concluded that, with regard to systemic nasal application of sprays, a smaller volume delivered into each nostril with a lower clearance rate must be preferred.

6.5. Influence of nasal abnormalities and diseases on deposition and clearance

Many parameters can be controlled in order to improve nasal deposition and clearance. However, there are various pathological conditions, such as cystic fibrosis, Kartagener's syndrome or Sjögrens syndrome, which have a decreasing effect on mucociliary clearance [69]. Lee et al. [59] investigated deposition and clearance following the application of a nasal pump spray in patients with nasal polyposis. Although the deposition pattern of the formulation was comparable to healthy subjects, probably resulting from the same nasal geometry in the first-third of the nasal cavity, clearance rates were extremely slower in the group of polyposis patients. While overall clearance of normal patients shows a

retention of 50% at 24–30 min after nasal application, the investigated patients had a retained nasal dose of about 80% after 80 min.

Many diseases are accompanied by an abnormally shaped nasal cavity. Due to the great influence of nasal geometry on deposition this results in a different efficacy of nasal delivery. Unno et al. [63] compared the deposition behaviour of a pressurized metered-dose inhaler and a capsule insufflator in three different nasal casts with a normal straight septum, a concave septum and hypertrophic turbinates, or a convex septum with atrophic turbinates. In the cast with concave septum and hypertrophic turbinates the pMDI showed an increased deposition in the vestibulum. In patients with this abnormality the DPI which is less affected by the different shape has to be preferred. Even a normal cold can change absorption behaviour due to varying clearance rates. Nasal congestion resulting in a slower clearance rate and the 'runny nose' with a very fast clearance are alternating phases during a common cold [45]. With the knowledge of the influence of these pathologies nasal application for systemic use has to be considered especially carefully.

7. Absorption and pharmacodynamic effect

So far only one study presents a direct relationship between deposition and clearance due to the application from different nasal devices, and subsequent absorption and biological response. Harris et al. [30] investigated the nasal absorption of desmopressin and its effect on circulating levels of antihemophilia factor FVIII using two metered-dose spray pumps with application volumes of 50 and 100 μl and nasal drops from a rhinyle catheter and a single-dose pipette. They clearly showed that the formulation delivered as spray deposited anteriorly in the nasal cavity resulting in a slow clearance, while the administration as drops led to a rapid clearance due to posterior deposition. The initial phase of the biphasic clearance pattern differentiates between application as spray and as drops. The clearance rate of 50% was achieved at 14 and 20 min for the drops from the pipette or rhinyle catheter, respectively. Furthermore half-lives of 120 and 240 min for the 200- and 100- μl sprays were obtained, respectively.

The resulting relative bioavailability of desmop-

ressin was 2–3-fold greater after application of the nasal spray compared to the application of drops. Within the different groups there was no significant difference in desmopressin plasma levels, although a tendency towards higher plasma levels with a high concentration of small-volume solutions was noticed. This corresponds to the investigations of Newman et al. [33] who showed that 100 μl of a nasal spray deposited over a larger area and more of the dose reaches the ciliated epithelium, so that the retention after 30 min was $46.5 \pm 4.4\%$ for the 100- μl spray compared to $57.1 \pm 4.5\%$ for the dosage of $2 \times 50 \mu\text{l}$ in one nostril. Harris et al. [68] also investigated the influence of concentration and application volume. Desmopressin (300 μg) was administered as 1×50 -, 1×100 - or 2×50 - μl doses from a nasal pump spray. The delivery of 50 μl in each nostril resulted in 2-fold higher bioavailability compared to the other administration techniques. Plasma levels were also significantly higher than they were after application of $2 \times 50 \mu\text{l}$ in only one nostril. In both studies the biological response reflected the absorption behaviour of desmopressin after different administration techniques. Peak response in Factor VIII activity differentiates between application as spray and drops with high significance. Also this biological effect clearly shows the superiority of nasal sprays compared to the use of drops in systemic nasal desmopressin delivery.

Newman et al. [65] determined blood glucose levels after four different administration modes from a nasal aqueous insulin spray. Different application volumes (80–160 μl) at gentle or vigorous inhalation air-flows did not result in different effects on blood glucose. This result was expected since nasal clearance was the same for the four administration techniques. However, the initial deposition area of the 80- μl volume with a lower dose of insulin was significantly smaller, but did not result in significantly higher blood glucose levels. It can be assumed that this effect is overlapped by large interindividual differences.

8. Conclusions

Nasal drug delivery has been intensively studied in order to improve and optimize both the formulation and the delivery device. Currently several options are

available for intranasal delivery of therapeutics either for local treatment of nasal disorders or for achieving systemic effects. Choosing the right drug delivery system and correct mode of administration, it is possible to adjust the deposition pattern and thereby optimize nasal absorption rate.

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