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Nasal delivery systems and their effect on deposition and absorption

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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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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 cm^2 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 cm^2) by the mean cross-sectional area (2.0–3.8 cm^2). 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 wether 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.

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