Nasal drug delivery for Chronic Rhinosinusitis: An Overview

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Abstract

Nasal delivery is the logical choice for topical treatment of local diseases in the nose and Paranasal sinuses such as allergic and non-allergic rhinitis and sinusitis. The nose is also considered an attractive route for needle-free vaccination and for systemic drug delivery, especially when rapid absorption and effect are desired. In addition, nasal delivery may help address issues related to poor bioavailability, slow absorption, drug degradation, and adverse events in the gastrointestinal tract and avoids the first-pass metabolism in the liver. However, when considering nasal delivery devices and mechanisms, it is important to keep in mind that the prime purpose of the nasal airway is to protect the delicate lungs from hazardous exposures, not to serve as a delivery route for drugs and vaccines. The narrow nasal valve and the complex convoluted nasal geometry with its dynamic cyclic physiological changes provide efficient filtration and conditioning of the inspired air, enhance olfaction, and optimize gas exchange and fluid retention during exhalation. However, the potential hurdles these functional features impose on efficient nasal drug delivery are often ignored. With this background, the advantages and limitations of existing and emerging nasal delivery devices and dispersion technologies are reviewed with focus on their clinical performance. The role and limitations of the in vitro testing in the FDA guidance for nasal spray pumps and pressurized aerosols (pressurized metered-dose inhalers) with local action are discussed. Moreover, the predictive value and clinical utility of nasal cast studies and computer simulations of nasal airflow and deposition with computer fluid dynamics software are briefly discussed. New and emerging delivery technologies and devices with emphasis on Bi-Directional™ delivery,

Keywords Drug delivery Nasal Device Paranasal sinuses Topical Systemic Vaccine Nasal valve Particle deposition Clearance

Introduction

Intuitively, the nose offers easy access to a large mucosal surface well suited for drug- and vaccine delivery. However, factors related to the nasal anatomy, physiology and aerodynamics that can severely limit this potential, have historically been challenging to address. The most recent FDA guidance for nasal devices provides detailed guidelines for in vitro testing of the physical properties such as in vitro reproducibility and accuracy of plume characteristics and dose uniformity of mechanical liquid spray pumps and pressurized metered-dose inhalers (pMDIs) for nasal use [1]. The guidance primarily addresses in vitro testing of nasal sprays and pressurized aerosols for local action. The reference to in vivo performance is limited to the recommendation of minimizing the fraction of respirable particles below 9 μm in order to avoid lung inhalation of drugs intended for nasal delivery. Thus, although important as measures of the quality and reliability of the spray pump and pMDI mechanics, these in vitro tests do not necessarily predict the in vivo particle deposition, absorption, and clinical response [2]. Furthermore, the guidance offers no or limited guidance on nasal products for systemic absorption and for alternative dispensing methods like drops, liquid jets, nebulized aerosol, vapors, and powder formulations. Finally, it does not address aspects and challenges related to the nasal anatomy and physiology that are highly relevant for the device performance in the position, need for coordination, and impact of airflow and breathing patterns at delivery.

The mechanical properties of different modes of aerosol generation are already well described in depth in a previous publication [3]. The anatomy and physiology of the nasal airway has also recently been summarized in an excellent recent review [4]. The aim of this paper is to take a step further by reviewing the characteristics of existing and emerging nasal delivery devices and concepts of aerosol generation from the perspective of achieving the clinical promise of nasal drug and vaccine delivery. Focus is put on describing how the nasal anatomy and physiology present substantial obstacles to efficient delivery, but also on how it may be possible to overcome these hurdles by innovative approaches that permit realization of the therapeutic potential of nasal drug delivery. Specific attention is given to the particular challenge of targeted delivery of drugs to the upper narrow parts of the complex nasal passages housing the middle meatus where the sinuses openings are located, as well as the regions innervated by the olfactory nerve and branches of the trigeminal nerve considered essential for efficient “nose-to-brain” (N2B) transport.

Nasal anatomy and physiology influencing drug delivery

Regulation of nasal airflow

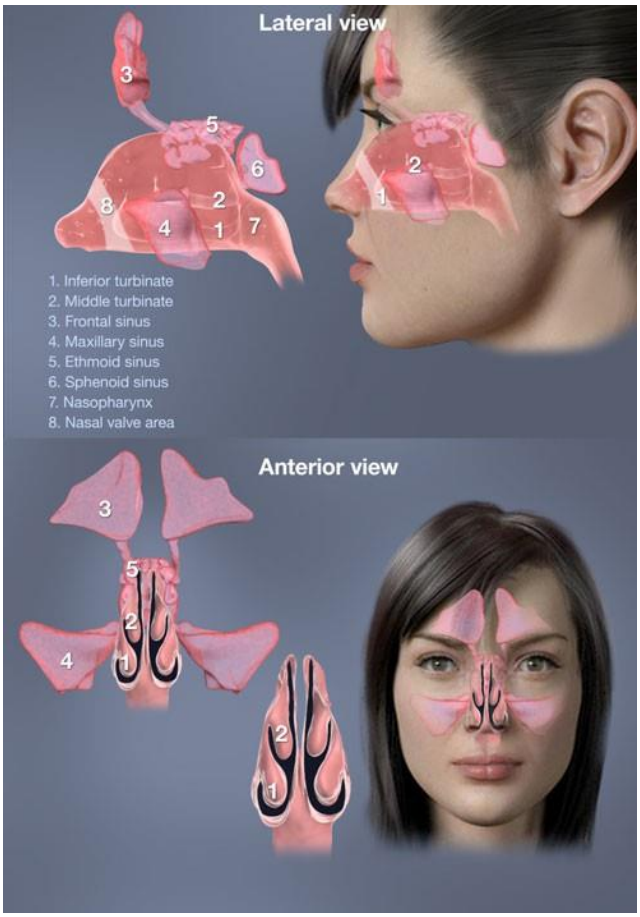
Nasal breathing is vital for most animals and also for human neonates in the first weeks of life. The nose is the normal and preferred airway during sleep, rest, and mild exercise up to an air volume of 20–30 l/min [5]. It is only when exercise becomes more intense and air exchange demands increase that oral breathing supplements nasal breathing. The switch from nasal to or nasal breathing in young adults appears when ventilation is increased to about 35 l/min, about four times resting ventilation [6]. More than 12,000 l of air pass through the nose every day [5]. The functionality of the nose is achieved by its complex structure and aerodynamics. Amazingly, the relatively short air-path in the nose accounts for as much as 50–75 % of the total airway resistance during inhalation [7, 8].

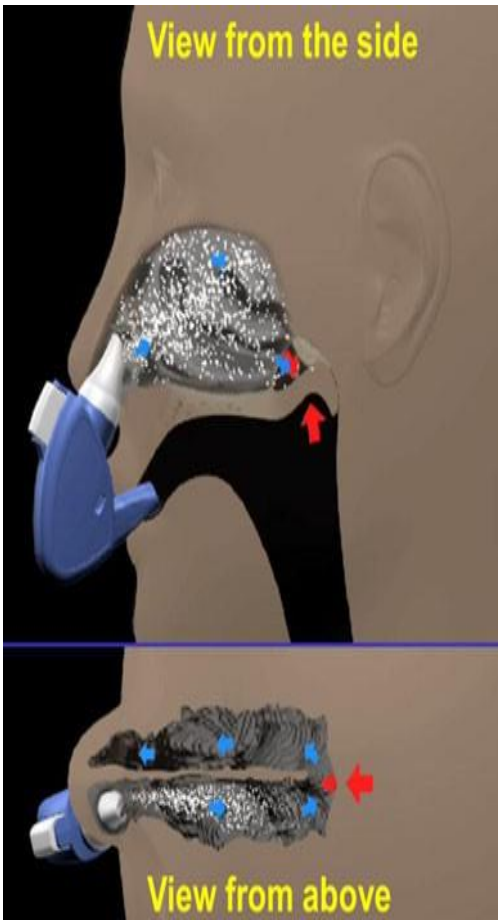
The nasal valve and aerodynamics

The narrow anterior triangular dynamic segment of the nasal anatomy called the nasal valve is the primary flow-limiting segment, and extends anterior and posterior to the head of the inferior turbinate approximately 2–3 cm from the nostril opening [9]. This narrow triangular-shaped slit acts as a dynamic valve to modify the rate and direction of the airflow during respiration [10, 11]. Anatomical studies de- scribe the static valve dimensions as 0.3–0.4 cm^2 on each side, whereas acoustic rhinometry studies report the functional cross-sectional area perpendicular to the acoustic pathway to be between 0.5 and 0.6 cm^2 on each side, in healthy adults, with no, or minimal gender differences [11–14]. The flow rate during tidal breathing creates air velocities at gale force (18 m/s) and can approach the speed of a hurricane (32 m/s) at sniffing [11, 15]. At nasal flow rates found during rest (up to 15 l/min), the flow regimen is predominantly laminar throughout the nasal passages. When the rate increases to 25 l/min, local turbulence occurs down- stream of the nasal valve [10, 11, 15]. The dimensions can expand to increase airflow by dilator muscular action known as flaring, or artificially by mechanical expansion by internal or external dilators [16, 17]. During inhalation, Bernoulli forces narrow the valve progressively with increasing inspiratory flow rate and may even cause complete collapse with vigorous sniffing in some subjects [5]. During exhalation, the valve acts as a “brake” to maintain a positive expiratory airway pressure that helps keep the pharyngeal and lower airways open and increase the duration of the expiratory phase. This “braking” allows more time for gas exchange in the alveoli and for retention of fluid and heat from the warm saturated expiratory air [4, 17, 18]. In fact, external dilation of narrow noses in obstructive sleep apnea patients had beneficial effects, whereas dilation of normal noses to “supernor- mal” dimensions had deleterious effects on sleep parameters [17]. However, in the context of nasal drug delivery, the small dimensions of the nasal valve, and its triangular shape that narrows further during nasal inhalation, represent important obstacles for efficient nasal drug delivery.

The nasal mucosa—filtration and clearance

The region anterior to the valve called the vestibule is lined by non-ciliated squamous epithelium that in the valve region gradually transitions into ciliated epithelium typical of the ciliated respiratory epithelium posterior to the valve region [4, 19]. Beyond the nasal valve, the nasal turbinates divide the nasal cavity into slit-like passages with much larger cross- sectional area and surface area (Figs. 1, 2 and 3). Here, the predominantly laminar airflow is slowed down to speeds of 2–3 m/s and disrupted with eddies promoting deposition of particles carried with the air at and just beyond the valve region [11]. The ciliated respiratory mucosa posterior to the nasal valve is covered by a protective mucous blanket designed to trap particles and microorganisms [4, 19].The beating action of cilia moves the mucous blanket towards the nasopharynx at an average speed of 6 mm/min (3–25 mm/min) [20, 21]. The large surface area and close contact enables effective filtering and conditioning of the inspired air and retention of water during exhalation (Figs. 1, 2 and 3). Oral breathing increases the net loss of water by as much as 42 % compared to nasal breathing [22].





The optimized during evolution to protect the lower airways from the constant exposure to airborne pathogens and particles.

Specifically, particles larger than 3–10 μm are efficiently filtered out and trapped by the mucus blanket [19]. The nose also acts as an efficient "gas mask" removing more that 99 % of water-soluble, tissue-damaging gas like sulfur dioxide [23]. Infective agents are presented to the abundant nasal immune system both in the mucous blanket, in the mucosa, and in the adjacent organized lymphatic structures making the nose attractive for vaccine delivery with potential for a longstanding combination of systemic and mucosal immune responses [24]. The highly vascularized respiratory mucosa found beyond the valve allows exchange of heat and moisture with the inspired air within fractions of a second, to transform cold winter air into conditions more reminiscent of a tropical summer [19].

The nasal cycle

The physiological alternating congestion and decongestion observed in at least 80 % of healthy humans is called the nasal cycle [5, 25]. The nasal cycle was first described in the rhinological literature by a German physician in 1895, but was recognized in Yoga literature centuries before [5]. Healthy individuals are normally unaware of the spontaneous and irregular reciprocal 1–4-h cycling of the nasal caliber of the two individual passages, as the total nasal resistance remains fairly constant [26]. The autonomic cyclic change in airflow resistance is mainly dependent on the blood content of the submucosal capacitance vessels that constitute the erectile component at critical sites, notably the nasal valve region. Furthermore, the erectile tissues of the septal and lateral walls and the turbinates respond to a variety of stimuli including physical and sexual activity and emotional states that can modify and override the basic cyclic rhythm [4]. The cycle is present during sleep, but overridden by pressures applied to the lateral body surface during recumbency to decongest the uppermost/contralateral nasal passage. It has been suggested that this phenomenon causes a person to turn from one side to the other while sleeping [5, 27]. The cycle is suppressed in intubated subjects, but restored by resumption of normal nasal breathing [28]. The cycle may also cause accumulation of nitric oxide (NO) in the congested passage and adjacent sinuses and contribute to defense against microbes through direct antimicrobial action and enhanced mucociliary clearance [29]. Measurements have shown that the concentration of NO in the inspired air is relatively constant due to the increase in NO concentration within the more congested cavity, which nearly exactly counterbalances the decrease in nasal airflow [30]. In some patients, as a result of structural deviations and inflammatory mucosal swelling, the nasal cycle may become clinically evident and cause symptomatic obstruction [19]. Due to the cycle, one of the nostrils is considerably more congested than the other most of the time, and the vast majority of the airflow passes through one nostril while the other remains quite narrow Consequently, the nasal cycle contributes significantly to the dynamics and resistance in the nasal valve region and must be taken into consideration when the efficiency of nasal drug delivery devices is considered.

Nasal and sinus vasculature and lymphatic system

For nasally delivered substances, the site of deposition may influence the extent and route of absorption along with the target organ distribution. Branches of the ophthalmic and maxillary arteries supply the mucous membranes covering the sinuses, turbinates, meatuses, and septum, whereas the superior labial branch of the facial artery supplies the part of the septum in the region of the vestibule. The turbinates located at the lateral nasal wall are highly vascularized with a very high blood flow and act as a radiator to the airway. They contain erectile tissues and arteriovenous anastomoses that allow shunting and pooling related to temperature and water control and are largely responsible for the mucosal congestion and decongestion in health and disease [19, 31].

Substances absorbed from the anterior regions are more likely to drain via the jugular veins, whereas drugs absorbed from the mucosa beyond the nasal valve are more likely to drain via veins that travel to the sinus cavernous, where the venous blood comes in direct contact with the walls of the carotid artery. A substance absorbed from the nasal cavity to these veins/venous sinuses will be outside the blood–brain barrier (BBB), but for substances such as midazolam, which easily bypass the BBB, this route of local "counter-current transfer" from venous blood may provide a faster and more direct route to the brain. Studies in rats support that a preferen- tial, first-pass distribution to the brain through this mechanism after nasal administration may exist for some, but not all small molecules [32, 33]. The authors suggested that this counter- current transport takes place in the area of the cavernous sinus– carotid artery complex, which has a similar structure in rat and man, but the significance of this mechanism for nasally delivered drugs has not been demonstrated in man [32, 33].

The lymphatic drainage follows a similar pattern as the venous drainage where lymphatic vessels from the vestibule drain to the external nose to submandibular lymph nodes, whereas the more posterior parts of the nose and paranasal sinuses drain towards the nasopharynx and internal deep lymph nodes [4]. In the context of nasal drug delivery, perivascular spaces along the olfactory and trigeminal nerves acting as lymphatic pathways between the CNS and the nose have been implicated in the transport of molecules from the nasal cavity to the CNS [34].

Innervation of the nasal mucosa

The nose is also a delicate and advanced sensory organ designed to provide us with the greatest pleasures, but also to warn and protect us against dangers. An intact sense of smell plays an important role in both social and sexual interactions and is essential for quality of life. The sense of smell also greatly contributes to taste sensations [35]. Taste qualities are greatly refined by odor sensations, and without the rich spectrum of scents, dining and wining and life in general would become dull [36]. The olfactory nerves enter the nose through the cribriform plate and extend downwards on the lateral and medial side of the olfactory cleft. Recent biopsy studies

in healthy adults suggest that the olfactory nerves extend at least 1–2 cm further anterior and downwards than the 8–10 mm described in most textbooks (see Figs. 1 and 2) [37, 38]. The density decreases, but olfactory filaments and islets with olfactory epithelium are found in both the anterior and posterior parts at the middle turbinate. In addition, sensory fibers of both the ophthalmic and maxillary branches of the trigeminal nerve contribute to olfaction by mediating a "common chemical sense" [39]. Branches of the ophthalmic branch of the trigeminal nerve provide sensory innervation to the anterior part of the nose including the vestibule, whereas maxillary branches inner- vate the posterior part of the nose as well as the regions with olfactory epithelium.

The olfactory and trigeminal nerves mutually interact in a complex manner. The trigeminal system can modulate the olfactory receptor activity through local peptide release or via reflex mechanisms designed to minimize the exposure to and effects of potentially noxious substances [39]. This can occur by alteration of the nasal patency and airflow and through changes in the properties of the mucous blanket covering the epithelium. Trigeminal input may amplify odorous sensation through perception of nasal airflow and at the chemosensory level. Interestingly, an area of increased trigeminal chemosensitivity is found in the anterior part of the nose, mediating touch, pressure, temperature, and pain [39]. Pain receptors in the nose are not covered by squamous epithelium, which gives chemical stimuli almost direct ac- cess to the free nerve endings. In fact, loss of trigeminal sensitivity and function, and not just olfactory nerve func- tion, may severely reduce the sense of smell [40]. This should not be forgotten when addressing potential causes of reduced or altered olfaction.

The sensitivity of the nasal mucosa as a limiting factor

In addition to the limited access, obstacles imposed by its small dimensions and dynamics, the high sensitivity of the mucosa in the vestibule and in the valve area is very relevant to nasal drug delivery. Direct contact of the tip of the spray nozzle during actuation, in combination with localized concentrated anterior drug deposition on the septum, may create mechanical irritation and injury to the mucosa resulting in nosebleeds and crusting, and potentially erosions or perforation [41]

high-speed impaction and low temperature of some pressurized devices may cause unpleasant sensations reducing patient acceptance and compliance.

The role of the high sensitivity of the nasal mucosa as a natural nasal defense is too often neglected when the potential of nasal drug delivery is discussed, in particular when results from animal studies, cast studies, and computer fluid dynamics (CFD) are evaluated. Exposure to chemicals, gases, particles, temperature and pressure changes, as well as direct tactile stimuli, may cause irritation, secretion, tearing, itching, sneezing, and severe pain [39]. Sensory, motor, and parasympathetic nerves are involved in a number of nasal reflexes with relevance to nasal drug delivery [4]. Such sensory inputs and related reflexes are suppressed by the anesthesia and/or sedation often applied to laboratory animals, potentially limiting the clinical predictive value of such studies. Further, the lack of sensory feedback and absence of interaction between

the device and human sub- jects/patients are important limitations of in vitro testing of airflow and deposition patterns in nasal casts and in CFD simulation of deposition. Consequently, deposition studies in nasal casts and CFD simulation of airflow and deposition are of value, but their predictive value for the clinical setting are all too often overestimated.

Methods of Delivery

Nasal drug delivery fluid dynamics is a rapidly growing area of intense research investigation. This high level of interest is directly tied to a number of commercial products, each with variable published experimental support. Studies on delivery methods have focused on the state of the para-nasal sinuses (non-operated vs. post-surgical) and the device dynamics (device, techniques, volume, position).

Nasal Surgery is a Prerequisite for Effective Sinus

Topical Drug Delivery

It is well established that the delivery of topical solution to the non-operated sinuses is very limited [6•]. Pressurized nasal spray provide only nasal cavity penetration at best, and squeeze bottle and Neti pot irrigation only provide some maxillary sinus and ethmoid sinus penetration [6•]. The frontal and sphenoid sinuses are essentially not accessible prior to surgery [6•]. Olson evaluated three methods of nasal irrigation in healthy non-operated individuals, and found distribution in the nasal cavity but poor distribution in the sinuses with all techniques [7]. With CRS, mucosal inflammation and edema further limit the penetration of nasal irrigation or sprays [8]. Grobler et al. showed that an ostial size of greater than 3.95 mm is required to see penetration into the maxillary sinus [9].

Endoscopic sinus surgery allows for more effective delivery of topical drugs, although the degree to which access is increased depends on the extent and technique of

even wider variability in the size of ‘‘post-surgical’’ sinus openings exists. This heterogeneity creates a confounding variable in determining the effectiveness of topical drug delivery in post-surgical sinus cavities. In Harvey’s cadaveric study, delivery to the sinuses improved after

Devices to Deliver Saline

There are a number of devices on the market for topical saline delivery into the nose and paranasal sinuses. They vary mainly in the volume and pressure of delivery (Table 1). Regardless of device or technique, penetration into the sinuses is very limited in non-operated sinuses [6•,

8, 9]. Two common high-volume techniques for delivery of nasal saline are the squeeze bottle (high pressure) and the Neti pot (low pressure). Large volume systems have been shown to have the best

efficacy in post-ESS cavities, with large volume high pressure devices being superior [6•, 9– 12]. Low volume devices, such as the pump spray (high pressure) or the nebulizer (low pressure), poorly penetrate the sinuses even after ESS [6•, 12]. Less than 50 % of most low volume devices reach the middle meatus [13]. Low volume systems should be considered a nasal cavity treatment because both pre- and post-surgical penetration into the sinuses is extremely poor.

Drug Delivery Devices

Nasal pump sprays are a popular option for topical drug delivery because of their ease of use, and many different formulations are available in this format. The main factors associated with particle penetration include the size of the sinus ostia, the size of the particle, and the flow rate of the aerosol [14, 15]. Particles [10 lm in size usually do not pass the nasal cavity, and particles \5 lm in size are needed to enter into the lungs. Hyoet al. theorized that ideal particle size for maxillary sinus penetration is between 3 and 10 lm, and further work by Saijo et al. demonstrated that smaller particle size (5.63 vs. 16.37 lm),

45 insertion angle (vs. 30 insertional angle), and higher flow rate improved maxillary sinus penetration [14, 16].

Typical nasal pump sprays generate droplets of 50–100 lm in diameter size, and deliver 70–150 ll of drug per puff, at standard velocities of 7.5–20 L/min [5]. A large fraction of the spray is deposited in the anterior nasal cavity without any significant penetration into the paranasal

Patient Positioning for Drug Delivery

There is no consensus on the most effective position for delivering topical drugs into the nose and paranasal sinu- ses. Many commercial products recommend a head-down, over-the-sink, or nose-to-ground position for nasal irriga- tion. This makes the residual runoff easy to collect and is practical for patients. The delivery of nasal drops relative to head position has been studied [13, 22]. One study found that the ‘‘Mygind’’ and ‘‘Ragan’’ (left lateral and supine) positions were more effective than the ‘‘Mecca’’ and

Head-back’’ positions for delivery into the middle meatus [22]. However, this has not been supported in other studies [13, 23–26]. Head-down or ‘‘vertex-to-floor’’ position has been suggested to lead to better frontal distribution post- ESS [27]. Positioning is more relevant for low-pressure delivery systems. For example, when using the neti pot, the Mygind head position allows for gravity-dependent drain- age into the contralateral nasal wall and sinuses. Posi- tioning with high-pressure delivery systems may have less clinical importance [5].

Drugs and Compounds

Saline

Saline irrigations and sprays are the most commonly used intervention for rhinitis and rhinosinusitis. Nasal saline has its roots in homeopathic medicine. Nasal washing is an ancient Ayurvedic technique known as ‘‘Jala neti’’, which means nasal cleansing in Sanskrit. Today, it is often used as an adjunctive treatment for chronic rhinos- inusitis. Its use has been advocated both before and fol- lowing sinus surgery, and in the latter case to thoroughly cleanse the Nasal passages and promote mucosal healing. Much of the support for this intervention has been anecdotal; however, recent literature has provided evidence to support the use of nasal saline for symptom improvement [28••].

Targeted nasal delivery

For most purposes, a broad distribution of the drug on the mucosal surfaces appears desirable for drugs intended for local action or systemic absorption and for vaccines [3]. However, in chronic sinusitis and nasal polyposis, targeted delivery to the middle and superior meatuses where the sinus openings are, and where the polyps originate, appears desirable [42, 43]. Another exception may be drugs intended for “nose-to-brain” delivery, where more targeted delivery to the upper parts of the nose housing the olfactory nerves has been believed to be essential. However, recent animal data suggest that some degree of transport can also occur along the branches of the first and second divisions of the trigeminal nerve innervating most of the mucosa at and beyond the nasal valve [44]. This suggests that, in contrast to the prevailing opinion, a combination of targeted delivery to the olfactory region and a broad distribution to the mu- cosa innervated by the trigeminal nerve may be optimal for N2B delivery. Targeted delivery will be discussed in more detail below.

Nasal drug delivery devices

comprehensive review from 1998 and will only be briefly described here, with focus instead on technological features directly impacting particle deposition and on new and emerging technologies and devices. Liquid formulations currently completely dominate the nasal drug market, but nasal powder formulations and devices do exist, and more are in development. Table 1 provides an overview of the main types of liquid and powder delivery devices, their key characteristics, and examples of some key marketed nasal products and emerging devices and drug–device combina- tion products in clinical development (Table 1).

Devices for liquid formulations

The liquid nasal formulations are mainly aqueous solutions, but suspensions and emulsions can also be delivered. Liquid formulations are considered convenient particularly for top- ical indications where humidification counteracts the dry- ness and crusting often accompanying

chronic nasal diseases [3]. In traditional spray pump systems, preserva- tives are typically required to maintain microbiological sta- bility in liquid formulations. Studies in tissue cultures and animals have suggested that preservatives, like benzalko- nium chloride in particular, could cause irritation and re- duced ciliary movement. However, more recent human studies based on long-term and extensive clinical use have concluded that the use of benzalkonium chloride is safe and well tolerated for chronic use [45]. For some liquid formu- lations, in particular peptides and proteins, limited stability of dissolved drug may represent a challenge [46].

Drops delivered with pipette

Drops and vapor delivery are probably the oldest forms of nasal delivery. Dripping breast milk has been used to treat nasal congestion in infants, vapors of menthol or similar substances were used to wake people that have fainted, and both drops and vapors still exist on the market (e.g., www.vicks.com). Drops were originally administered by sucking liquid into a glass dropper, inserting the dropper into the nostril with an extended neck before squeezing the rubber top to emit the drops. For multi-use purposes, drops have to a large extent been replaced by metered-dose spray pumps, but inexpensive single-dose pipettes produced by "blow-fill-seal" technique are still common for OTC prod- ucts like decongestants and saline. An advantage is that preservatives are not required. In addition, due to inadequate clinical efficacy of spray pumps in patients with nasal pol- yps, a nasal drop formulation of fluticasone in single-dose pipettes was introduced in the EU for the treatment of nasal polyps. The rationale for this form of delivery is to improve drug deposition to the middle meatus where the polyps emerge [47, 48]. some, their popularity is limited by the need for head-down body positions and/or extreme neck extension required for the desired gravity-driven deposition of drops [43, 49]. Compliance is often poor as patients with rhinosinusitis often experience increased headache and discomfort in head-down positions.

Delivery of liquid with rhinyle catheter and squirt tube

A simple way for a physician or trained assistant to deposit drug in the nose is to insert the tip of a fine catheter or micropipette to the desired area under visual control and squirt the liquid into the desired location. This is often used in animal studies where the animals are anesthetized or sedated, but can also be done in humans even without local anesthetics if care is taken to minimize contact with the sensitive mucosal membranes [50]. This method is, howev- er, not suitable for self-administration. Harris et al. [51] described a variant of catheter delivery where 0.2 ml of a liquid desmopressin formulation is filled into a thin plastic tube with a dropper. One end of the tube is positioned in the nostril, and the drug is administered into the nose as drops or as a "liquid jet" by blowing through the other end of the thin tube by the mouth [51]. Despite a rather cumbersome pro- cedure with considerable risk of variability in the dosing, desmopressin is still marketed in some countries with this rhinyle catheter alongside a nasal spray and a tablet for treatment of primary nocturnal enuresis, Von Willebrand disease, and diabetes insipidus.

Squeeze bottles

Squeeze bottles are mainly used to deliver some over-the- counter (OTC) products like topical decongestants. By squeezing a partly air-filled plastic bottle, the drug is atom- ized when delivered from a jet outlet. The dose and particle size vary with the force applied, and when the pressure is released, nasal secretion and microorganisms may be sucked into the bottle. Squeeze bottles are not recommended for children [3].

Metered-dose spray pumps

Metered spray pumps have, since they were introduced some four decades ago, dominated the nasal drug delivery market (Table 1). The pumps typically deliver 100 μl (25–200 μl) per spray, and they offer high reproducibility of the emitted dose and plume geometry in in-vitro tests. The particle size and plume geometry can vary within certain limits and depend on the properties of the pump, the formu- lation, the orifice of the actuator, and the force applied [3]. Traditional spray pumps replace the emitted liquid with air, and preservatives are therefore required to prevent contamination. However, driven by the studies suggesting possible negative effects of preservatives, pump manufac- turers have developed different spray systems that avoid the need for preservatives. These systems use a collapsible bag, a movable piston, or a compressed gas to compensate for the emitted liquid volume [3] (www.aptar.com and www.rexam.- com). The solutions with a collapsible bag and a movable piston compensating for the emitted liquid volume offer the additional advantage that they can be emitted upside down, without the risk of sucking air into the dip tube and compro- mising the subsequent spray. This may be useful for some products where the patients are bedridden and where a head- down application is recommended. Another method used for avoiding preservatives is that the air that replaces the emitted liquid is filtered through an aseptic air filter. In addition, some systems have a ball valve at the tip to prevent contamination of the liquid inside the applicator tip (www.aptar.com). These preservative-free pump systems become more complex and expensive, and since human studies suggest that preservatives are safe and well tolerated, the need for preservative-free systems seems lower than previously anticipated [45]. More recently, pumps have been designed with side-actuation and introduced for delivery of fluticasone furoate for the indication of seasonal and perennial allergic rhinitis [52]. The pump was designed with a shorter tip to avoid contact with the sensitive mucosal surfaces. New designs to reduce the need for priming and re-priming, and pumps incorporating pressure point fea- tures to improve the dose reproducibility and dose counters and lock-out mechanisms for enhanced dose control and safety are available (www.rexam.com and www.aptar.com). Importantly, the in vivo deposition and clinical performance of metered-dose spray pumps can be enhanced for some applications by adapting the pumps to a novel breath- powered “Bi-Directional™” delivery technology described in more detail below [13].

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