REVIEW ARTICLE

Recent Advancements in Nasal Drug Delivery Devices

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ABSTRACT

When it comes to external application for localized ailments of the paranasal sinuses and nose, like sinusitis rhinitis with allergic and non-allergic origins, nasal administration makes the most sense. Additionally, the nose is thought to be a desirable delivery mechanism for systemic drugs and needle-free vaccinations, particularly when quick absorption and effectiveness are required. Furthermore, while nasal administration circumvents the liver's first-pass metabolism, it may assist resolve issues related to low systemic availability, delayed intestinal absorption, drug destabilization, and GI adverse outcomes. However, it's crucial to remember that the nasal passage's primary function is to protect sensitive lungs since dangerous environmental factors, in order to avoid to act as a delivery system for medications as well as vaccinations, while thinking about nasal delivery mechanisms and devices. In addition to improving olfaction, optimizing the small nasal valve, along with the intricately complex nose structure and its cyclical and dynamic physiological change, facilitates effective conditioning and purification of inspired air, while also enabling exchange of gas and fluid retention occurring during exhalation. Nevertheless, such operational aspects possible obstacles to effective nasal medication delivery are frequently overlooked. In light of this, the benefits and drawbacks of both current and upcoming devices nasal transport as well as diffusion technologies are examined, by an emphasis upon how well they operate in clinical settings. The FDA guidance for nasal spray pumps and pressurized aerosols (pressurized metered-dose inhalers- pMDIs) intended for localized act is examined, along with the function and constraints of the in vitro testing. Furthermore, computer simulations of nasal airflow as well as deposition using nasal cast investigations have demonstrated their prognostic potential and clinical relevance. Software for computer fluid dynamics is briefly reviewed. More detail is provided on novel as well as developing drug delivery methods and devices, along a focus upon Bi-Directional TM delivery is an unique idea for nasal distribution which may be tailored toward a range of dispersion technologies.

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INTRODUCTION

It seems sense that the nose provides simple availability of a sizable mucosal layer that is ideal for the delivery of medications and vaccines. It has generally been difficult to address aspects of nasal structure, function, and airflow dynamics that may offer to significantly limit this capacity. The latest FDA recommendations for nasal devices offers comprehensive instructions. Testing is performed to evaluate the physical characteristics of liquid spray pumps which are mechanical and pressurized aerosol designed for in vitro nasal application, including their dose uniformity, reproducibility, and accuracy.[1] In vitro testing is conducted for the evaluation of pMDIs and nasal sprays intended aimed at localized effect which is important aim of the guidelines. The guideline to minimize the piece of respirable units under 9 μm is the only in-vivo performance that is mentioned. to prevent breathing in medications meant for nasal administration. Consequently, such in-vitro experiments may never always anticipate the in vivo distribution of particles, their uptake, and the corresponding clinical outcome, even if they are significant as indicators in relation to effectiveness as well as dependability of the spray pump and pMDI mechanics.[2] Additionaly, the guidelines provide little to absence of recommendations for nasal products intended for systemic absorption or on alternate ways of dispensing, such as liquid jets, powder formulations, drips, nebulized aerosol, as well as vapours. Lastly, it ignores issues and problems pertaining to the anatomy and physiology of the nose that are crucial to understanding how well the device works in a therapeutic situation. These include body posture, the necessity for coordination, and the influence of breathing patterns and airflow during delivery. The mechanical characteristics of various aerosol production methods are already thoroughly covered in an earlier publication.[3] A good. study was published lately that summarizes the structure and function of the nasal passage.[4] By examining the features of current and new nasal delivery devices as well as aerosol generation methods, this research seeks to go one step further in realizing the therapeutic potential of nasal medication and vaccine delivery. The article focuses upon explaining how the structure and function of the nose pose significant

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barriers to effective delivery, but it also discusses potential creative solutions that could enable the medicinal promise of nasal drug delivery to be realized. Particular focus is placed on the unique problem of targeted delivery of medications to the areas innervated through the olfactory nerve and its trigeminal branches that are thought to be necessary for effective "nose-to-brain" (N2B) transport, along with the upper constricted sections of the intricate nasal pathways that house the middle meatus, wherever the openings of the sinuses are situated.

Anatomy and physiology

Regulation of nasal airflow

For the majority of animals, including human newborns in their first few weeks of life, nasal breathing is essential. At an airflow volume of 20-30 liters per minute, the nose serves as the primary and preferred airway during light exercise, rest, and sleep.[5] Oral breathing only serves to support nasal breathing as exercise intensifies and air exchange demands rise. An increase in ventilation to about 35 liters per minute, equivalent to four times the resting ventilation, occurs when, young people begin to breathe via their mouths instead of their noses.[6] Every day, the nose filters through more than 12,000 litters of air.[5] The intricate structure of nasal cavity and aerodynamics enable its functionality (Figure1).[7] Remarkably, as much as 50–75 percent can be attributed to the comparatively compact nasal air channel.[8]

The nasal valve and aerodynamics

The slender anterior triangular dynamic section serves as the main flow-limiting structure of the nasal anatomy,

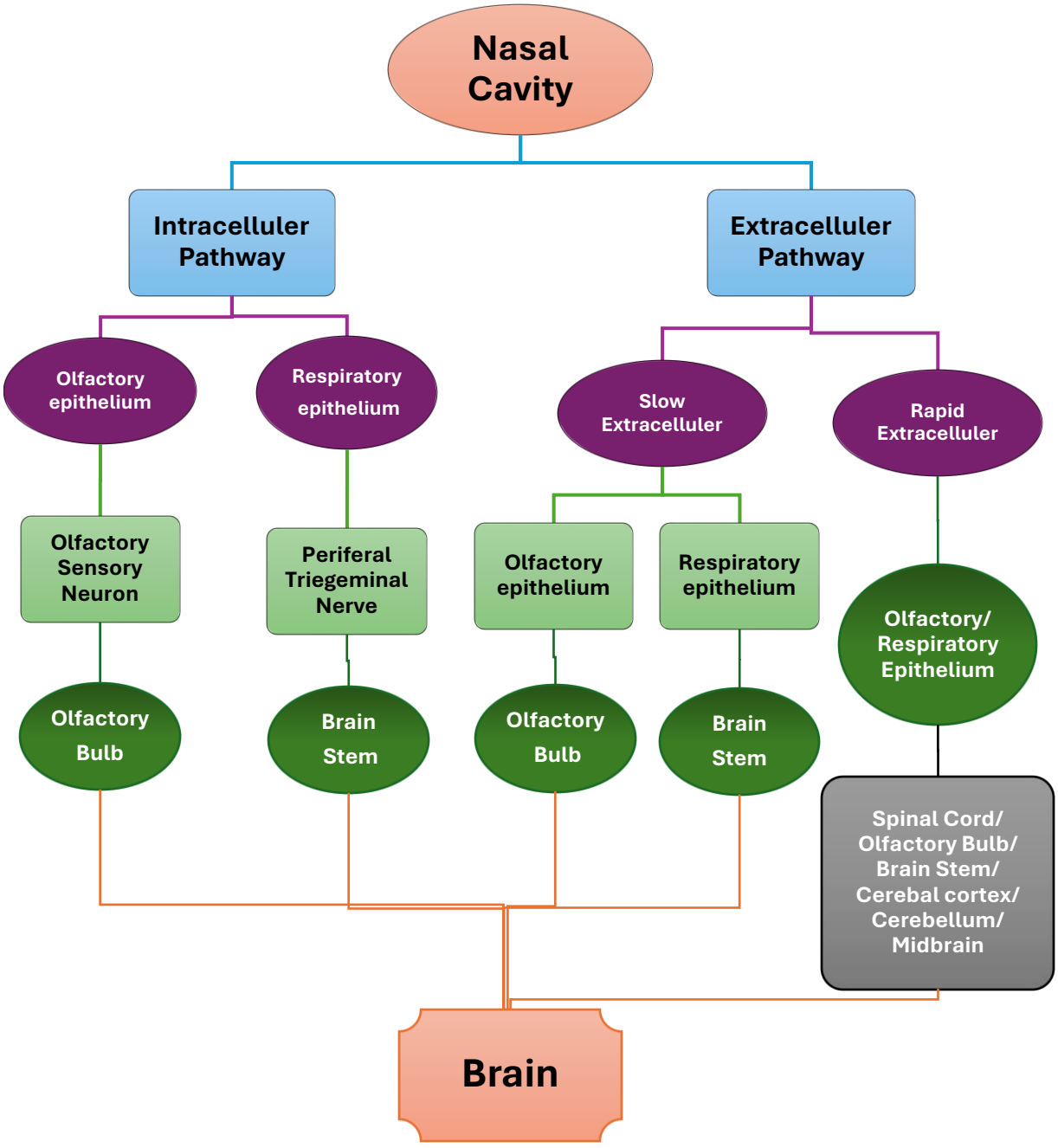

Figure 1: Structure and pathways of nasal cavity

spanning about 2 to 3 centimeters from opening of the nostril and surrounding the inferior turbinate's head both anteriorly and posteriorly is valve.[9] During respiration, serving as a dynamic valve to adjust both the direction and pace of airflow, the small, triangular-shaped slit plays a crucial role.[10,11] In healthy adults, the functional cross-sectional area measured perpendicularly to the auditory passage is reported by acoustic rhinometry studies to range ranging from 0.5 to 0.6 cm^2 on either side, showing minimal gender variations observed. Meanwhile, anatomical studies indicate that the measurements of static valve are approximately 0.3–0.4 cm^2 on both sides.[11–14] Air velocities created by tidal breathing can reach gale force (18 m/s) due to flow rate. the hurricane's speed (32.2 m/s) at sampling.[11,15] The passage ways of nose exhibit a primarily laminar flow regimen at resting nasal flow rates, which can reach up to 15 liter per minute. Localized flow disruption develops downstream of the nasal valve at a rate of 25 l/min.[10,11,15] The dimensions can be intentionally expanded by mechanical expansion using internal or external dilators, or they can be expanded by dilator muscle action, also known as flare, to enhance airflow.[16,17] With increased inspiratory flow rate while inhaling, the valve is gradually narrowed by Bernoulli forces, and in certain patients, strong sniffing may even cause full collapse.[5] The valve functions as a "brake" that maintains +ve pressure during expiration, keeping the both lower as well as pharyngeal airways open during exhalation as well as prolonging the time taken for the expiratory phase. This "braking" mechanism permits the alveoli additional gas exchange timeline and helps retain the fluid and warmth from the humidified exhaled air.[4,17,18] Externally dilating slender nasal structures in people suffering from obstructive sleep apnea really improved sleep metrics, but dilatation of normal noses to "supernormal" dimensions had the opposite effect.[17] Nonetheless, the nasal valve's small size and triangular shape—which narrows even more during nasal inhalation-represent significant barriers to effective nasal medication administration in this situation.

Filtration and clearance: nasal mucosa

Situated anterior to the valve, the vestibule is covered with non-ciliated squamous epithelium that slowly changes to ciliated epithelium at the valve area, which is representative of the ciliated respiratory epithelium found further back.[4,19] Situated Past the nasal valve, the nasal turbinates partition the nasal passage in the narrow channels, significantly increasing both surface area and cross-sectional area. In this context, the principally stagnant airflow is reduced upto 2-3 m/s and becomes turbulent due to eddies, which facilitate the deposition of airborne particles as well as slightly above the valve region.[11] Covering the ciliated respiratory mucosa located posterior to the nasal valve is a layer of mucus intended to capture particles as well as bacteria.[4,19] The mucous blanket's striking motion is moved by cilia at a rate of 6 millimeters per minute on average (3–25 mm/min).[20,21] The inspired air undergoes effective filtering and conditioning by the huge surface area and intimate contact, which also helps retain water during exhalation. When compared to nasal breathing, oral breathing might result in a 42% increase in net water loss.[22] In order to shield the lower respiratory tract to the continual contact with airborne contaminants also diseases, the nose passages were adapted during evolution. In particular, the mucus blanket effectively filters out and traps particles larger than 3–10 μm.[19] Additionally, the nose functions as a powerful "gas mask," eliminating almost 99% of gases that damage tissue and are soluble in water, such as sulfur dioxide.[23] The nose is an ideal site for vaccine delivery due to its abundant exposure to infectious agents and the presence of the nasal immune system, including the mucous layer, mucosa, and organized lymphatic structure. This system has capacity to provide a sustained mix of mucosal and systemic immune responses.[24] Located beyond the valve, the richly vascularized respiratory mucosa quickly replaces moisture as well as heat with the inhaled air, transforming frigid winter air into an atmosphere akin to a tropical summer in just a matter of seconds.

The nasal cycle

It is physiologically induced alternating decongestion and congestion that at least 80% of healthy adults experience.[5,25] First documented in 1895,by a German Physician in, the nasal cycle had already been acknowledged in Yoga literature centuries earlier.[5] Since the total nasal resistance stays relatively constant, fit persons typically oblivious of the impulsive as well as the irregular, alternating cycling of the nasal caliber in the 2 different airways, occurring every 1-4 hours.[26] The main determinant affecting the autonomic cyclic variation in airflow opposition is the content of blood inside the submucosal capacitance vessels, which serve as the erectile component in critical areas, particularly in the nasal valve region. Additionally, the turbinates, lateral walls, and septal erectile tissues react to a range of stimuli that have the power to alter and override the fundamental cyclic rhythm, such as sexual and physical activity.[4] It has been suggested that the phenomenon of turning from one side to the other during sleep results from the pressures exerted on the lateral body surface in a recumbent position, which clear the uppermost or contralateral nasal passage, surpassing the cycling that occurs during sleep.[5,27] When a patient is intubated, the cycle is repressed; nevertheless, it is reestablished when normal nasal breathing resumes.[28] Through improved mucociliary clearance and direct antibacterial action, an build-up of nitric oxide (NO) in the blocked tube as well as adjacent sinuses may also result from this cycle, which aids in the body's defence against microorganisms.[29] The results of measurements indicate that the amount of NO in the Because the higher NO concentration in the more crowded cavity almost perfectly offsets the lower nasal airflow, inspired air is comparatively constant.[30] In certain cases, nasal cycle can change into clinically noticeable as we as result in symptomatic blockage because of structural abnormalities and inflammatory mucosal edema.[19] Due to this cycle, 1 nostril is often more obstructed than the alternative, leading to the majority of airflow goes over one nostril though the other stays relatively narrow, particularly on the valve area.[5] As a result, while evaluating the effectiveness of nasal drug delivery systems, the nasal cycle must be taken into account because it greatly influences the behavior and opposition encountered in the nasal valve zone.

Nasal as well as sinus vasculature and lymphatic system
When drugs are administered via the nose, the location of deposition can affect the distribution of the target organ as well as the rate and mode of absorption. The portion of the septum in the vestibule region is supplied by the facial artery's superior labial branch, while branches from ocular as well as maxillary arteries provide blood to the mucosal tissues that cover, turbinates, sinuses, septum, as well as meatuses. Serving as a radiator for the airway, the turbinates situated upon the lateral nasal wall possess a rich blood supply and are highly vascularized. They primarily regulate congestion and decongestion in both healthiness and illness due to their erectile tissues as well as arteriovenous anastomoses, which facilitate diversion and accumulation associated with water along with temperature regulation.[19,31]

Materials taken up from the anterior, primarily directed into veins leading to the cavernous sinus, medications absorbed through the mucosa beyond the nasal valve come into close proximity with the carotid artery walls. Conversely, other regions typically drain through the jugular veins. Chemicals that enter these venous sinuses or veins from the nasal cavity generally cannot cross the "Blood-Brain-Barrier" (BBB). Nonetheless, materials like midazolam, that readily penetrate the "BBB", may take advantage of this local "counter-current transfer" from venous blood, providing a quicker as well as more direct pathway toward brain. According to research on rats, this mechanism may allow certain small compounds, though not all, to preferentially distribute to the brain after nasal administration.[32,33] This counter-current transport occurs in the cavernous sinus–carotid artery complex, that has comparable structures in

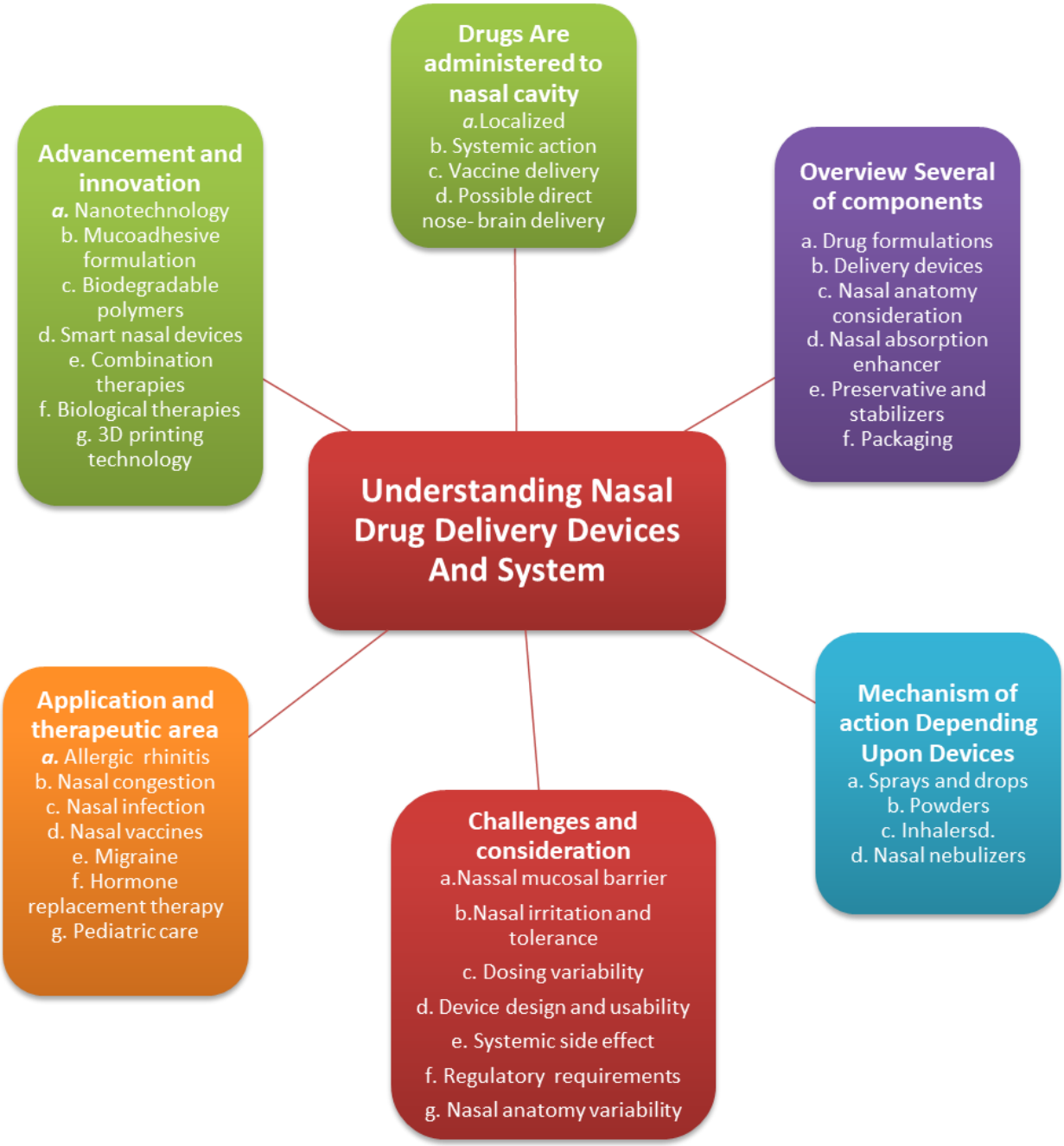

Figure2: Understanding nasal drug delivery devices and system

both rats as well as humans, according to author. However, evidence supporting the relevance of this process for nasal drug delivery inside humans is lacking.[32,33] Traveling towards the outer nose and the submandibular lymph nodes, lymphatic drainage closely resembles the pattern of venous drainage, particularly from the vestibule. Conversely, the more posterior parts of the nose as well as paranasal sinuses direct their drainage into the nasopharynx and internal deep lymph nodes.[4] The perivascular places surrounding the olfactory nerves as well as trigeminal nerves act as lymphatic ways connecting the central nervous system to the nasal cavity, facilitating the transfer of drugs during nasal medication administration.[34]

Nasal mucosa innervation

In addition to offering us the greatest joys, the nose is a highly developed and delicate organ of sensation that may warn and protects from harm. A well-functioning smelling sense is vital to one's quality of life and plays a significant part in social and sexual interactions. Taste perceptions are also significantly influenced by the sense of smell.[35] Odor perceptions substantially refine taste attributes; without the wide variety of Odors, life would be boring, especially when dining and entertaining.[36] The cribriform plate allows the olfactory nerves entering the nasal passages. They then extend downward on the medial and lateral sides of the olfactory cleft. The olfactory nerves seem to cover as a minimum 1-2 centimetre, based on recent biopsy findings tests conducted on fit adults. more anteriorly and subsequently than the 8–10 mm that are typically reported in textbooks.[37,38] Anterior and posterior areas of the middle turbinate contain olfactory filaments and clusters of olfactory epithelium, although their density decreases in these regions. Moreover, sensory fibers from The ophthalmic and maxillary divisions of the trigeminal nerve play a role in the sense of smell by mediating what is known as a 'common chemical sense.[39] The vestibule and the front portion of the nose are sensory regions innervated by divisions of the trigeminal nerve's ophthalmic branch, whereas the posterior portion of the nose and its olfactory epithelium are innervated by branches of the maxillary branch. There is intricate mutual interaction between the trigeminal and olfactory nerves. Trigeminal system modulation of the olfactory receptor activity by reflex processes intended to minimize contact to and impact of potentially harmful chemicals or by local peptide release.[39] This can happen through modifications to the mucus layer coating the epithelial surface, as well as adjustments to nasal patency and airflow. Trigeminal contribution has the power to increase olfactory perception by means of nasal airflow perception and chemosensory activation. It's interesting to note that the nose's anterior region, responsible for mediating touch, pain, pressure, along with temperature, exhibits increased chemosensitivity of the trigeminal nerve.[39] Because the squamous epithelium covering the nasal pain receptors is absent, chemical stimuli have nearly unrestricted admission to the free nerve endings. Indeed, diminution of olfactory nerve role alone may never be the exclusive cause of trigeminal sensitivity and function loss. drastically impair one's ability to smell.[40] While dealing with possible reasons related to decreased otherwise changed olfaction, this should not be overlooked.

Nasal mucosa sensitivity: A key limiting factor

The vestibule and valve mucosa exhibit a heightened sensitivity areas significantly influences nasal drug distribution, compounded by the limitations dictated by its limited size and dynamic characteristics. Additionally, the spray nozzle tip's direct contact during activation, along with localized drug deposition at the septum's anterior region, has the potential to induce mechanical irritation and damage, potentially resulting in nosebleeds, crusting, and even erosions or perforations.[41] Additionally, some pressured devices can provide discomforting feelings that lower patient consent and adherence due to their accelerated impaction and cool conditions. When exploring the potential of nasal drug delivery, all too often, the remarkable mucosal susceptibility, which functions as an innate protective mechanism, is disregarded. especially whenever the outcomes for research using casts, animals, as well as computer fluid dynamics (CFD) are assessed. Sneezing, itching, secretion, tearing, irritation, and excruciating pain can result from direct tactile stimulation, along with changes in temperature and pressure, as well as contact with chemicals, gases, and particles.[39] Many nasal reflexes related to nasal medication administration are facilitated by sensory, motor, as well as parasympathetic nerves.[4] The anaesthesia and/or sedation frequently used on experimental animals suppresses these sensory inputs and associated reflexes, which may reduce the study' clinical predictive value. The absence of sensory responses also interaction between the device and individuals limits the in vitro evaluation of airflow along with deposition forms in nasal casts, in addition to the CFD simulations of these processes. Consequently, although CFD simulations and deposition studies in nasal casts provide valuable insights, their predictive relevance for clinical scenarios is often exaggerated.

Targeted nasal delivery

For the most part, medications meant for systemic absorption or local action, as well as vaccinations, a wide drug dispersion on the surfaces of mucosa seems preferable.[3] Targeted delivery to the middle and superior meatuses, which contain both sinus apertures as well as origin of the polyps, seems preferable in cases of chronic sinusitis and nasal polyposis.[42,43] Medication meant for "nose-to-brain" administration might be an additional exception. In this case, it has been thought that more precise delivery towards nose areas that house the olfactory neurons is crucial. Recent animal research, however, indicates that a certain movement amount may too happen with 1st as well as 2nd divisions of trigeminal nerve's branches, which innervate focus is on the mucosa on besides beyond the nasal valve.[44] It indicates, contrary to popular belief, the best way to distribute N2B may be to combine broad coverage of the mucosa innervated by the trigeminal nerve, coupled with focused delivery to the olfactory area.

Nasal drug delivery devices

Vidgren as well as Kublik provided a thorough review regarding the processes involved in particle generation for

the diverse categories of nasal aerosols; these details and principles will only be briefly discussed here, with the main emphasis being regarding novel and developing technologies and devices as well as technological features that directly affect particle deposition. Although nasal powder formulations and devices are already available, with additional options being developed, liquid formulations currently hold a monopoly in the nasal medication industry. Figure 2 gives a summary of the powder as well as liquid delivery devices, salient features of them, applications, challenges, mode of action as well as new and developing devices and drug-device combinations that are undergoing clinical trials.[3]

Devices for liquid formulations

Although suspensions and emulsions can also be administered, aqueous solutions make up the majority of the liquid nasal formulations. Mainly for localized purposes wherever humidification mitigates both crusting as well as dryness that frequently accompany chronic nose disorders, liquid formulations are thought to be convenient.[3] Preservatives are usually needed in classic spray pump systems to keep liquid formulations microbiologically stable. Studies on animals and tissue cultures have revealed that preservatives, particularly benzalkonium chloride, may irritate the cilia and impair their motility. Nonetheless, more recent human research with substantial and long-term clinical use has determined that Benzalkonium chloride has proven to be safe and well-tolerated for extended periods.[45] Restricted drug stability after dissolution might pose a problem for certain liquid formulations, especially those containing peptides and proteins.[46]

Rhinyle catheter also squirt tube for liquid delivery

A doctor or trained assistant can easily dispense medication into the nose by visually controlling the target spot and squirting the liquid there with micropipette tip or small catheter tip. This is possible on humans despite lacking localized anaesthetics although precautions are made to prevent connection to the delicate mucosal membranes. It is frequently employed in animal research where the animals are sedated or anesthetized.[47] Still, self-administration is not a good use for this strategy. A variation on catheter delivery was reported by Harris et al,[48] in which a slim plastic tube fitted by a dropper is filled with 0.2 ml of a liquid preparation of desmopressin. The position of tube is within the nostril at one end as well as the medication is exhaled by the tiny tube's opposite end using mouth, either as drops or as a "liquid jet" into nose.[48] Desmopressin is also available in some countries in the form of a rhinyle catheter, together with a tablet and spray, for the cure of diabetes insipidus, Von Willebrand illness, along with primary nocturnal enuresis, despite being a very laborious process with a significant risk of fluctuation in the dosage.

Drops delivered with pipette

The first nasal administration methods are most likely drops and mist. Menthol vapors and similar compounds were historically employed to revive individuals who had fainted, and both drops and vapors remain commercially available today (e.g., www.vicks.com). Breast milk dripping has been utilized as a remedy for nasal congestion in infants. Initially, drops were given by using a glass dropper to suck liquid, positioning so as to insert the dropper into the nostril while tilting the head back, press down on the rubber top to release the drops. Metered-dose spray pumps have largely occupied the position of drops for multi-use applications; but, low-cost single-dose pipettes made using the "blow-fill-seal" method remain widely used for over-the-counter medications like saline and decongestants. The lack of need for preservatives is a benefit. Furthermore, because of Due to the spray pumps' insufficient clinical effectiveness in treating patients with nasal polyps, the EU introduced fluticasone nasal formulations in unit dose pipettes for the patient with nasal polyps. This method is justified by the desire to enhance medication deposition to the middle meatus, the site of polyp emergence.[49,50] Drops are effective for certain people, but their popularity is restricted since to achieve optimal gravity-driven drop deposition, patients require head-down body positions and/or significant neck extension.[43,51] Because rhinosinusitis patients frequently have greater headache and discomfort when lying head-down, compliance is frequently poor.

Metered-dose spray pumps

Since their introduction around forty years ago, dominating the nasal delivery market, metered spray pumps have become the standard. In in vitro studies, the pumps provide remarkable repeatability for emitted dose along with plume geometry, typically delivering 100 µl (25–200 µl) every spray. Particle size as well as plume shape are subject to variation within predetermined bounds and are determined using formulation, pump characteristics, actuator aperture, as well as applied force.[3] are necessary in conventional spray pumps because the liquid they release is replaced Preservatives with air. This leads to contamination. Nonetheless, pump manufacturers have created several preservative-free spray systems due to studies indicating potential adverse effects of preservatives. These devices make use of a foldable bag, a pressurized gas to make up for the volume of liquid released, or a moving piston.[3] In added benefit of using a collapsible bag also adjustable piston for controlling ejected liquid volume is their functionality when used upside down, without the risk of air entering the dip tube, preserving the spray consistency. It represents helpful for some products wherever a head-down application is advised and the patients are bedridden. An aseptic air filter is used to filter the air which displaces the expelled liquid, which is another way to avoid using preservatives. Furthermore, certain systems feature a ball valve at the tip to stop the liquid inside the applicator tip from becoming contaminated. Pump without preservatives free systems don't seem to be as necessary as previously thought, as systems get more sophisticated and costly, studies conducted on humans demonstrate that preservatives are regarded as safe and well-accepted.[45] In recent times, side-actuation pumps have been developed and released to administer fluticasone furoate for the diagnosis of both ongoing as well as seasonal allergic rhinitis.[52] The design of the pump's shorter tip aimed to maintain it away from the delicate mucosal surfaces. There are pumps with pressure point features to increase dose repeatability, dose counters in addition lock-out devices to

improve dosage management besides safety, and new designs that eliminate the need for priming and repriming. Crucially, it is possible to improve the metered-dose spray pumps' clinical efficacy and in vivo deposition for various uses with modifying the pumps to work with a cutting-edge breath-powered "Bi-DirectionalTM" delivery system that is elaborated mentioned beneath.[13]

Single as well as duo dose spray devices

For the indicated number of doses, metered-dose spray pumps need to be primed and somewhat overfilled in order to preserve dose uniformity. They work effectively towards drugs which are taken every day for an extended period, these show diminished effectiveness for medicines because of limited dosage regulation, there is a small therapeutic window. Therefore, single or else duo-dose spray devices are recommended for costly drugs along with vaccines aimed at one-time or infrequent use, when strict control over the dosage and formulation is especially crucial.

LMA offers a basic version of a single-dose spray device (MAD). A typical syringe is equipped with a spray tip nosepiece. The liquid medication is initially drawn into the syringe, followed by the attachment of the spray tip. This found applications in academic research for delivering a topical steroid to patients by chronic rhinosinusitis, along with the administration of a vaccine.[53,54] The Flu Mist influenza vaccine, authorized for use in the US for both adults and children, utilizes a pre-filled device built upon the similar value, enabling 1 or 2 doses (Accuspray™, Becton Dickinson Technologies, Research Triangle Park, NC, USA). A decade ago, a Swiss business marketed a device identical to this one that could administer two doses of influenza vaccine.[55,56] Due to the development of unfavourable outcomes (Bell's palsy) that may have been connected to the adjuvant cholera toxin used.[57] Crucell N.V., a vaccine company located in Leiden, the Netherlands, currently holds the device technology; however, for our understanding, it's non utilized in any commercial items.

The single with duo-dose devices stated earlier contain a swirl chamber, a piston, as well as a vial. When the liquid is forced through the swirl chamber, it generates the spray. Users hold these devices among the 2nd and 3rd fingers while placing their thumb on the actuator. Some models feature a pressure point mechanism that guarantees consistent actuation force and plume characteristics.[58] The market-ready obtainable nasal migraine medications FluMist (www.flumist.com;BectonDickinson), Imitrex (www.gsk.com), as well as Zomig (www.az.com; Pfeiffer/Aptar single-dose device). This kind of apparatus is used to administer single-dose spray devices.[59] Preservatives are not needed when using sterile filling, however overfilling is necessary, which produces a waste proportion that is comparable to that of metered-dose, multi-dose sprays. The Pfeiffer/Aptar single-dose device, utilized for administering the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan), requires a volume of 125 µl to deliver 100 µl. In contrast, a duo-dose design necessitates approximately half of that capacity.[58]

Squeeze bottles

Topical decongestants are among the over-the-counter (OTC) medications that are primarily packaged in squeeze bottles. Medication is atomized through a jet outlet when a partially air-filled plastic bottle is compressed. The dosage and particle size are influenced by the amount of force applied. However, upon releasing the pressure, there is a risk of bacteria and nasal secretions being drawn back into the container. Therefore, squeeze bottles are not suggested for use by children.[3]

Nasal pressurized metered-dose inhalers: pMDI

The primary method for administering most medications are spray pumps, which aimed at local nasal action, while a few are delivered as nasal aerosols generated by pressurized metered-dose inhalers (pMDIs). The implementation of a prohibition upon ozone-reducing chlorofluorocarbon (CFC) propellants led to a significant reduction in pMDI items for pulmonary as well as nasal delivery, culminating in their withdrawal from the US market in 2003.[60] Because of concerns of nasal irritation and dryness, utilization of previous generation of CFC pMDIs for nasal products was restricted. An unpleasant "cold Freon effect" is produced when a compressed gas expands due to the rapid discharge of particles from a pMDI.[61] Compared to a spray pump, the particles released by the conventional pMDIs exhibited a particle velocity that was significantly higher 5,200 verses1,500 cm/s at a recently, a pMDI based on hydrofluoroalkane (HFA) for nasal usage was introduced, which offers lower particle speeds and mitigates the "cold Freon effect" and high particle speeds.[60] Beclomethasone dipropionate (BDP), a first-generation topical steroid, was recently licensed for the treatment of allergic rhinitis in the USA through the application of the 1st nasal pMDI that uses HFA as a propellant.[62] Similar to spray pumps, nasal pMDIs lead to local deposition in anterior sections of the small nasal valve and on the anterior non-ciliated epithelium of the nasal vestibule; however, because the spray provided by a pMDI evaporates quickly, there may be less obvious "drip-out".[63]

Discrepancy between the geometry of the anterior nose as well as the spray plume

The liquid is propelled via the swirl chamber at applicator's tip in addition expelled via the spherical nozzle aperture due to the spray pump's force generated pressure.[64] A rotating thin film of liquid is formed by the combined action of axial and radial forces. However, after a few millimetres, this sheet turns into unsteady and splits inside "ligaments" before the particles (break-up length) form. Significantly, particles primarily in the perimeter produce a hollow spray cone. The dimensions of the nozzle orifice, break-up length, spray cone angle, and swirl effect are the primary factors influencing the plume's properties, which in turn affect the particle deposition pattern, as noted by Inthavong et al.,[64] 0.5 mm diameter's nozzle spray cone was recorded. At tipping juncture, the diameter measures 4 mm, with an approximate break-up length of 3.5 mm and a spray angle of 30°. One study indicates that at ranges of 1.0 and 2.5 cm from the nozzle, minimum spray cone diameters (D max/D min) achieved were 2.34/1.92 cm and 3.30/3.08 cm, respectively, with a spray angle of 54.6°.[2] For a spray angle of 39°, a different study found that the spray cone diameter

was 2.52/1.58 at 3 cm from the nozzle.[65] The pump's diameter (about 2 cm) as well as narrow triangular valve hole clearly do not match, even when pump is pushed deeply for ten to fifteen mm in nasal passage. The majority of the particles are located in the outermost However, it is clear that many particles land inside vestibule's of mucosal walls which are non-ciliated, and are in front of the valve. If delivery occurs during sniffing, the delivery pattern is emphasized, with particles largely entering the valve over the broader along with lower triangle's section. Similar mismatches would occur between the restricting Considering the shape of nasal vestibule in addition to conical plumes generated using various devices, including powder devices, nebulizers/atomizers, and powered devices such as pMDIs, it is important to note the differences in the mechanics of aerosol production.

Powered nebulizers and atomizers

With the usage of compressed gases (oxygen, air as well as nitrogen), ultrasonic, mechanical, or other powers, nebulizers can disperse medical suspensions as well as solutions into tiny aerosol droplets which may breathed in through nostril or orally. It is recommended that the nebulized aerosol's slower speed and smaller particle size enhance achieving penetration into the target areas of the paranasal sinuses, middle meatuses, superior meatuses, with additional regions.[42] Inhalation via nebulizer, compared with a metered-dose spray pump, has shown enhanced deposition in upper narrow nose region. However, in patients studied, 33% and 56% of the administered dose were found to deposit in the lungs.[66] It is hardly unexpected, given this lung delivery issue, that nasal inhalation of nebulized in individuals with chronic rhinosinusitis, topical antibiotics causes cough also rise demand for the inhaled medicines after nasal inhalation.[67]

Vibrant pulsation membrane nebulizer

Recently, VibrENT PARI Pharma GmbH unveiled a new nebulizer that uses a pulsing aerosol produced by a perforated vibrating membrane to deliver medication to the nasal passages and sinuses of patients with chronic rhinosinusitis. It is believed that the pulsing in conjunction with the microscopic particles will allow for greater penetration into the sinuses, and it is recommended that certain breathing techniques be taught during delivery in order to reduce inhalation.[68] Two distinct methods were employed to deliver an aerosol containing small particles with a mass median aerodynamic diameter (MMAD) of 3.0 μm, and the results were compared with a spray pump. When departure filter was connected with another nasal passage while inhaling, aerosol was administered into one nostril for 20 seconds at a mass output rate of 0.3 ml/min. This produced 4.5considerable lung deposition (10%), 27% in the exit filter, and 63% of portion deposited inside nose that reaches the sinuses (2.8 percentage of the administered dosage). When a stream resistor was attached to left nostril and the patients were asked to keep their soft palate closed, nasal aerosol administration was also carried out. After this process, the nose retained 70% of the radioactivity, the exit filter retained 30%, the lungs retained a tiny portion, and the sinuses retained 7% of the nose's proportion (4.9 percentage of the administered dosage).[68] After administering 100 μl using a conventional spray pump, the nose retained 100% of the dosage, with no lungs exhibiting any substantial deposition and minimal deposition elsewhere. between the sinuses.[68] While tissue attenuation was not corrected for, background radiation and decay were taken into account, which could alter the relative distribution and raise the amount that is really deposited in the lungs.[68–71] However, the findings imply that using a pulsing aerosol together with inhaling method as well as an exit resistor can improve sinus deposition in volunteers in good health. It is yet unknown, nevertheless, whether these findings from healthy volunteers have any clinical significance for those with rhinosinusitis who have blocked sinus apertures. Unlike the automatic coordination of velum closure as well as drug delivery through exhalation, the suggested breathwork methods to minimize lung deposition might be more difficult to implement. Devices like OptiNose's Bi-Directional™ technology offer a solution by generating positive pressure in the sinuses and nasal passages using an exit resistor.[69] Additionally, a highly noticeable "hot spot" was noted for spray pump as well as nebulizer delivery; however, in the trial using the pulsing aerosol nebulizer, no evaluation of regional deposition in the nose was carried out.[68]

Deposition outcomes with nebulizers: clinical significance

Nasal nebulizers face challenges with lung deposition as well as deliver comparatively little fractions to the nasal cavity. Techniques such as co-aspiration from opposite nostril in addition precise breathing advices help reduce lung deposition. However, this intricate process and the need for strict patient adherence to breathing techniques can be difficult, especially in children and other special population.[66,68,72] Due to its design, the study makes it highly challenging to assess the data comparing nasal nebulizers with regard to deposition efficacy along with clinical relevance, as it involves both two different nebulization methods and a diverse range of breathing habits.

To enhance delivery into the sinuses, tiny particles and sonic/pulsation techniques are used; however, this comes at the cost of limited delivery efficacy and a substantial risk of lung depositary. Furthermore, deposition quantification across different planes (cartography) indicates a typical preference for deposition in anterior (2-3 centimetre from the front) as well as lower (1-2 cm from the bottom) sections of the nasal cavity, despite the vibrating mesh nebulizer's intended advantages, utilizing aspiration through the opposite nostril, the main focus areas for treating chronic rhinosinusitis and nasal polyposis are the middle and superior meatuses or sinuses., appear to be unaffected by the nebulizer's delivery method based on the deposition pattern.[42,72] The novel nebulizer systems have not yet been the subject of any published clinical data.[68,72]

Aeroneb solo vibrating mesh nebulizer

Another recent publication confirms the separate anterior deposition observed inside valve region along nebulizers. It compares nasal inhalation from a novel nasal mesh nebulizer scheme, planned to reduce lung inhalation (Aeroneb Solo®, Aerogen, Galway, Ireland; DTF-

Aerodrug, Tours, France), by a nasal sonic/pulsating jet nebulizer (Atomisor NL11S® sonic, DTF-Medical, France), both having the same mean particle size of 5.6 ± 0.5 μm.[72] The novel scheme is made up of two integrated parts: a nebulizer compressor that delivers aerosol inside single nostril using nozzle at a steady airflow rate, and a pump that simultaneously aspirates at the same airflow rate from a onother nozzle in the second nostril while instructing the patient to refrain from nasal breathing.[72] In terms of volume, The recently developed nasal mesh nebulizer resulted in greater liquid deposition within the nasal cavity, achieving 27% compared to just 9% (0.81 ml versus 0.27 ml). The investigation assessed PARI pulsating nebulizer, which administered treatment for 20 seconds at a rate of 0.3 ml/min to every nostril, in contrast to a 3 ml delivery over a span of up to 10 minutes prior to evaluating deposition. likely contributed to the significantly an increased fraction detected in nasal passage.[68,72] A substantial dose fraction administered above nasal valve will clear to GI tract. with a significantly longer delivery duration.

ViaNase atomizer

ViaNase, a portable, operated with battery, nasal atomizer medicine delivery, has been made available (Kurve Technology Inc., Lynnwood, WA, USA). By creating a vortical flow upon liquid droplets as they leave device, this apparatus atomizes liquids (www.kurvetech.com). By altering the circular velocity and direction of triggered vortical flow properties, different droplet trajectories might be achieved.[42,73] As noted earlier, it remains uncertain whether vortex flow is optimal for penetrating beyond nasal valve. Though, this method is proposed as a means to target the sinuses, along with several published gamma-deposition pictures indicate that sinuses are the intended target. Nevertheless, there is no data pertaining to the effects of previous surgery or numerical measurements of nose or sinus deposition that support the stated enhanced deposition to the nasal upper regions have been published.[42,73] Clinical benefit has been observed when nasal insulin is administered via the ViaNase device to individuals with early Alzheimer's disease (AD).[74,75] In these studies, nasal inhalation was employed to deliver insulin over a duration of 2 minutes. However, the use of this device raises the likelihood of lung deposition of insulin. During the brief period when Exubera was available as a diabetes treatment, concerns were raised regarding Prolonged contact to inhaled insulin, particularly associated with airway annoyance as well as potential reductions in pulmonary function.[71,76] This illustration brings to light the problem of unintentional lung delivery, a significant possible clinical hazard related to the use of nebulizers and atomizers that produce respirable particulates for the administration of drugs through the nose.

Impel nitrogen-driven atomize

Impel Inc. is currently developing a nasal atomizer powered through extremely compressed nitrogen gas. This device is intended to improve N2B delivery by enabling effective drug administration to the upper areas of the nasal cavity.[77] Since nasal deposition and how it is measured in animal models differ greatly from human nose deposition, it is challenging to assess the potential of this technology for usage in people as only animal data have been provided thus far. However, as was already said, pMDIs have a number of drawbacks. Therefore, it is unclear whether a pressured "open-palate" nebulizer will be able to produce the required pattern of distribution.

Powder devices

Preservatives might not be necessary in powdered pharmaceutical formulations, which is one of their many benefits over liquid forms. Before being dissolved and expelled, powders often adhere to the nasal mucosa's wet surface. It may be possible to reduce clearance rates as well as increase absorption through using drugs or bio-adhesive excipients that inhibit ciliary function.[46,78] Deposition and absorption are influenced by several parameters, including flow characteristics, particle size, shape, solubility, and moisture sensitivity.[3]

One of three concepts typically underpins the operation of nasal powder devices:

1. Powder sprayers equipped by a squeezable compartment release pressure to generate a plume of powder particles which resembles a liquid spray upon activation.
2. Inhalers that work on breath where the person breathes in the powder from a blister or capsule through his nose; as well as
3. Nasal insufflators devices incorporate mouthpiece as well as nosepiece that are fluidly interconnected. By exhaling in mouthpiece to close velum, patients enable delivery of powder particles into the nasal cavity via nosepiece, resembling the previously described rhinyle cathete. The breath-powered Bi-DirectionalTM delivery technique (see below) is an extension of the principle, which may be used to other dispersion technologies.

Nasal powder inhalers

Budesonide powder is sold by Astra Zenaca and is administered using the Rhinocort Turbuhaler® (www.az.com) multi-dose inhaler device, which has been adjusted for nasal inhalation.[79] In certain areas, it is sold as a substitute for the liquid spray for treating allergic rhinitis and nasal polyps, although it doesn't seem to have any special benefits.[80] Both the Rhinocort Turbuhaler® (140 $\mu g \times 2$) and the aqueous budesonide spray (128 $\mu g \times 2$), when administered twice daily to patients with nasal polyps, meaningfully decreases the extent of the polyps when likened with placebo, nonetheless there was o discernible difference between the active treatments. On the other hand, the liquid spray dramatically lowered nasal sign ratings more than the powder.[80] Rhinocort Turbuhaler was used in gamma-deposition research that revealed primarily anterior deposition with a "hot spot" atthe region of nasal valve as well as roughly 5% lung deposition.[79] The fraction would probably be much larger if lung tissue attenuation were taken into account.[69,79]

An easy-to-use powder inhaler with a blister is available from Aptar Group (www.aptar.com). Before using, the swelling is punctured, as well as device's nosepiece inserted inside 1 nasal passage. While sealing one nostril with a finger, the individual inhales the powder through the other nostril. This method employs the BiDose™/Prohaler™ blister-based powder inhaler from Pfeiffer/Aptar, which

was used in clinical progress for a powder formulation of apomorphine targeting Parkinson's disease by Britannia, a UK company lately taken by Stada Pharmaceutical. However, it seems that further development of this formulation has been halted. Additionally, dexamethasone cipecilate, a topical steroid, is marketed in Japan by Nippon Shinyaku Co., Ltd. and is delivered using a powder-based inhalation device for allergic rhinorrhea. There are two chambers in the Twin-lizerTM gadget, and therein are capsules. The capsule is punctured, and the powder is dispersed and inhaled by the subject through the nosepiece as wind carries it into the nose.

Nasal powder insufflators

Direct Haler, a Danish business, originally designed a gadget that has been bought by Trimel (www.trimel.com). This little device that resembles a drinking straw comes in two different forms. There are two versions of the device: one for nasal medication administration, one setup involves the subject blowing into first end of the tube is in the nostril, and the other is open vestibule, while another setup is used for pulmonary drug delivery, wherever the patient inhales via a minor tubular device. Conceptually, this apparatus can be observed as a powdered version of the Rhinyle catheter, which is intended for liquid delivery. There are corrugations in the central region of this tubular device. The device can bend due to the corrugations, which also provide turbulence that breaks up the powder. The little tubular gadget is inserted with one end between the lips and the other enters the vestibule of the nose. The powder is subsequently released from the tube and into the subject's nostril by exhaling through the apparatus. Exhaling into the device, like with the rhinyle catheter, enables the soft palate to by default rise, keeping nasal passages as well as mouth cavity apart and avoiding lung inhalation during delivery. Other than a tiny gamma learning reported in a patent, the device demonstrated deposition as well as clearance areas that were similar from those of a "state-of-the-art" powder inhalation system, no clinical data pertaining to the device are known.[81] A breath-powered Bi-DirectionalTM nasal delivery system for liquid as well as powder pharmaceuticals has been developed by Opti Nose (www.optinose.com), which uses exhaled air to transport the medication into the nose. but with other essential characteristics that set them apart and have a significant impact on clearance trends, drug deposition, as well as clinical device performance.

Nasal powder sprayers

Recently, data on a Phase 1 study using a cyclodextrin formulation of zolmitriptan powder (μcoTM System) aimed at improved uptake explained earlier in in-vitro study was reported by SBNL Pharma (www.snbl.com) and published in a press release on the same website.[82] Compared to the commercially available tablet and nasal spray, zolmitriptan had a faster rate of absorption and a greater relative bioavailability (www.snbl.com). Fit-lizer, the company's proprietary capsule-based single-dose powder device, is available.[83] Sharp blades chop off the capsule's top and bottom as it is put into a chamber. When a one-way valve and the capsule are activated by hand-compressing a plastic chamber, pressurized air is allowed to flow through them and release the powder. Particle size distribution and minimum residuals are demonstrated by in vitro testing; however, no information is available on clearance and in vivo deposition designs seem to be accessible. The company has completed Phase 2 trials of the medication granisetron for treating late chemotherapy-induced nausea and vomiting, employing the similar preparation methods along with Fit-lizard device.[81] Additionally, they (www.snbl.com) have revealed ambitions to produce an influenza vaccine based on powder.

Fit-lizer and Bespak (www.bespak.com) share a similar idea, which is the basis for Unidose-DPTM. A pin rupturing membrane releases pressure inside an air-filled container, causing a powder plume to be released. The powder preparation's delivery containing a model antibody (IgG) is assessed using nasal cast model derived from human MRI scans. About 95 percentages of dosage reached the nasal cavity, althoughOnly around 30% of it was deposited into the nasal cavity's deeper compartments; the remainder was only deposited into the nasal vestibule.[83] According to the company's website (www.bespak.com), they have partnered with this gadget to create an unnamed nasal powder formulation.

The Monopowder powder device from Aptar Group (Pfeiffer/Valois) (www.aptar.com) similar to the previously described devices, this one features a plunger that creates positive pressure to rupture a membrane, releasing the powder. Despite its used in rabbit research, no clinical study or human deposition data have been reported.[84,85]

Additionally, BD (www.bdpharma.com) offers a powder device called SoluVentTM that uses a plunger to create positive pressure. it punctures tissue to release the powder. Powder vaccines are being used to test a device that uses this technique.[86]

Breath-powered bi-directional™ nasal drug delivery

This innovative idea provides a delivery system that may be able to get around many of the intrinsic drawbacks of conventional nasal devices by taking advantage of the natural functioning features of the upper airways. Significantly, any kind of dispersion expertise for liquids as well as powders can be utilized with the breath-powered Bi-DirectionalTM technology. Breath-powered Bi-DirectionalTM devices, which mechanically expand the initial half of the nasal valve, are composed of a mouthpiece and a sealing frusto-conical nosepiece form as well as a pleasant surface. The nasal triangle valve's narrow slit-shaped portion is mechanically expanded by the user after sliding a sealing nosepiece in one nasal passage and forming a seal with the flexible soft tissue of the nostril opening. After then, the user exhales through an mouth piece affixed. When exhaled into the mouthpiece, the device's resistance raises the soft palate (velum) through positive oropharyngeal pressure, thus separating the nasal cavity from the respiratory system. The dynamic pressure generated as air travels from mouth via device towards nose, aided by the sealing nosepiece, further widens the narrow nasal airways. Importantly, the sealing nosepiece ensures that the positive pressure in the entry nostril counteracts the oropharyngeal pressure across the closed velum, preventing excessive elevation of the velum and

allowing for an unobstructed airflow between the two nasal passages in front of the elevated velum and behind the nasal septum. Employing this 'breath-powered' mechanism, liquid or powder particles are released into an airstream that enters one nostril, navigates around the nasal septum, and exits through the other nostril, all in a "Bi-DirectionalTM" flow pattern. Devices adopting this technique have been reported to activate drug release by mechanisms activated by flow and/or pressure, as well as through manual triggering.[13,69,70,87–90] Enhancing design characters, including the configuration of the nosepiece, particle size distribution, release angle, and airflow rate, can facilitate effective deposition of particles deep within the nasal cavity without exiting through the opposite nostril, prevent lung deposition, and maximize Targeted delivery to sites beyond the nasal valve. Currently undergoing phase 3 clinical trials, the Bi-DirectionalTM devices with multi-dose liquid delivery system generally comprises a standard spray pump and a powder-based, multi-use capsule equipped with a disposable medication chamber and nosepiece. Nonetheless, numerous configurations can be designed. Notably, various dispersion technologies for both liquids and powders can be integrated into these systems with the Bi-Directional TM delivery idea.

Patterns of nasal deposition with bi-directional™ delivery: human evidence

Variations of device that make use of this drug delivery mechanism were examined in gamma-deposition experiments, which involved a detailed examination of regional deposition as well as clearance designs in individuals.[13,14,69] When similar nebulizer form tiny droplets was used for both traditional nasal inhalation and Bi-DirectionalTM administration, lung inhalation could be avoided even with the presence of tiny respirable particles delivery was used.[69] Bi-Directional™ powder device was straight associated to a conventional spray device in 2nd available study. Meanwhile, the first study compared a breath-actuated Bi-Directional™ device with a standard to similar nasal spray pump operated manually.[13,14] Less deposition was seen in the non-ciliated nasal cavity in both investigations. In contrast to traditional delivery methods utilizing a spray pump, Bi-Directional™ devices achieved markedly greater deposition in the vestibule as well as upper posterior regions past the nasal valve.[13,14]

Clinical results of breath-powered bi-directional™ delivery devices

Apart from humanoid deposition pattern investigations, several clinical trials have assessed devices that utilize the breath-powered Bi-DirectionalTM technology. Currently, dual drug-device combinations are in Phase 3 trials: fluticasone propionate for chronic rhinosinusitis with nasal polyposis and sumatriptan powder for acute migraines. The findings indicate that enhanced bottomless nasal deposition by means of significant clinical implications can be attained in clinical settings.[87] Sedation caused by midazolam: This shows high systemic availability, a fair amount of BBB crossing capacity, and easily noticeable pharmacodynamic effects. The delivery of 3.4 mg of midazolam using a breath-powered Bi-Directional™ device prototype was measured against a standard nasal spray as well as intravenous route in a three-way crossover examination with 12 healthy volunteers. It is not surprising that the drug's pharmacokinetics (PK) were similar for both nasal delivery methods, given that the drug is a tiny molecule with a high blood absorption percentage (about 70%). Interestingly, despite significantly reduces maximum serum levels (Bi-DirectionalTM with median C max = 3 Ng/ml vs. IV with median C max = 5 ng/ml), the pharmacologic effects (onset as well as degree of drowsiness) recorded with Bi-DirectionalTM delivery were quite similar to IV treatment. However, even though the PK values of traditional spray delivery were equal to those of Bi-DirectionalTM delivery, the onset and level of sedation were lower.[91] These findings suggest the potential that the sedative impact of Bi-DirectionalTM nasal delivery may come from more than just the drug's absorption into the blood and subsequent transit through the blood-brain barrier. BBB as it happens when using a typical nasal spray. The sedative effects could be attributed to alternate routes of transport to the brain that circumvent the blood–brain barrier, as reported in animal studies.[32–34,44] Uptake from back of the nose, facilitated by a specialized venous drainage pathway called “counter-current transfer,” may provide a direct path to arterial blood in the brain.[32,33] Furthermore, unsheathed cells that create channels surrounding the trigeminal and olfactory neurons may facilitate direct transport of both big and small chemicals to the brain.[34,44] Sumatriptan for migraine: In contrast to midazolam, Sumatriptan, a serotonin antagonist, has a low basal activity (BA) of 14% when administered orally, and a slightly higher BA Using the Pfeiffer single-dose device for nasal spray administration, roughly 10% of the medication from a conventional nasal spray (Imitrex) is thought to be rapidly absorbed through the nasal mucosa within the first 20 minutes. In contrast, most of the dose is gradually absorbed from the gastrointestinal tract, reaching its peak concentration (T max) around 90 minutes later.[92,93] In order to test the hypothesis that breath-actuated Bi-DirectionalTM powder delivery could yield clinically distinct outcomes from those previously documented for nasal spray delivery, researchers compared a crossover pharmacokinetic (PK) study involving 12 migraine patients compared subcutaneous administration of 6 mg sumatriptan to intranasal sumatriptan powder doses of 10 mg and 20 mg. Nasal sumatriptan powder administered in two directions was pharmacodynamically comparable to injection, eliciting a comparable EEG profile, as well as shielding individuals from migraine symptoms when given 15 minutes prior to the glyceryl trinitrate test. The PK curves displayed a biphasic absorption pattern resembling that of sumatriptan nasal spray delivery, instead using a significantly larger 20 minutes preliminary peak that was primarily nasal and is thought to have accounted for about Thirty percent of the overall absorption, or roughly 3 times the 10% fraction assessed to have been absorbed nasally for the commercially available Imitrex nasal spray.[89,92] ompared to earlier findings with conventional nasal spray delivery, these PK results support the conclusion that the breath-powered Bi-DirectionalTM device produces clinically distinct nasal deposition. A more conclusive

study that contrasts the administration of sumatriptan by a breath-powered Bi-DirectionalTM device trials are being done to give by injection, oral administration, and regular nasal spray; findings must be available soon (www.clinicaltrials.gov). In a randomized, double-blind, parallel-group, placebo-controlled investigation, a solo migraine attack was remedied in-clinic using dual doses of intranasal sumatriptan powder (7.5 mg or 15 mg delivered doses, or placebo) administered via a novel Bi-Directional™ powder delivery device. Both doses showed a rapid onset of pain relief.[90] Despite significantly reduced systemic exposure, the pain alleviation rates were comparable to previous results from SC injection.[90,92] The findings imply that the improved deposition linked to sumatriptan powder's breath-powered Bi-DirectionalTM delivery may increase early nasal absorption as well as provide therapeutic advantages.[94] Nevertheless, rooted in contrasts by previous PK data. It has been hypothesized that variations in headache response may not be solely explained by the systemic absorption rate of nasal sumatriptan, indicating capacity for an alternative pathway to the targeted site, as previously mentioned, and the pharmacodynamic profiles of sumatriptan administered via various routes.

Influenza vaccine

In a four-armed parallel group examination, the delivery of a whole-virus influenza liquid vaccine deprived of an adjunct using breath-powered Bi-Directional™ OptiNose device as well as nasal drops lead to more favorable overall immune response compared to both a traditional nasal spray as well as an oral spray, compared to self-administration with the OptiNose device, an assistant supplied the nasal drops through carefully placing the pipette tip past the nasal valve while extending the neck.[50] These findings imply that Bi-DirectionalTM devices are a workable delivery technique that can result in a clinically significant deeper and wider vaccine delivery to the nasal mucosa, rich in dendritic cells and lymphoid tissue, providing opportunities for variety of vaccines to yield enhanced immunological reaction in administration methods other than parenteral.[24,50,95–97] Evaluation of Clinical Aspects of Nasal Deposition as well as Clearance.

CFD simulations

Improvements in high-resolution computed tomography and magnetic resonance imaging technology have allowed for precise three-dimensional models of intricate nasal structures. Additionally, the rapid progress in computational fluid dynamics (CFD) within the medical field now enables simulations of nasal aerodynamics and deposition patterns.[98] More realistic conditions may now be implemented thanks to much enhanced grid and algorithm densities and quicker simulation computers. Recent articles, for instance, propose algorithms to more closely model the genuine qualities of aerosol formation and plume characteristics, as well as post-surgical alterations, heat and water exchange, and septal anomalies.[99] Undoubtedly, CFD simulations will become more significant and enable more as the quality and capabilities rise. realistic model of medication distribution and nasal physiology. This review will not delve further into the intricacies of this intriguing topic.

Deposition and clearance: In vivo evaluation[100,101]

The administration of pMDIs, powder devices, nebulizers, and conventional spray pumps All methods lead to deposition predominantly in anterior non-ciliated regions of nose, specifically anterior to as well as at the slender nasal valve. This distribution is observed as inadequate for clinical effectiveness, which requires both deep and widespread nasal deposition. This has been corroborated by various gamma deposition investigation, research by radiopaque contrast, as well as investigations that utilized dyes of different color.[13,43,63,66,72,79] In order to improve deposition as well as the clinical administration result by spray pumps also drops, several studies have evaluated deposition patterns using dyes. Coloured dyes might provide a rapid as well as affordable partial quantitative evaluation of deposition as well as clearance.[43] While outcomes may differ, the impact of various body positions in order to improve deposition and the clinical result of administration with spray pumps and drops, several studies have evaluated deposition patterns using dyes. Coloured dyes may provide a rapid and affordable semi-quantitative assessment of deposition and clearance.[43] Different body postures and delivery strategies appear to have modest effect on early deposition patterns, but results vary. Indeed, a current single-blind, cross-over investigation using endoscopic video imaging to compare seven alternative methods of administering coloured dyes to healthy subjects came to the conclusion, it appears that there could be an absence ofa singular 'optimal' method for topical nasal drug delivery when using traditional nasal sprays.[78] These delivery strategies' clinical effectiveness is further diminished by noncompliance from patients.

Deposition studies in casts

Modern 3D printing techniques such as stereolithography have enabled the ability to create physical models inside rigid materials with accurate nasal geometry and proportions, thanks to advancements in imaging and reconstruction software. In the context of a more practical device design contact, casts composed of softer materials, such as silicone, might be advantageous. But care must be taken as even the softer silicone casts fail to accurately eplicate the dynamics of the nasal valve, cyclical mucosal changes, or the in vivo surface properties of the nasal mucosa and their effects on mucociliary clearance.[102–104]

Effect of administration guidelines, patient adherence, as well as body position

When comparing deposition studies, it is all too common to overlook the question of whether the subjects or an aid carried out the delivery technique. Although the respondents' delivery is obviously far more in line with real-life circumstances, it nonetheless necessarily adds additional variability. A trained assistant handles the spray device and executes the propulsion in accordance with a precise procedure in the majority of gamma-deposition experiments. This was noted in a study evaluating the considerable transport of radiolabelled cromoglycate deposited along the nasal floor beyond the nasal valve. On the other hand, individual delivery technique led to most

doses located in the anterior region instead of the posterior research using radiolabelled insulin where the spray was activated by the individuals themselves. Conversely, in a study involving radio labeled insulin, personalized administration techniques lead to the most of dos being deposited in anterior nasal cavity instead of the posterior in 5/6 individuals, alog spray activated by the participants themselves. Consequently, the doses were cleared through the nares instead of the nasopharynx. The authors expressed concern that method of separate administration increases questions about the suitability of nasal spray doses for delivering insulin meant for bioavailabilty, as there was no evidence of systemic absorption of insulin, contrary to expectations.[92]

Overall, versus regional clearance patterns

The site of initial deposition plays a crucial role in influencing clearance rates, and recent research has shown that total nasal clearance is an imprecise as well as Possibly deceptive indicator which lack accurate forecast of clinical presentation. These studies offer regional clearance curves for 4 or 6 nasal segments.[13,14] It's interesting to note that, according to a current analysis on pulmonary drug delivery, localized deposition must be evaluated in order to predict treatment success; lung deposition, in general, appears to be an unreliable indicator of clinical outcomes. Research has compared nasal deposition as well as clearance following personal administration of a conventional 100 µl spray pump using a Bi-DirectionalTM delivery system (details below) versus breath actuation by hand in the usual manner found that the proportion remaining in half as much as that of breath actuation in the nostril half an hour after hand actuation (46% vs. 23%). Following hand-actuated spray delivery, the regional deposition patterns, separated into 4 nasal sections, indicate that this variation is largely due to retaining in mostly non-ciliated anterior 2 nasal quadrants. The Bi-DirectionalTM device reverses the deposition pattern and is said to provide 3 times wider, broader, and extra consistent deposition onto the ciliated respiratory mucosa outside the nasal valve, specifically within the upper posterior segments, with clearance taking place at a pace that matches the anticipated mucociliary clearance rate.[13] A comparable substantial variance in the regional deposition as well as absorption was observed in another investigation contrasting the self-administration of a spray pump as well as a Bi-DirectionalTM breath-actuated powder device.

Deposition and clearance: influence of delivery site and volume

The primary deposition location has a significant influence upon the rates of clearance, according to the findings of the study mentioned above that compared deposition as well as clearance following same spray pump's delivery operated inside various ways.[3,13,14] It's interesting to note that McLean et al. distinguished between three nasal clearance phases.

1. First phase begins a minute after administration as well as becomes most pronounced once high, concentrated doses are given. These quickly travel from the nose floor to the pharynx, where they are ingested. It is especially true for drop delivery, which helps to explain why desmopressin administered in drop form is absorbed at a significantly lower rate. It also holds true for spray delivery at greater spray volumes.[3,14,51] The Because of the comparatively low dosage of radioactivity utilized (for ethical reasons), the initial gamma image frequently comprises an average of registration of sums ended a two-minute period, making initial and extremely quick removal difficult to detect.[14]

2. During the second phase, lasting approximately 15 minutes, the percentage firstly deposited upon ciliated respiratory mucosa at and beyond the nasal valve is cleared through mucociliary clearance.[13,14,51,63,70]

If the residual medication is not mechanically cleared by blowing or wiping the nose, the third extended late phase, which can take hours, is the gradual elimination of residual drug accumulated in the anterior non-ciliated nasal surface regions.[63] Therefore, based on whether the material in question. It is theoretically possible to increase exposure in a different, complementary, and possibly better way by altering or improving the delivery method or approach. The objectives should focus on minimizing the volume of medication rapidly swallowed through the nose during the initial phase, reducing the quantity that deposits externally, and enhancing the amount that bypasses the nasal valve and the covered nasal respiratory mucosal surface. When compared to drop administration and the repeated delivery of smaller volumes, utilizing a standard spray for smaller particle delivery offers advantages in absorption and biological response. For example, systemic absorption has been found to be better with a 2-×-50-µl spray than a 1-×-100-µl spray.[51] However, another study discovered that misting 1 × 100 produced a greater deposition than 2 × 50 µl beyond the nasal valve and a faster total clearance; however, absorption and a biological response were not evaluated in this investigation.[63] Drops that are deposited more posteriorly are cleared more rapidly, while a narrower cone angle results in increased posterior deposition and quicker clearance compared to a 60° cone. Additionally, the non-ciliated surface of the vestibule is not the intended target for locally acting anti-inflammatory medications like steroids and antihistamines, nor is it the goal for vaccinations.[42] Notwithstanding, current literature persists in endorsing concentrated anterior deposition as well as retention as preferable also a crucial benefit of the innovative HFA-based nasal pMDI containing topically active medication. A 1987 study using CFC-based pMDI is cited, demonstrating that up to 6530 minutes after treatment with an aqueous spray, the majority of the primary radioactivity is still present inside the anterior nose regions, despite the false claim that a nearly complete clearance was seen.[63] In contrast to the general consensus, a new paper asserts that the anterior retention after pMDI administration shows signs of increased efficacy.[42]

CONCLUSIONS

Although the nose is a desirable location for the delivery of numerous medications as well as vaccines, its full power has yet to be realized. It is not well known that there are inherent difficulties with the structural, functional, and aerodynamic characteristics of the nasal cavity that could significantly reduce the potential and clinical efficacy. The

anterior architecture and the nasal cavity's small, dynamic dimensions are two of the biggest obstacles to more effective nasal medication delivery. To a limited degree, this has translated into better clinical performance even with significant advancements in the technological features of the device that can provide more consistent and dependable in vitro result. Even though these studies are valuable for assessing product excellence, its ability to predict in vivo clinical results is extremely contested.[2] CFD modelling of the aerodynamics of the nose as well as cast examinations might be helpful throughout the device design development phase, and subsequent developments might increase their predictive value. Studies on humanoid in vivo deposition as well as clearance may be highly significant and informative, especially if they make use of recent developments that enable regional quantification as well as tissue attenuation correction.[14,70] However, the performance of the gadget in a clinical setting could not be fully reflected in its administration by skilled assistants in controlled settings. Although utmost cutting-edge nebulizer technologies have demonstrated low delivery effectiveness, resulting in issues with lung inhalation exposure and undesired localized distribution in the non-ciliated anterior nasal region as well as floor of the nose's.[72] As per the previous analysis, rigorously controlled clinical trials are presently necessary to measure alterations in terms of both functional characteristics and symptoms, and eventually to assess the effectiveness of new medication/device combinations.[42] The Bi-DirectionalTM medication administration idea offers a fresh method that might get over the intrinsic restrictions placed on traditional nasal delivery by the dynamics of the nasal valve. Gamma-scintigraphy studies using both powder and liquid Bi-Directional™ device types confirm significant improvements in regional in vivo deposition and clearance patterns. Additionally, numerous clinical trials suggest that deep nasal deposition offers clinical benefits for patients. This delivery method has the potential to enhance nasal drug delivery possibilities, as it can be integrated with various dispersion technologies for both liquids and powders.

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