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Advancements in acoustic drug delivery for paranasal sinuses: A comprehensive review

Oveis Pourmehran [a,b,*], Kavan Zarei [c], Jeremie Pourchez [d], Sarah Vreugde [a,b], Alkis Psaltis [a,b], Peter-John Wormald [a,b,*]

[a] Department of Surgery-Otolaryngology Head and Neck Surgery, Adelaide Medical School, The University of Adelaide, Adelaide 5011, Australia
[b] Department of Surgery-Otolaryngology Head and Neck Surgery, Basil Hetzel Institute for Translational Health Research, Central Adelaide Local Health Network, Woodville, South Australia, Australia
[c] Faculty of Mechanical Engineering, Tarbiat Modares University, Tehran, Iran
[d] Mines Saint-Etienne, Université Jean Monnet Saint-Etienne, INSERM, Sainbiose U1059, Centre CIS, F-42023 Saint-Etienne, France

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ABSTRACT

Chronic rhinosinusitis (CRS) impacts patients' quality of life and healthcare costs. Traditional methods of drug delivery, such as nasal sprays and irrigation, have limited effectiveness. Acoustic Drug Delivery (ADD) using a nebulizer offers targeted delivery of drug to the sinuses, which may improve the treatment of CRS. This review examines the influence of aerosol particle characteristics, aero-acoustic parameters, inlet flow conditions, and acoustic waves on sinus drug delivery. Key findings reveal that smaller particles improve the ADD efficiency, whereas larger sizes or increased density impair it. The oscillation amplitude of the air plug in the ostium is crucial for the ADD efficiency. Introducing acoustic waves at the NC-sinus system's resonance frequency improves aerosol deposition within sinuses. Future research should address advanced models, optimizing particle characteristics, investigating novel acoustic waveforms, incorporating patient-specific anatomy, and evaluating long-term safety and efficacy. Tackling these challenges, ADD could offer more effective and targeted treatments for sinus-related conditions such as CRS.

1. Introduction

Prolonged inflammation of the paranasal sinuses is the defining trait of a condition known as Chronic Rhinosinusitis (CRS). This is typically a result of inflammatory reactions occurring in the mucous membrane of the sinuses and nasal passage (Xu et al., 2021; Vlaminck et al., 2021). CRS was previously believed to be caused by a bacterial infection in response to sinus ostium obstruction. In the prevailing scholarly consensus, CRS is understood to be influenced by an array of potential determinants. These range from host-specific factors, such as polyp occurrence, obstructions in nasal structure, and the existence of growths, to environmental factors including bacteria, pollutants, fungal entities, and allergenic initiators. Additional host factors, including deficiencies in the immune system, genetic susceptibilities, and specific conditions such as cystic fibrosis, have also been identified as contributors to CRS (Rosenfeld et al., 2015; Marple et al., 2009; Bachert et al., 2014). It is more accurate to perceive CRS as a spectrum of symptoms emerging from a variety of origins, rather than a singular disease entity (Bhattacharyya, 2012; Cho et al., 2010; Liu et al., 2018; Pilan et al., 2012). As per the protocols provided by the American Academy of Otolaryngology-Head and Neck Surgery, CRS is characterized as a condition lasting for more than 12 weeks annually. Conversely, they classify acute and subacute rhinosinusitis based on the symptom's duration – less than 4 weeks for acute, and between 4 and 12 weeks for

Abbreviations: ADD, Acoustic Drug Delivery; ATDD, Active Targeted Drug Delivery; CFD, Computational Fluid Dynamics; CT, Computed Tomography; CRS, Chronic Rhinosinusitis; CRSsNP, Chronic Rhinosinusitis with Nasal Polyps; ECDD, Electrically Charged Drug Delivery; ES, Ethmoid Sinuses; FEA, Finite Element Analysis; FESS, Functional Endoscopic Sinus Surgery; FS, Frontal Sinuses; HIFU, High-Intensity Focused Ultrasound; HR, Helmholtz Resonator; IM, Inferior Meatus; LES, Large Eddy Simulation; MAD, Median Aerodynamic Diameter; MDT, Magnetic Drug Targeting; MM, Middle Meatus; MRI, Magnetic Resonance Imaging; MS, Maxillary Sinuses; NaF, Sodium Fluoride; NC, Nasal Cavity; NO, Nitric Oxide; PTDD, Passive Targeted Drug Delivery; SM, Superior Meatus; SS, Sphenoid Sinuses; TDD, Targeted Drug Delivery.

* Corresponding authors.
E-mail addresses: oveis.pourmehran@adelaide.edu.au (O. Pourmehran), peterj.wormald@adelaide.edu.au (P.-J. Wormald).

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subacute instances (Bachert et al., 2014; Benninger et al., 2003).

Globally, it is estimated that between 4.9 and 10.9% of the population is affected by CRS (Liu et al., 2018; Pilan et al., 2012). In the United States alone, about 30 million individuals are estimated to have this condition, with close to 600,000 people choosing surgical treatment annually (Lam et al., 2014). To diagnose CRS, at least two symptoms are identified. A diverse array of symptoms is associated with CRS, encompassing nasal blockages noticed by 81–95% of patients, facial discomfort (70–85%), an impairment in smell discernment known as hyposmia (61–69%), and nasal secretions experienced in 51–83% of cases (Rosenfeld et al., 2015; Meltzer et al., 2004). Various methodologies are available for the management of CRS, including localized drug administration, systemic drug delivery, and surgical interventions on the sinus (Moghadam et al., 2018). The selection of an appropriate therapeutic strategy is contingent upon elements such as the severity of the disease, the anatomical configuration of nasal pathways, and the patient's adherence to the treatment plan. Initial treatment procedures for CRS typically involve corticosteroids, saline solutions for nasal irrigation, and antibiotic regimens (Benninger et al., 1997; Lund, 2005).

The first line of action for treating CRS usually consists of topical antibiotics, a form of anti-inflammatory drugs. These are dispensed through a variety of delivery techniques including nasal douching (Taccariello et al., 1999), aerosolized nasal sprays, and nebulization procedures (Moffa et al., 2019). Nasal douching method involves washing the nasal cavity (NC) with a medicated solution to eradicate nasal and sinus infections (Taccariello et al., 1999). The use of this technique can alleviate congestion and potentially lessen the necessity for functional endoscopic sinus surgery by curtailing the presence of bacteria and viruses in the sinus cavities. However, it may increase the risk of acute infections by flushing out the beneficial mucus containing antimicrobial agents (Principi and Esposito, 2017; Cnockaert et al., 2022). Due to the significant amount of drug waste produced by nasal douching, it is not a cost-effective approach for delivering drugs to sinuses (Tai et al., 2021; Albu, 2012).

To reduce drug waste, more effective technologies of drug delivery to the sinuses, such as pump sprays and nebulizers, are being explored (Farzal et al., 2019). Drug solutions are typically delivered locally through the nasal pump spray in cases such as allergic rhinitis and nasal congestion (Djupesland, 2013). The median aerodynamic diameter (MAD) of aerosol particles/droplets produced by nasal pump sprays typically ranges from 50 to 100 μm. However, most medications are delivered to the anterior regions of the NC, from the nostril to the nasal valve, and do not effectively reach the posterior regions, including the sinuses, due to poor air circulation and inefficient drug delivery (Moeller et al., 2014; Suman et al., 1999).

Functional Endoscopic Sinus Surgery (FESS) is a technique applied for the management of CRS and related issues that influence nasal polyps and paranasal sinuses (Iro et al., 2004; Stammberger and Posawetz, 1990). This surgical procedure involves the use of an endoscope - a slender, flexible tube featuring a miniature camera and illumination at its end. The endoscope is inserted via the nostrils, enabling a clear visualization of the sinus interior. The chief objectives of FESS include the enhancement of sinus drainage and the excision of any structural abnormalities, such as nasal polyps, obstructing the sinus apertures. This is achieved by meticulously reshaping the bone and tissue within the nose-sinus complex to widen the ostia, tiny openings that facilitate the drainage of mucus from the sinuses into the NC. FESS is generally conducted under general anesthesia, and the duration of the procedure can extend to several hours, depending on the intricacy of the cases (Khalil and Nunez, 2006; Kennedy, 1985; Kane, 2020). It has been demonstrated that FESS is efficacious in mitigating CRS symptoms, including nasal obstructions, facial discomfort, and respiratory difficulties. The success rate of FESS is usually high, with studies documenting improvement rates of 70–90% (Delgado-Ruiz et al., 2022; Lee et al., 2022; Hamilos, 2011).

Post-operative care and non-invasive strategies play a pivotal role in the successful recovery following FESS, as these measures help diminish the risk of complications. Inadequate post-operative care may necessitate additional surgical intervention, which could render the entire procedure ineffective (Moghadam et al., 2018). Long-term treatment using a topical steroid nasal spray has been evidenced to lessen sinus inflammation and alleviate symptoms related to CRS (Moghadam et al., 2018; Grzincich et al., 2004). Daily usage of nasal steroids can help to mitigate their associated side effects; nevertheless, sustained use of this medication can potentially lead to significant adverse outcomes such as epistaxis, irritation, and alterations in bone density (Grayson and Harvey, 2019; De Corso et al., 2022; Gillespie and Osguthorpe, 2004). Consequently, to ensure the effective administration of drugs to the nose and sinuses while minimizing side effects, it is imperative to develop a targeted drug delivery (TDD) methodology.

1.1. Nasal cavity

For the formation of an effective sinus drug delivery system, an exhaustive understanding of the anatomy of the upper respiratory passage, which includes the NC and paranasal sinuses, is indispensable. The nose in humans is bifurcated into two distinct parts - the external and the internal. The external component, standing out as a conical prominence from the facial structure, is constituted by a part that is both bony and cartilaginous in nature, colloquially known as the nose (Koppe et al., 2011; Stevens and Emam, 2012). The internal part of the nose, known as the NC, serves as the main entrance to the respiratory system (Sosnik, 2016). Air and aerosols enter the NC through the two nostril openings at the base of the nose and reach the lungs through the respiratory system. The nasal septum, which is the cartilage that separates the two nostrils, plays a crucial role in this process (Fig. 1) (Nease and Sturm, 2023; Wong et al., 2021).

The various sections of the NC are illustrated in Fig. 2 (a-f). The NC primarily contains three main airways: the vestibule, the olfactory, and the respiratory airways. The vestibules extend from the nostril entrances to the nasal valves, the latter being the narrowest sections of the nasal passage (Sobiesk and Munakomi, 2019). The respiratory system comprises the inferior meatus (IM), middle meatus (MM), and superior meatus (SM), located between the nasopharynx and the nasal valve. The olfactory epithelium, which enables our sense of smell, is located on the NC's roof (Harkema et al., 2006). Fig. 3 demonstrates the upper epithelium layer covered with jelly mucus, which oscillates 7–8 times per second and is located on a watery saline layer (Zhou et al., 2009). The cilia, being viscoelastic, facilitate the transportation of mucus towards the nasopharynx by converting energy from oscillations (Fig. 3). Approximately 125 mL of mucus is produced daily, moving at a rate of 1–2 cm per hour towards the nasopharynx (Illum, 2003; Mistry et al., 2009; Ugwoke et al., 2005).

The mucociliary escalator carries inhaled particles deposited to the nasopharynx, where they are swallowed and enter the stomach (Randell and Boucher, 2006). While mucociliary transport is a vital part of filtration, it hinders nasal drug delivery because the medication is transported to the gastrointestinal system, thus reducing the amount of drug diffused into the blood (Fry and Black, 1973; Schmidt et al., 1998). In recent studies, polymer-coated nanoparticles have shown improved efficiency of drug diffusion into the blood after being deposited on the NC and sinus walls (Illum, 2012; Protection of the Upper Airway, 2012).

1.2. Paranasal sinuses

The NC is surrounded by four sinuses: the sphenoid sinuses (SS), ethmoid sinuses (ES), frontal sinuses (FS), and maxillary sinuses (MS). These sinuses derive their names from the bones that encapsulate them (Drake et al., 2020; Cappello et al., 2018). The SS, which develop within the sphenoid bone after adolescence, is located deep in the skull, between the eyes and behind the nasal structure. The ES, which develops at birth and grows with the individual, is positioned between the eyes and

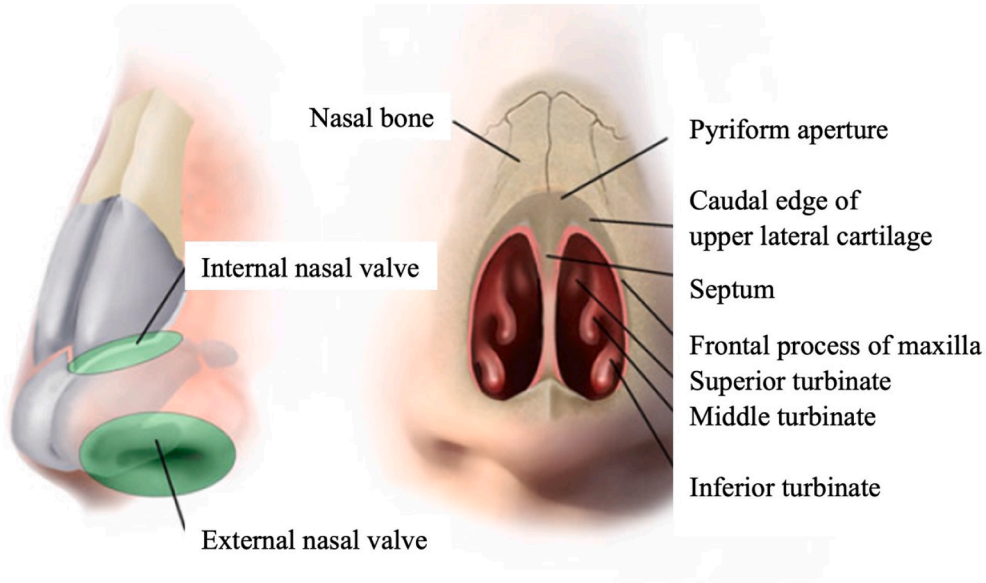

Fig. 1. An overview of the (a) side and (b) front cross-section view of human nasal cavity anatomy, reprinted from Wong et al. (2021), with permission from Springer Nature.

behind the bridge of the nose. The FS, situated above the eyes in the forehead region, begins forming after the seventh year of life. The MS, the most substantial among the paranasal sinuses, is nested in the cheekbones, flanking the nose. The MS starts forming at birth, grows throughout childhood, and typically reaches its final size around the age of 17 or 18 (Drake et al., 2020; Cappello et al., 2018). Fig. 4 depicts the positioning of these paranasal sinuses within the skull (T.W. (Illustrator), 2012).

One of the earliest reliable portrayals of the sinuses is Leonardo Da Vinci's sketch of the paranasal sinuses, dating back to 1489 (Crowe, 2005). In 1651, a more precise illustration of the paranasal sinuses, known as the antrum of Highmore, was introduced (Blanton and Biggs, 1969). In the past, it was commonly believed that the secretions in the nose were produced by the brain and flowed into the NC. However, Schneider discovered that it was actually the mucosa in the sinuses that produced the fluid, which may be due to CRS or other conditions (Stammberger, 1989).

Paranasal sinuses perform three main functions: resonating the voice, lightening the skull, and producing lysozyme, which helps prevent bacterial infections in the nasal mucus (Boysen, 1982; Tu et al., 2012). The sinuses are connected to the NC by small channels called ostia. These channels allow the mucus to drain into the nose and allow air to circulate in and out of the sinuses. The presence of numerous conditions, including allergies, infections, polyps, and structural issues, can instigate the mucous membranes of the sinuses to inflame and swell. This process manifests as symptoms such as nasal obstruction, headaches, and discomfort in the face, which are indicative of CRS (Dykewicz and Hamilos, 2010; Kim, 2019). Dealing with CRS can be quite arduous, requiring precise drug delivery to the paranasal sinuses as a fundamental aspect of effective management. It is common for topical medication delivery to be required after FESS to manage inflammation and ensure satisfactory treatment results. However, current treatment options are limited in their effectiveness in delivering medication to the paranasal sinuses, making it challenging to manage symptoms and achieve the desired therapeutic results. The upcoming sections will delve into TDD techniques that have been designed to augment the efficacy of medication delivery in sinusitis treatments.

2. Targeted drug delivery methods

TDD aims to deliver medication to specific cells or tissues in the body with increased efficacy and reduced side effects (Tewabe et al., 2021). Unlike systemic drug delivery methods, TDD delivers active compounds at higher concentrations to the target site, reducing undesirable systemic side effects (Sultana et al., 2022). TDD can be used to address several diseases, including cancer, neurological disorders, and hearing loss, where reducing adverse effects is crucial (Liu et al., 2019). There exist numerous limitations linked to TDD, which include aspects such as its high expenditure, intricacy of the equipment involved, and the discomfort that the patient may encounter (Dikmen et al., 2011).

The NC presents a favourable setting for TDD owing to its expansive and well-perfused surface area. This characteristic makes it apt for managing ailments linked to the nose and paranasal sinuses, as well as for administering aerosolized medications and needle-less immunizations (Djupesland, 2013). Two fundamental categories of TDD are recognized: passive and active. Methods of Passive Targeted Drug Delivery (PTDD) - such as aerosol sprays and nebulizers - are non-invasive and user-friendly, but their efficacy can be limited. On the other hand, Active Targeted Drug Delivery (ATDD) exhibits greater selectivity and specificity, employing a distinct agent to aim at a specific receptor on the cell surface (Lewis et al., 2007; Sengupta and Balla, 2018).

2.1. *Passive targeting*

Passive targeting is a methodology in the domain of nasal drug administration that is designed to deliver therapeutics to specified zones in the airway such as the NC, MS, pulmonary region, and olfactory areas. Accomplishing this targeting involves the manipulation of numerous variables such as therapeutic dosage, aerosol droplet dimensions, schedule of administration, rate of inhalation, and gas density (Dolovich and Dhand, 2011). There is a vast array of tactics and instruments intended for the execution of PTDD to dispense medicines to the NC, sinuses, and olfactory zones. This discussion delves into the variety of PTDD modalities and instruments, identifying the optimal PTDD method of administering drugs to NC and MS.

Numerous devices and approaches, custom-made for this exact goal, comprise methods like droplet delivery using a pipette, the introduction of liquid by means of a rhinyle catheter, the employment of squeeze bottles, the application of multi-dose spray pumps, and the utilization of nebulizers. Out of these, nebulizers have been recognized to be the most effective PTDD device for assuring that medications make their way to the paranasal sinuses and the olfactory network.

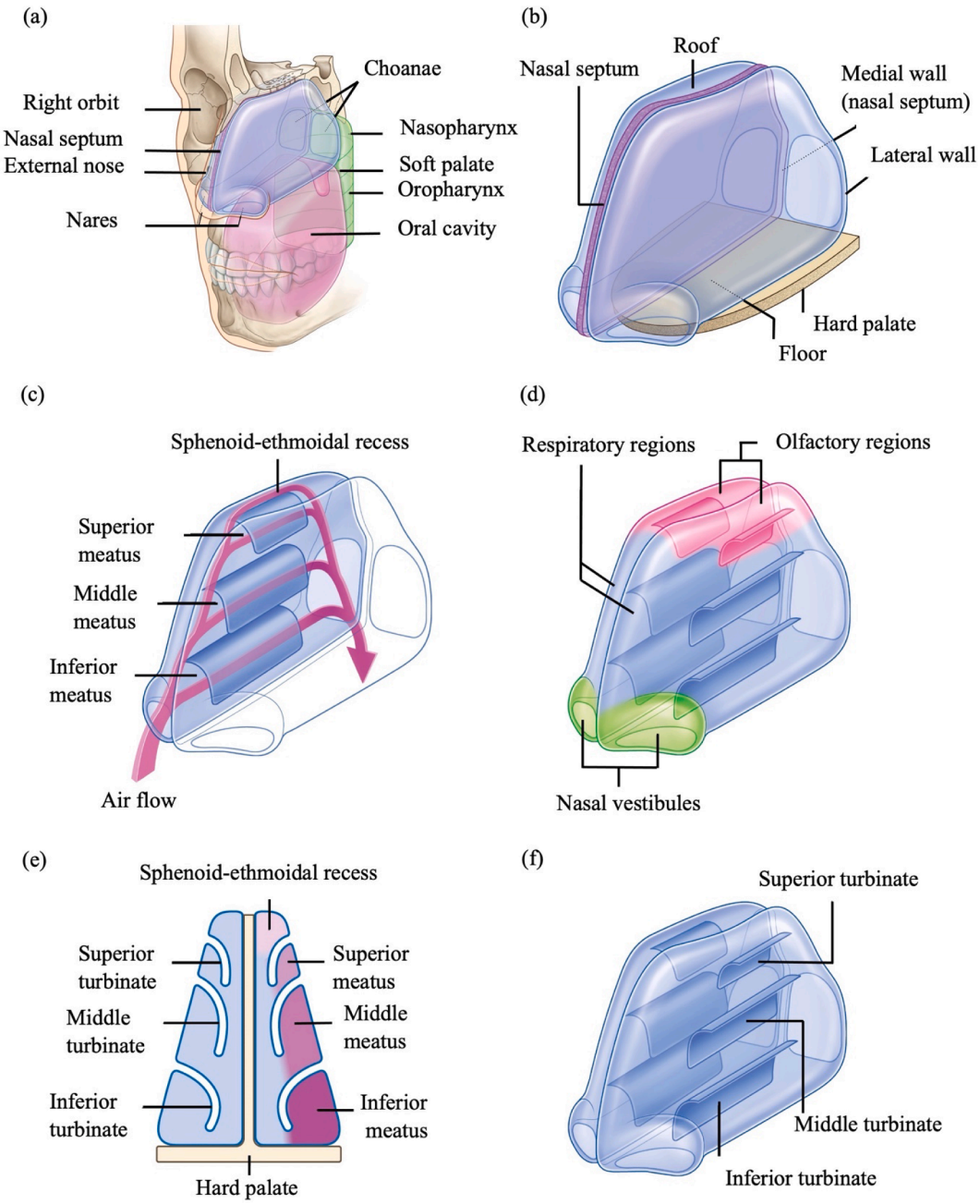

Fig. 2. An overview of a) the location of the NC within the skull (b) the nasal cavity's side walls; (c) the airflow pattern in the right NC; (d) the respiratory and olfactory systems, in addition to the nasal vestibules; (e) a coronal slice of the NC; (f) the three turbinates on the nasal cavity's side walls are also included, reprinted from Drake et al. (2020), with permission from Elsevier.

The technique of delivering drops via pipette is a well-entrenched method in the realm of nasal drug delivery that capitalizes on the PTDD approach (Djupesland, 2013). This methodology encompasses the administration of drops and vapor to the NC utilizing economical saline solutions and decongestants housed in blow-fill-seal pipettes (Keith et al., 2000; Penttilä et al., 2000). While a rhinyle catheter and syringe can be used to accomplish liquid delivery to the NC (Bakke et al., 2006), this method isn't popular due to its high probability of dosage errors and cumbersome process. A squeeze bottle is another PTDD method that delivers the liquid medication into the NC by pressing on the bottle and directing the flow through the nozzle situated in the nostril. However, severe nasal diseases such as CRS may not be effectively treated with it given its unacceptable wastage of active drug of >97% (Smith et al., 2013).

The majority of nasal medications are dispensed through multi-dose spray pumps, generating microparticles (tiny droplets) that are between 50 and 100 μm in size (Moffa et al., 2019). These have been demonstrated to be effective in managing nasal polyps and seasonal allergic rhinitis (Berger et al., 2007; Newman et al., 1987). Moreover, approximately 90% of the sprayed medication settles in the anterior section of the NC, including the nasal valve, while considerable drug transport to posterior region for effective treatment of CRS is needed (Kimbell et al., 2007). It's important to note that multi-dose spray pumps require some initial priming to ensure dosage consistency. This makes them unsuitable for use with expensive vaccines and medications the dose of which must be carefully controlled and administered only once as they require a single dose (Moffa et al., 2019).

Nebulizers offer a solution to the issue of overly large particles

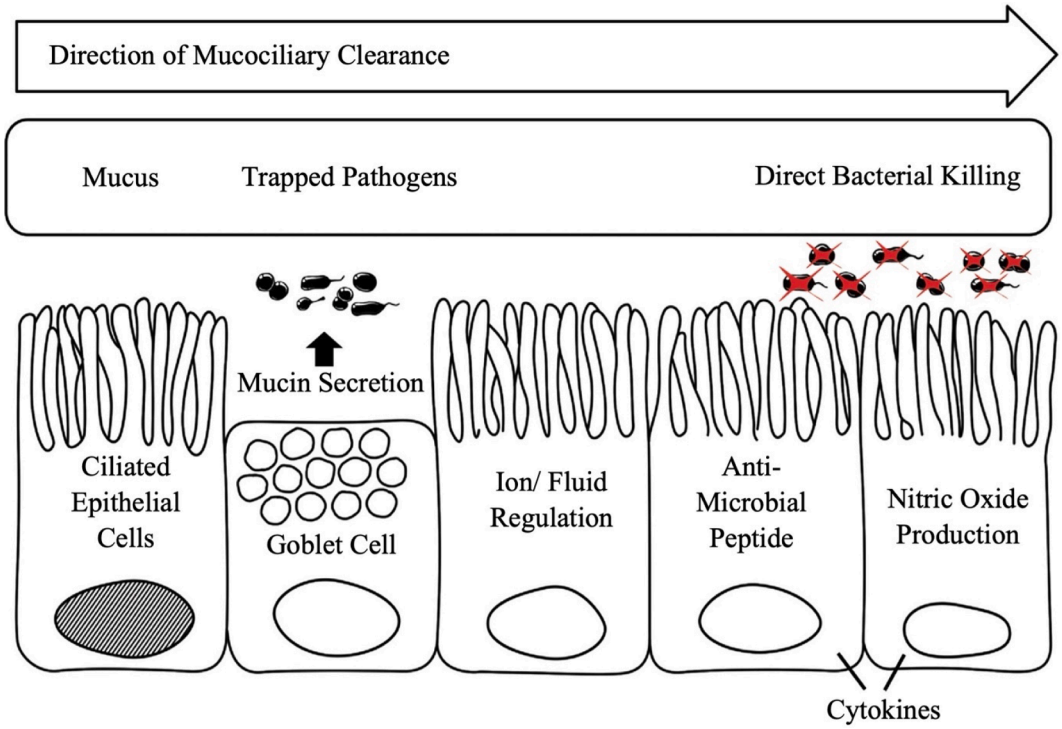

Fig. 3. Schematic of the clearance of nasal mucosa and how mucociliary secretion transport works, reprinted from, with permission from Springer Nature. Reprinted from Maxillary Sinusitis Ganesan et al. (2021) licenced under CC BY 4.0.

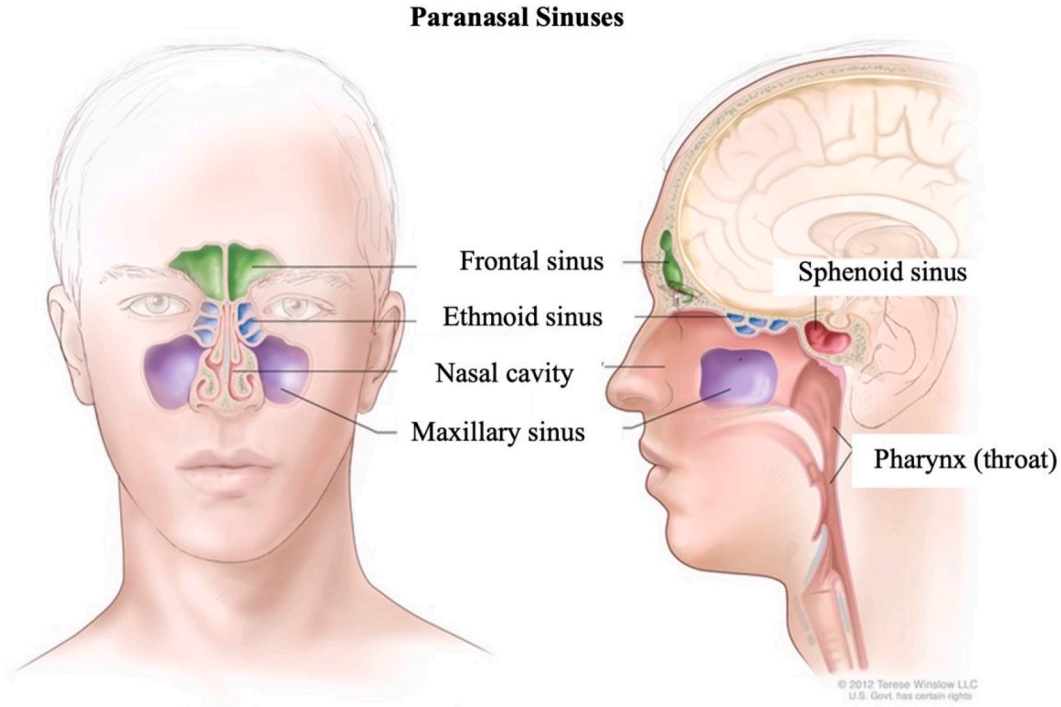

Fig. 4. A graphical illustration of paranasal sinuses anatomy, reprinted from Paranasal sinus anatomy by Terese Winslow (2012), with permission from the rights holder.

(50–100 μm) typically produced by nasal spray pumps. By employing mechanical force or compressed gases, these devices produce finer aerosol particles ranging from 1 to 30 μm in size (Moffa et al., 2019) most commonly with a MAD of about 3–5 μm. Studies have pointed out that nebulizers hold the edge in delivering medications to the SM, MM, and paranasal sinuses, generally because of the size reduction and slower velocities of airborne particles they produce (Moffa et al., 2019). Due to the very fine size of nebulized droplets, over 60% of the dispensed medication reaches the posterior region. Therefore, nebulizers are the most effective PTDD devices to deliver drugs to the posterior region and the olfactory system due to their ability to produce smaller aerosol particles and slower speed of aerosol particles (Moffa

et al., 2019). However, the amount and distribution of medication delivered to the paranasal sinuses is still not acceptable in most cases. Despite the different PTDD methods/devices available, the challenge of delivering the desired amount of medication to paranasal sinuses still needs to be addressed to ensure that patients receive the full benefits of nasal drug delivery. Active drug delivery methods may offer a solution to this challenge.

2.2. Active targeting

Drug delivery efficiency can be greatly improved by adopting an ATDD approach instead of a PTDD approach.

There are several methods to accomplish active targeting. One approach involves using drug-loaded nanoparticles coupled with cell-specific ligands. In this context, it's important to identify the characteristics of the receptor on the targeted cancerous or tumour cell. The end goal is to have these nanoparticles capable of binding to cancerous or tumour cells that have matching receptors (Galvin et al., 2012). Additionally, besides the methods discussed above, which are mostly based on chemical and biological factors, it has been shown that some physical and environmental resources can also be used to trigger the active delivery of medication to a targeted site (Vasir et al., 2005). The following are brief descriptions of ATDD methods.

2.2.1. Magnetic drug targeting

Magnetic fields have been in therapeutic use for a variety of illnesses since 1941. It was evident from a 1957 study by Gilchrist and colleagues (Gilchrist et al., 1957) that magnetic particles could be used to treat cancer by causing thermal effects on lymph nodes. Magnetic Drug Targeting (MDT), using drug-laden microparticles, has been developed for the purpose of active targeting. The first clinical trial involving MDT took place in 1996 for tumour therapy (Lübbe et al., 1996), and since then, numerous researchers have explored MDT as a treatment option for cancer and other medical conditions (Bose et al., 2013; Mathieu et al., 2006; Riegler et al., 2011; Hedayati et al., 2018; Shapiro et al., 2014). To maneuver through the circulatory system, MDT needs to balance viscous drag forces by leveraging an external magnetic field exerts a magnetic force on particles (Ranjbari et al., 2023). However, MDT in the respiratory system presents additional complexity, as the mucus layer lining the airway walls adds further challenges to the process (Ally, 2010). Pourmehran et al. (2016) determined the optimal properties of magnetic drugs and coordinates of the magnetic source for maximizing efficiency of MDT in human airways. In a different study, Xi et al. (2015) reported a significant 64-fold increase in the effectiveness of drug delivery to the olfactory region, as shown in Fig. 5 (a). In the circulatory system, particle deposition and retention processes are similar due to the blood being the only surrounding fluid. However, Magnetic Drug Targeting (MDT) is more complex in the respiratory system. Drug-infused particles carried by airflow can deposit on mucus-lined airway walls and are moved by the mucociliary transport mechanism, a process that does not exist in the circulatory system. Hence, particle deposition and retention in the respiratory system must be separately considered, increasing the complexity of MDT.

2.2.2. Electrically-charged drug delivery

Electrically charged drug delivery (ECDD) is an approach for respiratory drug delivery that uses external electrodes to direct charged particles to a target region. Aerosol droplets can be charged through conduction or induction during the generation of the aerosol. ECDD has been studied for nasal drug delivery and olfactory region drug delivery, with significant increases in particle deposition demonstrated (Xi et al., 2014; Xi et al., 2015). The concept of using ECDD for particle deposition in the lungs was primarily discussed by Wilson (1947), and subsequent studies have shown enhanced particle deposition in rats' and humans' lungs (Ferin et al., 1983; Prodi and Mularoni, 1985; Vincent et al., 1981). Nevertheless, ECDD is not applicable in the circulatory system since the blood discharges the particles. As humidity increases in the lower respiratory tract, electrostatic impacts of charged particles are more prominent in the upper airways given that the humidity dissipates the electric charges of individual particles (Xi et al., 2014; Elajnaf et al., 2007; Pourmehran, 2021). Although ECDD can efficiently boost particle deposition by a factor of 10 in the ostiomeatal complex (Xi et al., 2015) and improve the drug delivery to the olfactory region (Fig. 5 (b)), it is unable to deliver drug particles to the paranasal sinuses.

2.2.3. Acoustically-driven drug delivery

In biomedical applications, acoustics is employed for non-invasive drug delivery, which is divided into two main types: high-intensity focused ultrasound (HIFU) for enhanced drug delivery and low-frequency acoustic drug delivery (ADD) (Lynn et al., 1942; Ballantine et al., 1960; Fry and Fry, 1960; ter Haar and Coussios, 2007). HIFU has various therapeutic scenarios, including topical heating for tissue ablation and enhancement of TDD through sonodynamic therapy (Jeffers et al., 1991; Kennedy, 2005; Leslie and Kennedy, 2007; Rosenthal et al., 2004; Kinoshita and Hynynen, 2006; McHale et al., 2016). However, the use of HIFU for therapeutic purposes in the respiratory system is limited

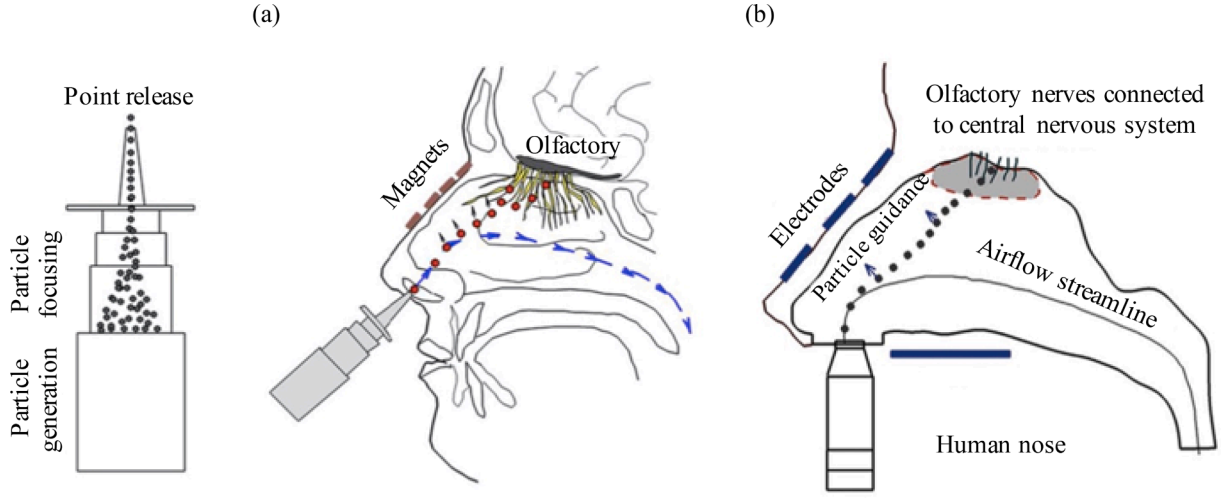

Fig. 5. (a) Schematic of particle generation and illustration of magnetic drug targeting to olfactory region, reprinted from Xi et al. (2016) with permission from Springer Nature; (b) drug delivery using ECDD to the olfactory region, reprinted from Electrophoretic particle guidance significantly enhances olfactory drug delivery: a feasibility study by Xi et al. (2014) licenced under CC BY 4.0.

due to the scattering and reflection of ultrasound caused by the gas-filled nature of the lungs and airways (Pitt et al., 2004). Conversely, use of low-frequency ADD for nasal drug delivery has been shown to increase drug deposition in the paranasal sinuses (Navarro et al., 2019; El Merhie et al., 2016; Farnoud et al., 2020; Leclerc et al., 2014; Möller et al., 2010). Combining a nebulizer with an acoustic wave has been proposed as a way to deliver drugs efficiently to the MS (Möller et al., 2010; Möller et al., 2011). Despite this, the approach has yet to prove itself fully effective in managing CRS (Leclerc et al., 2015). In order to improve the efficiency of drug delivery to the paranasal sinuses, a more profound insight into the operational principles of active drug delivery is essential, as echoed in the related citation (Möller et al., 2011).

3. Improving sinus deposition with acoustic humming

Historically, investigations into acoustic drug delivery originated several decades ago, with foundational studies carried out in 1959 by Guillerm et al. (1959). They designed an *in vivo* experiment using blown glass that simulated the frontal sinuses of a dog, serving as the sinus cavity model for their research. The findings from their investigation indicated that a combination of sound waves and a jet nebulizer could push nebulized droplets into a sinus-like structure. More recent studies have corroborated that acoustic waves can augment aerosol penetration into the NC. The initial suggestion of the effectiveness of acoustic waves in drug delivery to sinuses came from research into humming. This practice has been linked with a higher exchange of air between the NC and the paranasal sinuses by raising the quantity of exhaled nitric oxide (NO) (Lundberg et al., 1995; Lundberg and Weitzberg, 1999).

In the investigation led by Weitzberg et al.'s (2002), the capabilities of acoustic waves, similar to humming, were examined to boost NC-MS air exchange rate during exhalation. This clinical study monitored NO levels in the exhaled breath of ten healthy male participants using a chemiluminescence system (NIOX, Aerocrine AB, Stockholm, Sweden). The subjects were guided to exhale for five seconds via three distinct methodologies: with NC humming, without NC humming, or through oral phonation. The outcome revealed that NC humming considerably increased NO levels in exhaled air, leading to a 15-fold surge compared to a silent exhalation (2818 $\pm$ 671 nL/minute versus 189 $\pm$ 30 nL/minute). Conversely, oral phonation did not incite any substantial alteration in NO levels compared to a quiet exhalation (103 $\pm$ 43 nL/minute vs. 104 $\pm$ 48 nL/minute). These outcomes suggest the potential of using acoustic waves, akin to humming, during nasal exhalation to efficiently boost NC-sinuses gas exchange. Given these findings, the integration of acoustic waves into nasal drug delivery tactics could present a promising avenue for augmenting the efficiency of sinus drug delivery. Through harnessing the improved gas exchange driven by acoustic waves, novel techniques can be developed by researchers, engineers, and healthcare professionals to more effectively manage a variety of sinus-related ailments (Weitzberg and Lundberg, 2002).

Maniscalco et al. (2003) drew inspiration from Weitzberg *et al.*'s work and conducted a clinical and *in-vitro* study to investigate the impact of acoustic waves on NC-MS air exchange (Fig. 6). Employing a similar measurement method, they discovered that the concentration of exhaled NO was influenced by both humming frequency and the maxillary ostium diameter. Testing three frequency ranges (120, 200, and 450 Hz), they discovered that a 200 Hz frequency led to the highest NO exchange at 295 nL/min. Furthermore, as the ostium diameter increased, NO exchange also increased, with 100% exchange observed for a 4 mm diameter. Consequently, many studies have focused on exploring the effects of acoustic wave superposition in acoustic drug delivery to better comprehend its underlying principles and optimize drug delivery efficiency.

4. Principle of acoustic drug delivery to sinuses

The use of acoustic drug delivery to the paranasal sinuses is a recent drug delivery method that has gained attention due to its non-invasive and non-toxic characteristics, which makes it a promising alternative to other delivery methods (Durand et al., 2012; Ciancia et al., 2020; Abdollahzadeh Jamalabadi and Xi, 2022). Acoustic drug delivery works by utilizing low-frequency sound waves to create small pressure gradients in the NC and sinuses, which enhances drug transport across the ostia (Ciancia et al., 2020; Abdollahzadeh Jamalabadi and Xi, 2022; Lafond et al., 2017).

Traditionally, sinus drug delivery has utilized 50 Hz and 100 Hz acoustic frequencies. These frequencies were identified by researchers who observed workers operating a rotating electrical machine that generates sinusoidal waves at a specific frequency (Navarro et al., 2019). However, recent studies propose that the increased aerosol deposition in the sinuses during ADD may be linked to the Helmholtz resonator (HR) principle (Pourmehran, 2021).

In a NC-MS combination the MS and ostium bear similarities to the cavity and neck of a HR (Navarro et al., 2019; Pourmehran et al., 2022). As per the HR concept, when the external acoustic wave shares the same frequency as the resonance frequency of the NC-MS combination, which consists of a cylindrical neck and a sphere, the air plug within the ostium experiences maximum oscillation. This results in the most effective drug penetration into the MS (Fig. 7) (Helmholtz, 2009; Pourmehran et al., 2020).

For HR featuring cylindrical necks and spherical cavities, the

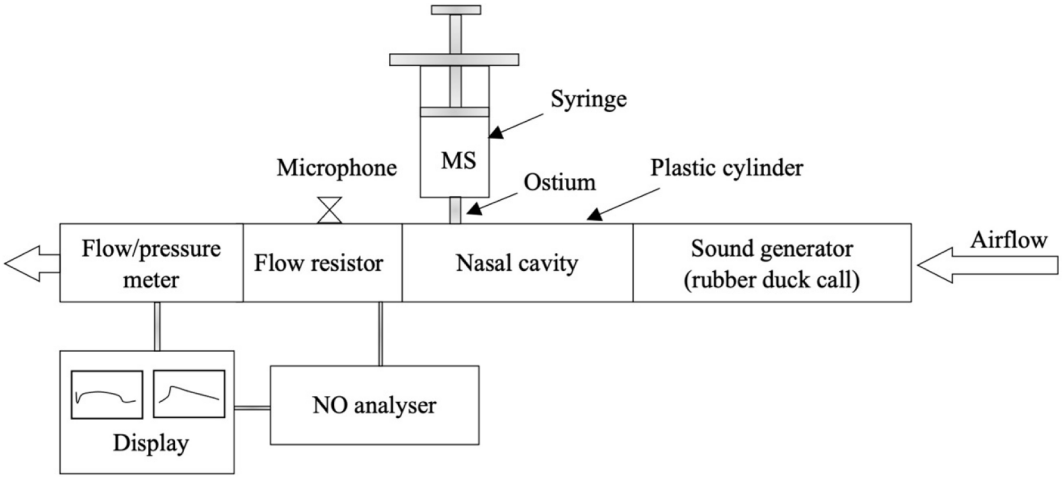

Fig. 6. Schematic diagram of a model depicting the sinus (represented by a syringe), the ostium (represented by the syringe tip), and the NC (represented by a plastic cylinder), reproduced from Maniscalco et al. (2003), with permission from the European Respiratory Society.

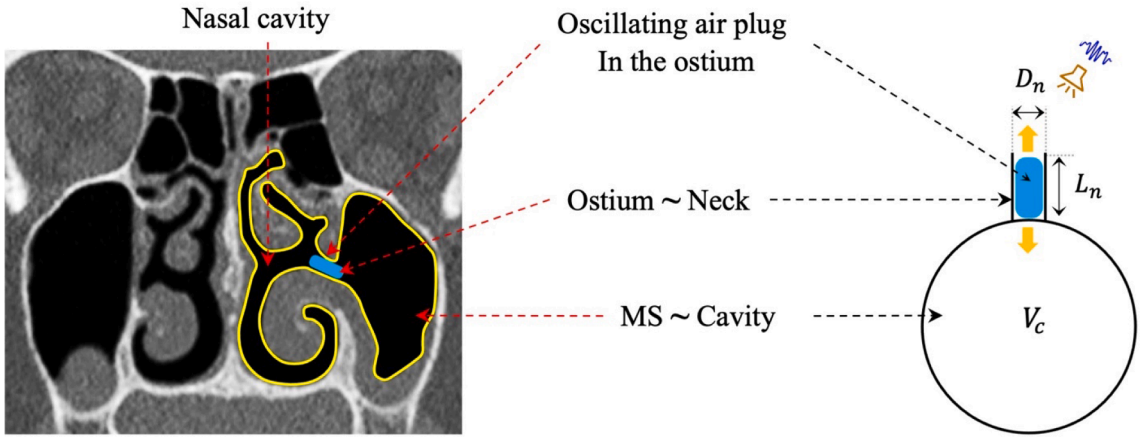

Fig. 7. An illustration of the Helmholtz resonator's structure and function, adapted with some changes from Pourmehran (Pourmehran, 2021) with permission.

following method can be used to calculate the resonance frequency (Möller et al., 2010):

$$f_r = \frac{c}{2\pi}\sqrt{\frac{S_0}{V_c L_n}} \tag{1}$$

where c stands for the sound speed, $S_0 = \pi D_n^2/4$ refers to neck cross-section (where D_n denotes the neck diameter), V_c represents the cavity's volume, and L_n is the neck length. A more detailed definition can be derived and reported based on the shape of the cavity (Howard et al., 2000; Alster, 1972).

Following the principles of HR, applying a sound wave to the NC with a frequency that aligns with the nose-sinus resonance frequency system should lead to an enhanced efficiency between the NC-sinuses air exchange (Dikmen et al., 2011). The key factor influencing particle movement from NC to sinus is the exchange of gas between these two regions (Pourmehran et al., 2021).

Using an acoustic wave to improve particle penetration or droplets, such as medication, into the sinuses results in the particles being affected by the acoustic waves, causing them to vibrate at a particular frequency and phase that typically differs from that of the original acoustic wave. According to Marshall *et al.*, (2014) (Marshall and Li, 2014), the oscillating particle velocity (orthokinetic motion) is:

$$u_p = \eta_p A_u \sin\left(2\pi f t - \phi_p\right) \tag{2}$$

Where f, A_u, η_p, and ϕ_p represent the acoustic frequency, the maximum amplitude of particle velocity, the coefficient of particle entrainment, and the phase factor, respectively, which are given as follows (Marshall and Li, 2014):

$$\eta_p = \frac{1}{\sqrt{1 + (St_{ac})^2}} \tag{3}$$

$$\phi_p = \tan^{-1}(St_{ac}) \tag{4}$$

where St_{ac} represents the acoustic Stokes number given by (Marshall and Li, 2014):

$$St_{ac} = \frac{2\pi f \rho_p d_p^2}{18\mu} \tag{5}$$

where f, ρ_p, d_p, and μ are the acoustic wave frequency, particle density, particle diameter, and the dynamic viscosity, respectively (Marshall and Li, 2014).

As particle size increases, acoustic Stokes number (represented by Equation (5)) increases, leading to a lower particle entrainment coefficient (represented by Equation (3)); this, in turn, decreases the amplitude of the particle velocity as given by Equation (2). Hence, with an increased particle diameter, fewer particles are capable of penetrating into the MS (Marshall and Li, 2014).

In a study conducted by Leclerc et al. (2014), they investigated the impact of factors such as particle dimensions, breathing patterns, and 100 Hz sound waves on the settling of aerosols in the MS. To accomplish this, they utilized a realistic NC-sinus replica, crafted from a clear, impenetrable resin through the process of stereolithography. They used a jet nebulizer for 10 min to generate 4 mL of gentamicin antibiotic aerosols. The study discovered that in comparison to regular respiration, the introduction of a 100 Hz frequency resulted in a 2- to 3-fold enhancement in the deposition of aerosols in the MS. Aerosol particles with a size of 9.9 μm displayed minimal settling, while particles measuring 2.8 μm exhibited considerable deposition. The observed discrepancy can be ascribed to the particle's orthokinetic movement while being subjected to an acoustical field.

5. Pulsating airflow for sinus drug delivery

The augmentation of air ventilation within the paranasal sinuses can be achieved by utilizing pulsating airflow as a carrier phase. Additionally, pulsating airflows have been shown to deliver topical drugs effectively in sufficient quantities to the nose and the ostiomeatal complex, including the paranasal sinuses (Farnoud et al., 2020).

Möller et al. (2008) demonstrated the impact of ADD on a nasal cast that covered all paranasal sinuses and was made of polyoxymethylene, by utilizing pulsating airflow to simulate the exchange of gas between the NC and individual sinuses (Fig. 8). A cylindrical glass vial was used to form the sinuses and ostia. In comparison to a gas flow with no pulses, the NC and all sinuses exchanged gas 6 times more often with pulsation. In a clinical research study conducted by Möller *et al.* (2010) (Möller et al., 2010), the results were quantitatively confirmed.

The same nasal-sinus model, nebulizing device, and test setup for gas exchange evaluations were utilized by Möller et al. (2008) using dynamic ^{81m}Kr-gas imaging in conjunction with pulsating airflow to evaluate sinus ventilation efficacy in a nasal cast. In two minutes of running time, ^{99m}Tc was detected via gamma camera imaging (Fig. 8). During this study, they examined the deposition of aerosols in the sinuses in relation to ostium diameter (1 mm, 2 mm, 3 mm, and 5 mm), as well as sinus volume (5 mL, 10 mL, and 20 mL). Based on the results, pulsating airflow enhanced ^{81m}Kr-gas ventilation and aerosol deposition when sinus volume was increased. In contrast to 0.2% deposition efficiency without pulsation, nebulized drugs could deposit as much as 8% in the sinuses during pulsating airflow. Pulsating airflow is highly efficient for sinus ventilation and nasal drug delivery in this study. As a result, it can be demonstrated that topical drug delivery can be achieved in relevant quantities in the paranasal sinuses (Möller et al., 2008).

Farnoud et al. (2017) used computational fluid dynamics (CFD) modelling with OpenFOAM to study the impact of pulsating airflow on

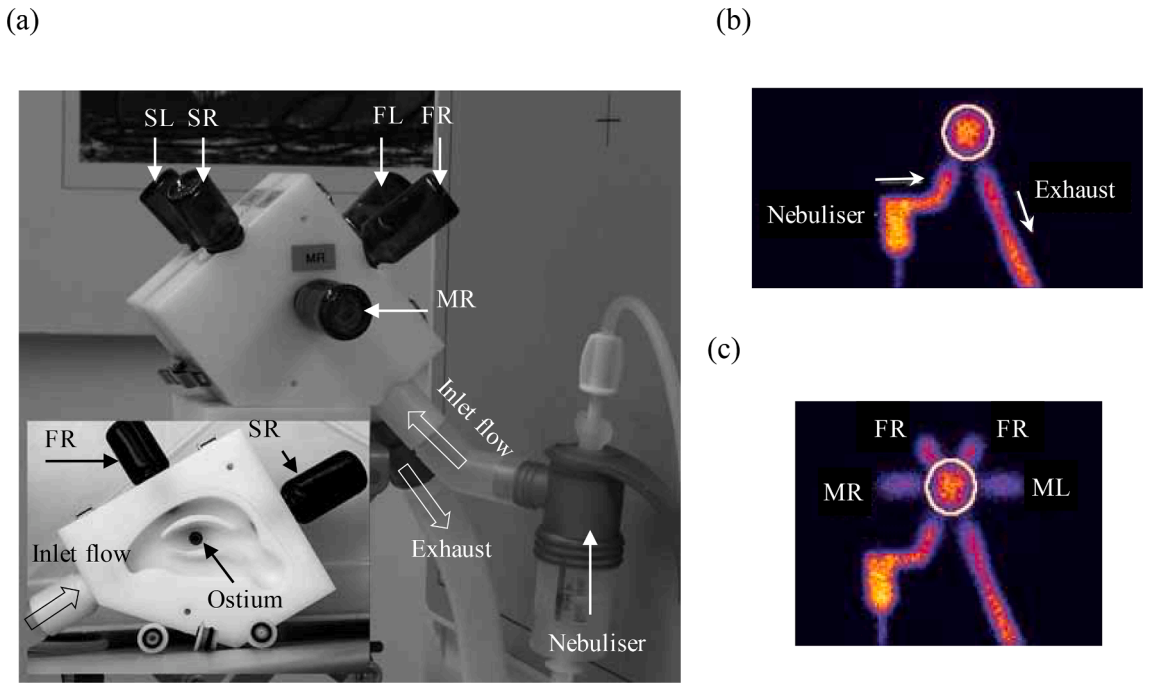

Fig. 8. (a) The nasal cast, with the nebulizer connected to the right nostril, is positioned in front of the gamma camera.; (b) The gamma camera image of the nasal cast in a frontal view without acoustic; and (c) with acoustic, reprinted from Möller et al. (2008), with permission from Rhinology; modification has been applied to the labelling as adapted from Pourmehran (Pourmehran, 2021).

particle deposition in a human nose. The researchers created a 3D model of the NC based on a CT scan and used a two-way coupling approach to model airflow and liquid spray distribution. They used a combination of a large eddy simulation (LES) and a dynamic Smagorinsky sub-grid scale model to analyse the spray under different airflow conditions, including steady inflow rates and pulsating airflow at a frequency of 45 Hz. They injected 10,000 mono-disperse particles randomly into the nostrils to identify the fraction of particles deposited in the NC. The results indicated that the pulsating airflow improved the penetration of medication into the sinuses. They also found that most of the droplets deposited in the nasal valve, septum, and nasopharynx, which was attributed to the change in the direction of airflow (Farnoud et al., 2017).

In 2020, Farnoud et al. (2020) examined influence of pulsating airflow on deposition of particles in paranasal sinuses. They superimposed a frequency of 45 Hz on nebulised particles while the nosepieces were inclined in a clockwise direction at angles of 45° and 90°, with the soft palate remaining closed. They reported that pulsating airflow improved the efficiency of particle delivery to sinuses with more homogenous deposition pattern compared with non-pulsating airflow. In particular, they demonstrated that pulsating airflow improved particle deposition by 1.5 and 2.5 times for nosepiece inclinations of 90° and 45°, respectively. The results provides important information for the development of more efficient drug delivery systems (Farnoud et al., 2020).

6. Variation of acoustic waves in ADD

Sound wave technology, specifically acoustic waves, is a burgeoning field that holds promise in the sector of drug delivery. This concept is grounded on the physical attributes of acoustic waves, fundamentally sound waves that travel through a medium. Besides their non-invasive nature and ability to hone in on targeted tissues, these waves have the capability to discharge medicinal compounds from nanoparticle (Husseini and Pitt, 2008). When it comes to drug delivery applications, acoustic waves are primarily divided into two categories: fixed and sweep frequency acoustic waves (Pourmehran et al., 2020).

6.1. Fixed frequency acoustic wave

Acoustic waves of a fixed frequency have been probed as a prospective technique for drug delivery to the sinus cavities. This technique harnesses sound waves emitted at a consistent frequency to transport medications non-invasively and directly via the nasal passages, ensuring targeted delivery of drugs into the sinus cavities. This method of drug delivery presents multiple benefits, such as being non-intrusive, having better accuracy, and being capable of reaching deep within the body without causing tissue damage (O'Reilly and Hynynen, 2012; Seip et al., 2009). Furthermore, these fixed acoustic waves encourage prompt drug dispersion along with consistent and reproducible release rates, which can be crucial for prolonged treatments or chronic disease management.

Building on the findings made by Maniscalco et al.'s (2003) that highlighted the impact of humming frequency on NO exchange, a subsequent study was conducted by Maniscalco et al. (2006). This research aimed to examine the effect of 200 Hz nasal humming on the deposition of droplets within the sinuses. Their results demonstrated that compared to non-acoustic drug delivery methods, acoustic airflows increased particle deposition in the sinuses by 2 to 4 times. This indicates that not only does the acoustic frequency influence NO exchange, but it also has an impact on drug delivery to the sinuses, potentially improving the effectiveness of treatments.

Durand et al. (2001) compared and investigated the aerosol penetration by the nasal and sinus models of two adult males. CT images of palatine models were compared to check their accuracy. In order to nebulize the aerosols, they used the ATOMISOR NL11S® "sonic nebulizer" contains a vibrating capsule that produces a 100 Hz frequency sound. In comparison to traditional methods of drug delivery without sound waves, the results showed a significant improvement with 1.3 times increase in the ability of the aerosol to reach the sinuses (Durand et al., 2001).

Using a human palatinate nasal cast as a test bed, Durand et al. (2011) investigated the effect of a 100 Hz acoustic wave on aerosol deposition in the MS. Compared with non-ADD, gentamicin was deposited 3 times more in the MS under the influence of an acoustic

wave (100 Hz and 107 dB). Nebulized gentamicin was injected into the NC via a jet nebulizer as a drug tracer. A syringe was used to flush the MS through physiological serum for 10 min in order to collect the gentamicin deposited in it. A TDxFLx® analyser was used to quantify the gentamicin collected from each sinus.

Möller et al. (2013) examined the effects of an acoustic nebulizer with a 25 Hz acoustic frequency and a gamma camera imaging technique on aerosol deposition. 11 patients with CRSsNP (Chronic Rhinosinusitis with Nasal Polyps) were given ^{99m}Tc-DTPA pulsating aerosols pre- and post-surgery of the sinuses. In addition, eleven healthy individuals were compared with nasal pump sprays for pulsating aerosols. Gamma camera imaging was used to determine the distribution of aerosols in the NC and frontal, maxillary, and sphenoidal sinuses, as well as any lung penetration. Among healthy participants, the nasal pump sprays led to complete nasal deposition, without any significant deposition in the sinuses or lungs, while the pulsating aerosols led to nasal deposition of 61.3+/-8.6%, with 38.7% being released through the opposite nostril. About 9.7+/-2.0% of the nasal dose reached the SS and MS. The total nasal deposition in CRS patients was 57.9+/-13.3% before and after sinus surgery (Fig. 9) (Möller et al., 2013).

In a few studies, acoustic waves have been imposed on nebulization during sinus drug delivery according to the HR concept. By utilizing a stereolithography technique to produce a replica of the NC and employing the experimental configuration outlined in (Leclerc et al., 2014), Leclerc et al. (2015) conducted an assessment of the effects of the vibration of acoustic airflow, high frequency sound waves ($f \geq 100$ Hz) and low frequency sound waves ($f \leq 45$ Hz), on intrasinus drug deposition. Also, they measured the length and diameter of the left MS's narrow and long ostia (each 4–5 mm wide and 4–5 mm long), as well as the diameter and length of the right MS's long and narrow ostia (each 3–4 wide mm and 7–8 mm long) (Leclerc et al., 2015). A resonance frequency of 300–400 Hz for both left and right MS was determined by using the HR equation (Equation (1)). Nebulization was carried out using two different jet nebulizers that were driven by compressors. An acoustic wave at 200 Hz was superimposed on one nebulizer (NL11SN ATOMISOR device, DTF Medical, Saint-Etienne, France), while 45 Hz was superimposed on another nebulizer (Pari sinus device, Pari GmbH, Starnberg, Germany).

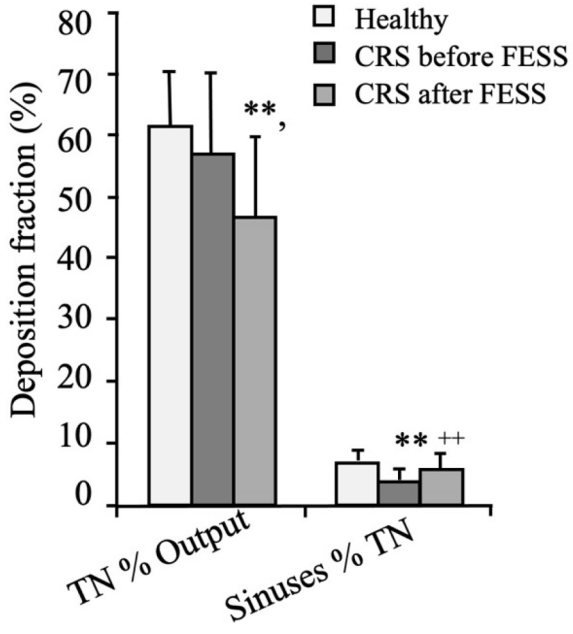

Fig. 9. Image analysis of anterior gamma cameras to determine deposition fractions., reprinted from Möller et al. (2013), licenced under CC BY 4.0; An original part of the figure has been removed.

Leclerc *et al.* (2015) compared the effectiveness of a 200 Hz acoustic wave to non-acoustic nebulization in terms of aerosol deposition in the left and right MS. The results indicated that the 200 Hz acoustic wave increased aerosol deposition by at least 4-fold in the left MS and at least 2-fold in the right MS. When comparing the 45 Hz acoustic condition to non-acoustic condition, aerosol deposition increased by 2–4 fold. The study also found that the higher-frequency acoustic airflow (200 Hz) improved efficiency for the deposition of aerosolized drugs in shorter and broader ostia, while aerosolized drugs were better deposited in longer, narrower ostia with low-frequency airflow (45 Hz). This could be attributed to the fact that, according to Equation (1), longer, narrower ostia possess a lower resonance frequency. Therefore, a 45 Hz acoustic wave might align more closely with this resonance frequency, and the inverse would hold true for shorter, broader ostia.

Previous research has extensively examined the utility of fixed sound frequencies, such as 45 Hz, 100 Hz, and 200 Hz, in enhancing aerosol delivery to the sinuses. Nonetheless, earlier studies that employed the HR equation to examine the resonance frequency of the combined human nose and sinus system have not yielded precise outcomes. The inaccuracy predominantly arises from the equation's inability to accommodate the complex anatomical structure of the human nose and sinuses, thereby potentially failing to adequately stimulate oscillation in the air plug within the ostium.

Xi et al. (2017) investigated the impact of geometric features on resonance frequency in the NC and MS using experimental data and computational simulations. The study found that resonance frequency increases with ostium diameter but is inversely related to ostium length and sinus volume. NC width and MS shape were found to have no effect on resonance frequency in the nose-sinus models. These findings have important implications for the design of aerosol drug delivery systems that can effectively target specific regions of the NC and MS. Fig. 10 shows that the highest aerosol deposition was observed within the small bottle (representing the MS) at the frequency corresponding to combination of NC-MS resonance in the two-bottle model.

Pourmehran *et al.* (2019) (Pourmehran et al., 2020) delved into an investigation of the effects of geometric parameters on the resonance frequency of an idealized nose-sinus model. Their approach comprised the construction of acoustic models grounded on experimental data, CFD, finite element analysis (FEA), and theoretical analysis. While experimental data and CFD modeling displayed a significant correlation, both FEA and theoretical analysis exhibited notable divergence from the experimental findings. Furthermore, an idealized nose–sinus model shows that resonance frequency increases by up to 2-fold when the ostium diameter is increased from 3 to 9 mm. The NC width and MS shape in the nose–sinus models had negligible effect on resonance frequency, thus reinforcing the earlier findings of Xi et al. (2017).

In 2020, Pourmehran et al. (2020) examined the effects of particle size and density on the acoustic delivery of drugs to the MS using a CFD model and a simplified nose-sinus model. Their findings showed that reducing particle mass by decreasing particle size increases the entrainment coefficients of particles due to the increased particle motion amplitudes. Conversely, increasing particle diameter or density has a negative impact on drug delivery as it reduces the Stokes number of the acoustic system. Their study suggests that reducing particle size can enhance drug delivery to the MS via acoustic delivery, whereas increasing particle size or density may impede the effectiveness of the drug delivery system. It is important to note that these findings are based on a simplified nose-sinus model, and further research is necessary to determine the impact of particle size and density on drug delivery in more complex models.

In 2022, Pourmehran et al. (2020) delved into the study of aero-acoustic factors, such as resonance amplitude, frequency, and the average inflow rate at the inlet, and how these affected the successful application of the ADD method to the human MS. Employing a CFD model together with a discrete phase model, the researchers inspected the actions of pharmaceutical particles in an externally imposed acoustic

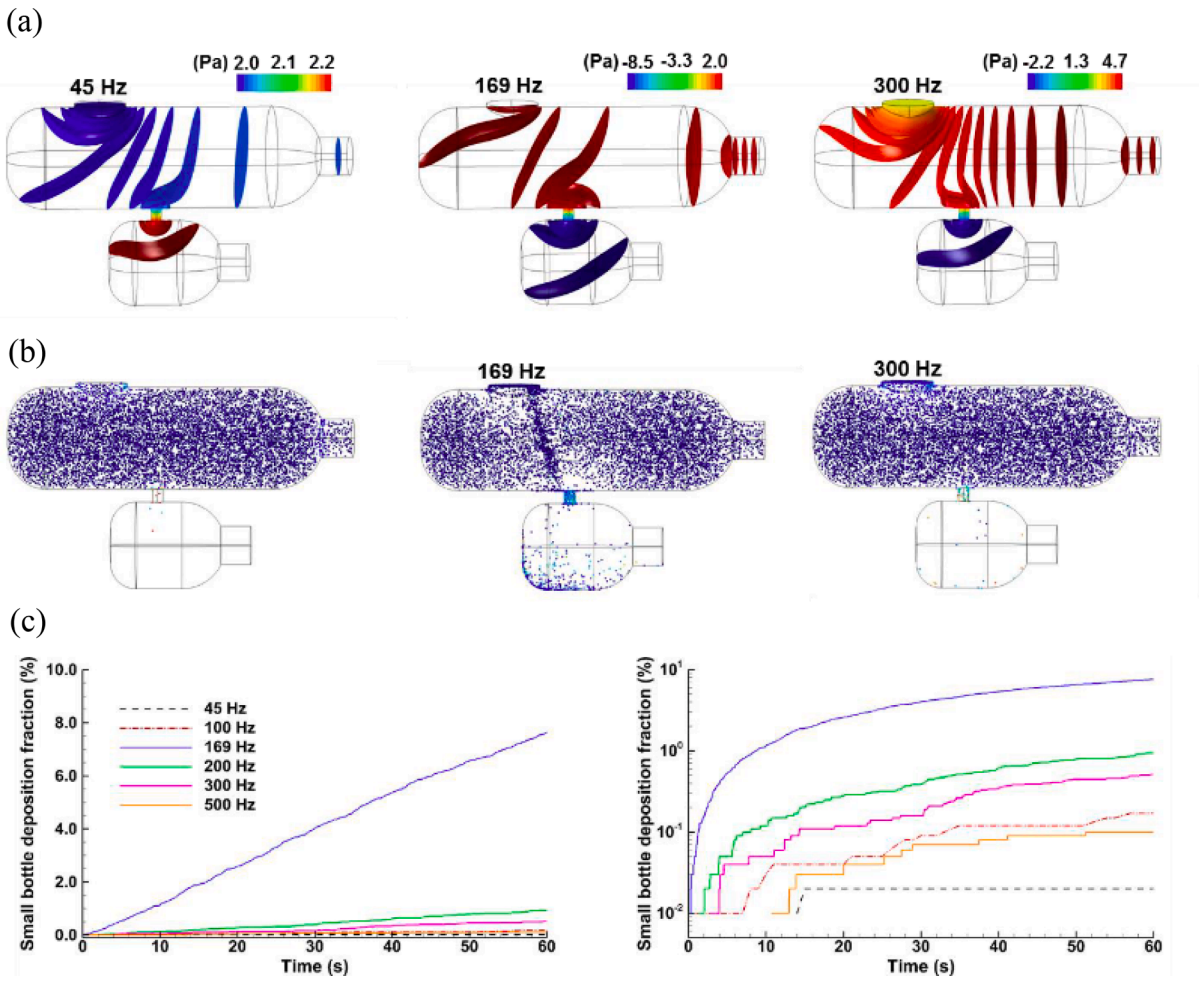

Fig. 10. Snapshots of (a) Distribution of the pressure and (b) Following 60 s of pulsating sound application. With 169 Hz, the small bottle has the largest differential pressure across the neck. (c) the deposited fraction for sound frequencies of 45–500 Hz over time, reprinted from Xi et al. (2017), with permission from Elsevier.

environment. The air plug oscillation amplitude within the ostium was identified as a key factor for effective drug delivery. A subtle increase in the frequency at the inlet was found to marginally elevate the particle concentration entering the sinus. The research also established a direct correlation between the inlet acoustic wave amplitude and the drug delivery efficiency. Intriguingly, they also noted that a higher average inlet airflow rate negatively impacted the efficiency of drug delivery, corroborating findings from a previous study by Leclerc et al. (2014). Consequently, it was deduced that the use of an external acoustic field to deliver drug particles without a mean flow is more beneficial.

In their subsequent study in 2021, Pourmehran et al. (2021), further assessed the efficacy of ADD when applied to the maxillary sinus. The goal was to distinguish the most influential factors that effectively govern the ADD method. To examine the impact of various parameters on MS aerosol deposition, they employed an experimental setup, along with particle tracking simulations using CFD models in a realistic nasal NC-MS geometry. They experimentally determined the exact resonance frequency of the NC-MS model and utilized 2.5 wt% sodium fluoride (NaF) as a drug tracer, nebulized with a mesh nebulizer. The research concluded that introducing an acoustic wave at the resonance frequency of the combined NC-MS system has the potential to substantially enhance the aerosols deposition within the MS (Fig. 11). The optimal conditions for ADD were an input frequency of 328 Hz, amplitude of 126 dB re 20μPa, and particle flowrate of 0.267 mL/min. Nonetheless, the study observed that raising the amplitude beyond 120 dB re 20μPa did not significantly impact aerosol deposition, suggesting the existence of a saturation point for aerosol deposition at a specific acoustic amplitude. The study also noted that reducing the particle flow rate entering the nostril enhances aerosol deposition in the MS. However, this also leads to an increased duration of nebulization for a fixed volume of the drug solution, resulting in a more extended treatment period.

Pourmehran et al. (2022) investigated a CFD model to examine the impact of various inlet flow conditions and nozzle diameters on the delivery and deposition patterns of particles in a realistic NC and MS model in ANSYS® Fluent. Inlet flow conditions for different levels of turbulence intensities and swirl numbers were investigated with a monodispersed particle of 5 μm diameter. The results demonstrated that increasing the swirling effect of the flow at the inlet and reducing the nozzle diameter significantly enhanced the concentration of particles within the nasal vestibule. This increase was attributed to the formation of centrifugal force. By decreasing the diameter of the nozzle, it was found that drug delivery to the surrounding ostium in the MM could be enhanced over 45% (Pourmehran et al., 2022).

A study by Pourmehran et al. (2022) aimed to improve the resonance frequency prediction for ADD in the human MS. They used CFD to simulate acoustic airflow in a 3D model of a healthy human nose, including the NC and MS connected through an ostium. The accuracy of the model was validated through experiments, with the resonance frequency of the NC-MS combination used as a criterion. The CFD simulation showed a strong correlation with experimental data, displaying a 10% difference, while the traditional HR equation overestimated resonance frequency by 50%. Considering the fluid mass in both the MS and MM allows for precise prediction of resonance frequency, which is essential for efficient drug delivery. This research has implications for

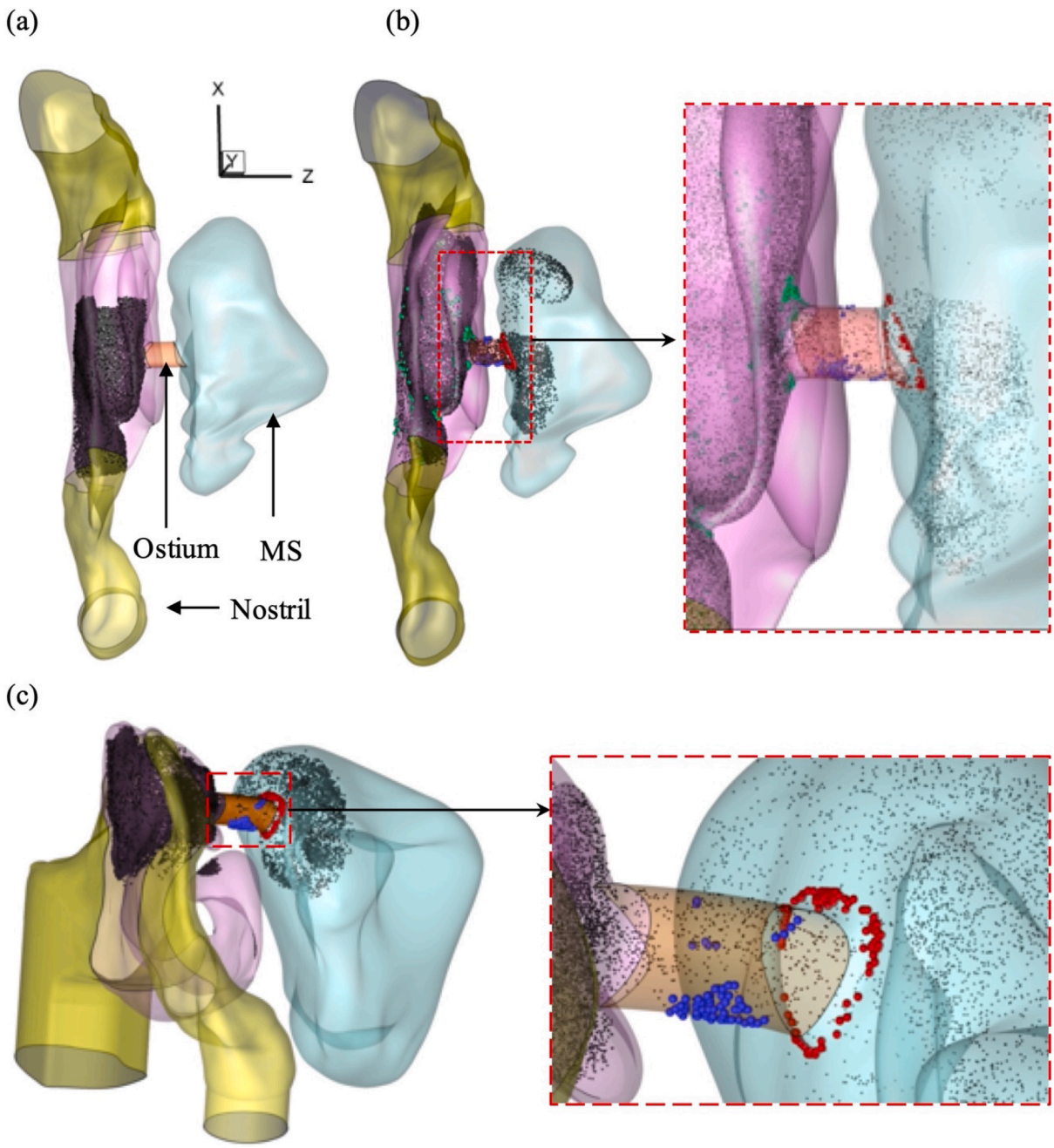

Fig. 11. (a) Particle distribution before the application of the input acoustic wave; (b) Top view and (c) perspective view of particles deposition and transportation in NC-MS model after 70 cycles when the frequency and amplitude are 352 Hz and 126 dB re 20μPa, respectively. Particles deposited on the computational domain, ostium, MS, and NC walls are indicated by black, blue, red, and green dots. Particle deposition over 70 cycles is visualized by enlarged blue and red dots. reprinted from Pourmehran et al. (2021), with permission from Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the advancement of ADD.

In a recent study, Leclerc et al. (2023) utilized oscillating airflow at different frequencies to deliver targeted acoustic aerosols to the MS using nasal delivery techniques and nebulizing technologies. The researchers used NaF, tobramycin, and ^{99m}Tc-DTPA as markers in order to determine the amount of aerosol deposited in the NC on a nasal cast. Their study compared the PARI SINUS nebulizer (45 Hz) and NL11SN ATOMISOR (100 Hz), as well as delivery methods through the NC. During drug administration, patients may have open or closed soft palates, as well as flow resistance in the nostril opposite the aerosol-administering nostril. The study found that having a closed soft palate (i.e., PARI SINUS nebulizer) significantly increased sinus drug deposition without affecting the rest of the nasal fossae. The PARI SINUS nebulizer demonstrated a 2–3 times higher intrasinus aerosol deposition compared to the NL11SN ATOMISOR (Fig. 12). These results underscore the importance of selecting an appropriate nebulizing technology, specifically focusing on the frequency of pulsating aerosols, in addition to employing the most effective nasal delivery methodology to augment aerosol deposition within the sinuses.

6.2. *Sweep frequency acoustic wave*

In recent studies, using sweep acoustic frequency to optimize aerosols deposition in the MS have shown an increase by 10 times after nasal

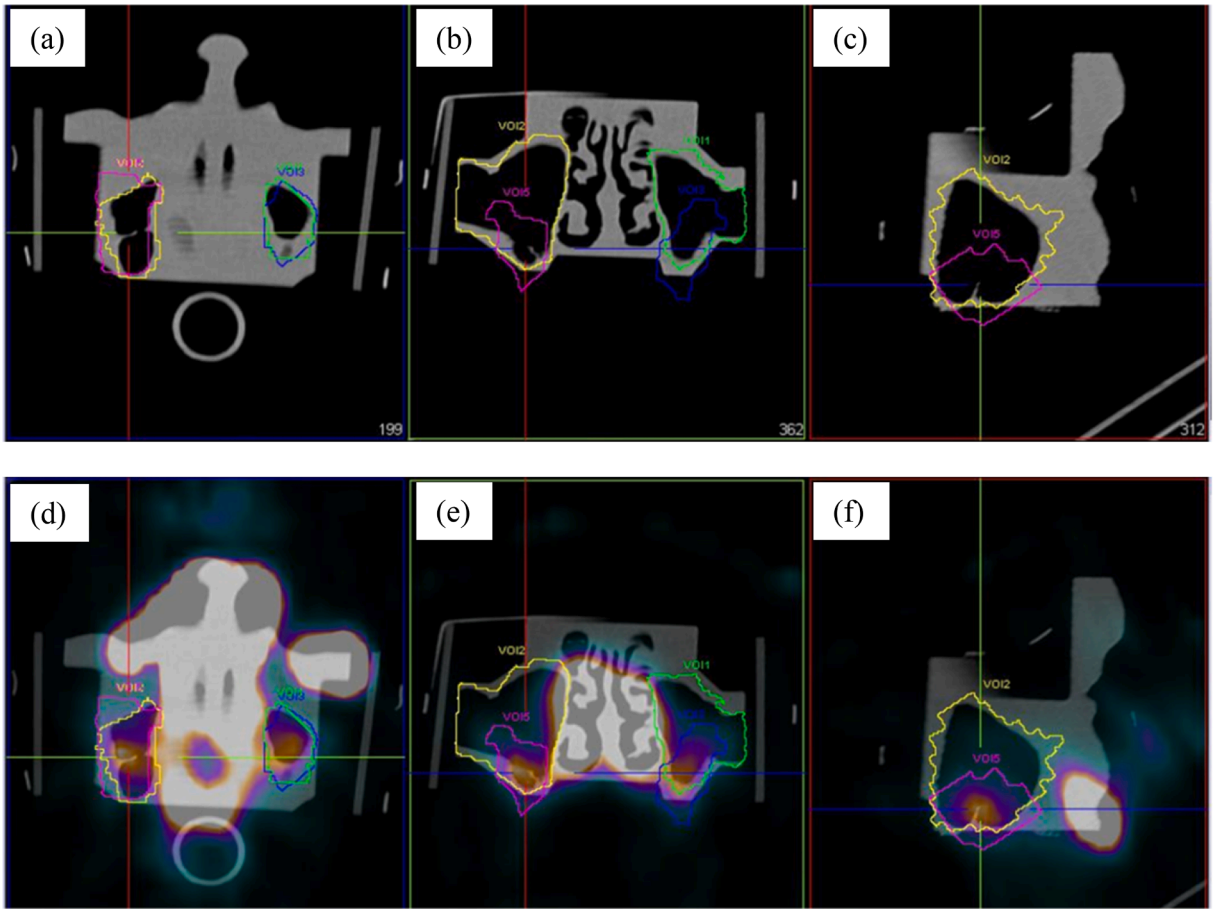

Fig. 12. Overview of the delimitations of the region of interest for ^{99m}Tc-DTPA nebulization using the PARI SINUS device in MS, with and without the use of acoustics. The figure shows six different views: (a) transverse view without acoustics, (b) coronal view without acoustics, (c) sagittal view without acoustics, (d) transverse view with acoustics, (e) coronal view with acoustics, and (f) sagittal view with acoustics. The SPEC images depict aerosol deposition in the upper airways, with pink and blue isocontours representing hot spots and yellow and green indicating the entire MS region. Acoustics were used at a frequency of 45 Hz for the views with acoustics, reprinted from Leclerc et al. (2023), licenced under CC BY 4.0.

acoustic frequency sweeps (Moghadam et al., 2018; El Merhie et al., 2016).

El-Merhie et al. (2016) used an optimized ADD technique based on frequency sweep acoustic airflow to enhance drug delivery to the MS. They used a 3D printed nasal replica of a human plastinated cast to perform aerosol deposition experiments. CT scan images were analyzed to obtain the dimensions of maxillary ostia and sinus volume, allowing calculation of resonance frequency using HR principle (Equation (1). An ATOMISOR NL11 jet nebulizer was employed, producing an aerosol with a mass median aerodynamic diameter of 2.75 ± 0.2 μm. Inlet airflow (carrying aerosols) was measured using fixed frequency values (50–800 Hz) as well as frequency sweep acoustic airflow in different frequency ranges and intensity levels (45–500 Hz, 45–800 Hz, and 100–500 Hz, with sweep cycles lasting 0.3 s, 3 s, and 30 s). According to the results, frequency sweep acoustic airflow can enhance aerosolized drug deposition in the intranasal sinuses. Using a NC replica, frequency sweep acoustic airflow deposited drugs more effectively than fixed frequency acoustic airflow. Further, a shorter sweep cycle was found to be more effective at enhancing drug deposition (Fig. 13 (a)) (El Merhie et al., 2016).

Moghadam et al. (2018) studied the application of frequency sweep acoustic airflow technology in treating CRS. In order to trace the drugs, a 2.5 wt% solution of NaF with MAD of 2.8 μm was employed. Additionally, they performed acoustic frequency sweeps with a range of 100–500 Hz and 100–850 Hz, with sweep cycles lasting 0.1 s, 0.3 s, 1 s, 1.5 s, and 2 s. In the left MS, aerosol deposition increased by 3 times when the frequency range was increased from 100 to 500 Hz to 100–850 Hz, but not in the right MS. Due to its resonance frequency between 500 and 800 Hz, the left MS might have Increased the number of aerosols deposited. Further, the NaF deposition in MS increased with shorter sweep cycle durations. Based on the results, the highest intrasinus drug deposition was achieved using a frequency range of 100–850 Hz, a sweep cycle duration of 1 s, and an intensity of 80 dB (Fig. 13 (b)) (Moghadam et al., 2018).

Aerosol deposition in MS can be slightly increased by using the acoustic frequency sweep technique, but it requires more time to inject the nebulized drug administered through the nose to cover a broader frequency range. Therefore, an increase in injection duration will result in an increase in the total dose of the drug administered by aerosol. Due to this, the respiratory system is more vulnerable to adverse side effects (Moghadam et al., 2018).

Table 1 summarizes the studies investigating ADD with fixed/sweep acoustic frequencies for drug delivery to NC and sinuses.

7. Conclusions and future perspectives

TDD techniques, including MDT, ECDD, and ADD, have been assessed for drug delivery application. MDT can enhance the effectiveness of drug delivery by employing hyperthermia or magnetic targeting. However, hyperthermia is only effective in a fluid medium, rendering it unsuitable for delivering medication to airways such as the NC or sinuses. In contrast, ADD and ECDD have demonstrated significant

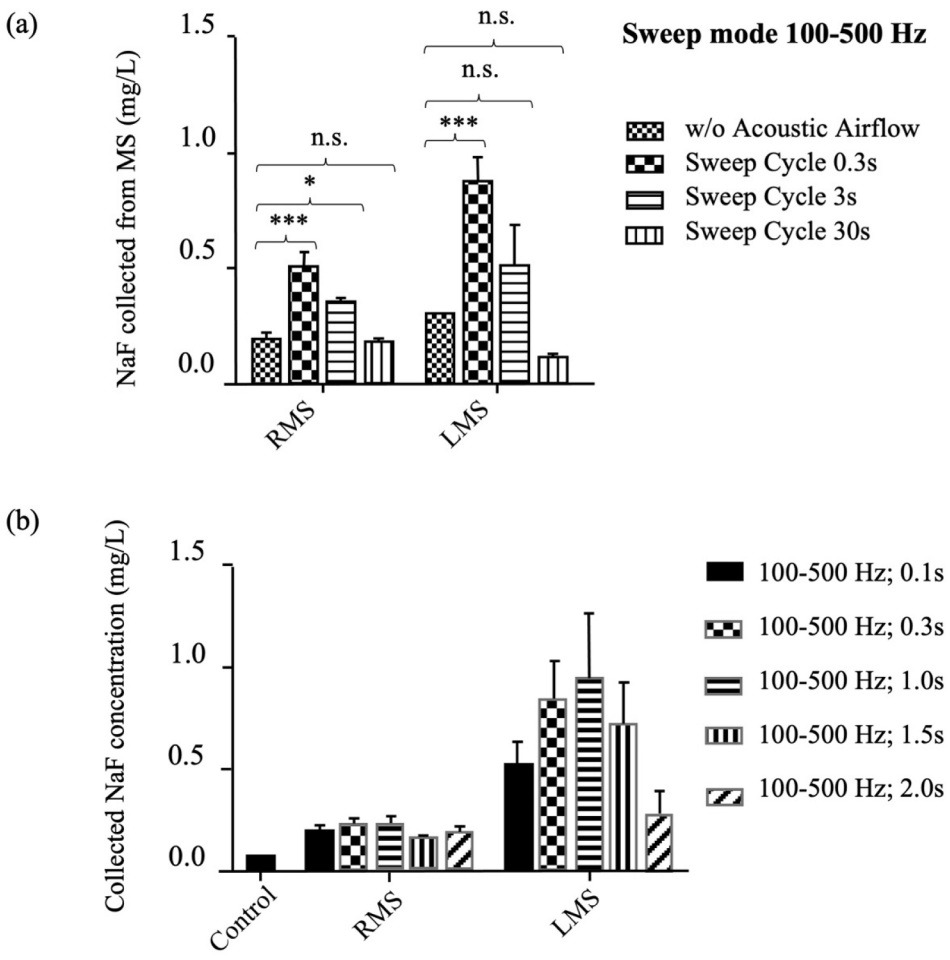

Fig. 13. (a) NaF concentration in the MS after (a) three sweep cycles (in mg/L) (El Merhie et al., 2016), reprinted from El-Merhie et al. (2016), Copyright (2016), with permission from Springer Nature; (b) 100–500 Hz and five sweep cycles, reprinted from Moghadam et al. (2018), with permission from Elsevier.

improvements in drug delivery to the olfactory and NC regions within gaseous media. ADD is particularly promising for sinus drug delivery due to its non-invasive nature, high efficiency, and ability to target hard-to-reach sinus cavities. It also has the potential to improve drug delivery efficiency and reduce systemic adverse side effects.

There are two primary forms of acoustic mediated drug delivery, one that uses ultrasonic-enhanced drug delivery and another that employs low-frequency acoustic wave (i.e. ADD). Although the ultrasonic-enhanced drug delivery technique shows potential for therapeutic applications within the circulatory system, it is less suitable for the respiratory system. Due to the presence of gas in the lungs and airways, ultrasound scatters and reflects, making it difficult to focus an ultrasound beam on specific areas in the NC and sinuses. In contrast, low-frequency acoustic fields have proven effective in delivering drugs to the paranasal sinuses.

Recent investigations have indicated the viability of employing ADD for administering medication to the MS in both *in-vitro* and *in-vivo* experiments. Although the use of fixed frequencies, such as 45 Hz and 100 Hz, has led to a threefold increase in drug deposition in the MS, their effectiveness may be limited in some instances. Optimal drug delivery to MS occurs at the resonance frequency of the NC-MS system, a concept that can be approximated by HR theory. To assess ADD effectiveness, the resonance frequency of the NC-MS system can be estimated using HR equations and applied to the nostril. Compared to non-ADD approaches, drug delivery to the MS was increased fivefold using this methodology. However, the drug delivery efficiency can be increased by more than 45-fold if an exact resonance frequency of the sinus is predicted experimentally. This principle utilizes technologies with fixed-frequency sound waves to deliver drugs into the sinus cavities without invasive procedures. It has several advantages, including its precision, non-invasive nature, and deep penetration without tissue damage. Moreover, by using sweep frequency acoustic waves, drugs can be delivered into the sinuses with greater precision and efficacy. However, more research is necessary to gain a comprehensive understanding of the safety and effectiveness of this latter technique.

Optimizing acoustic features like frequency, amplitude, and sweep duration is crucial for achieving maximum drug delivery efficiency while minimizing adverse side effects in ADD technique. It is also important to develop new drug formulations that can tolerate acoustic waves. The utilization of imaging techniques such as computerized tomography, magnetic resonance imaging, and ultrasound scans can help visualize and monitor drug delivery to the sinuses using a trace element sush as Iodin. Further exploration and research are necessary to improve the application of ADD in the context of drug delivery to paranasal sinuses. The use of artificial intelligence can be advantageous in this process, as it can potentially improve the efficiency of drug delivery, optimize the measurement of resonance frequencies, and contribute to the development of personalized treatment plans.

CRediT authorship contribution statement

Oveis Pourmehran: Conceptualization, Investigation, Formal analysis, Supervision, Writing – review & editing. **Kavan Zarei:** Investigation, Formal analysis, Writing – original draft. **Jeremie Pourchez:** Formal analysis, Writing – review & editing. **Sarah Vreugde:** Formal analysis, Writing – review & editing. **Alkis Psaltis:** Formal analysis,

Table 1
Summary of ADD studies on the NC and paranasal sinuses.

Target site	Acoustic characteristics	Method	Description	Major findings	Ref
MS	Fixed, 100 Hz	*in-vitro*	A plastinated NC-sinus model was used. Models were validated by CT scans. Droplet Technetium ^{99m}Tc with 4.7 μm MAD was used as the drug tracer.	Despite saturation phenomena and nonlinear modelling, humidity sensors are easier to use than scintigraphy to describe NC aerosol deposition.	Durand et al. (2001)
NC & PS	Humming	*in-vitro*	Ten healthy non-smoking subjects involved. Using chemiluminescence technique to measure nasal NO.	Humming increases, NO levels 15-fold over quiet exhalations.	Weitzberg et al. (2002)
NC & PS	Fixed 120, 200, and 450 Hz	*in-vitro*	The physiological and anatomical effects of NO release during humming were studied in 10 healthy non-smoking volunteers. In addition, a syringe and cylinder were used as a model of sinuses and NC.	Nasal NO levels decreased by 22–35% as a result of oscillating airflow	Maniscalco et al. (Maniscalco et al., 2003; Maniscalco et al., 2006)
MS	Fixed 100 Hz	*in-vitro*	A human-plastinated NC cast was used and was validated by endoscopy and CT scans. the gentamicin was used as a marker and each sinus was quantified using a TDxFLx® analyser.	Acoustic wave deposited gentamicin 3 times more in MS than non-ADD. The use of 100 Hz acoustic frequency resulted in 2–3 times more in drug deposition.	Durand et al. (2011)
PS	Fixed 25 Hz	*in-vitro*	Eleven healthy volunteers and eleven CRS patients involved. Using gamma camera imaging technique on aerosol deposition (^{99m}Tc-DTPA).	As a result of pulsating aerosols, there was 61.3%+/-8.6% nasal deposition, and 38.7% of the aerosols exited the other nostril.	Möller et al. (2013)
MS	Fixed 45 Hz, 200 Hz	*in-vitro*	Using a plastinated human cast to study the ventilation of 81 m Kr-gas. Using a nasal replica to study the deposition of gentamicin.	The 200 Hz acoustic wave increased aerosol deposition 4 times in the left MS and twice in the right MS.	Leclerc et al. (2015)
MS	Fixed RF	CFD & Exp	Using the realistic two-bottle NC-MS model. Using COMSOL, a computational model was developed and validated using experimental and theoretical data.	Deposits were highest at resonance frequencies, and decreased gradually off-resonance. Nose cavity anatomy has no effect on resonance frequency.	Xi et al. (2017)
MS	Fixed RF	CFD & Exp	21 different 3D printed, idealized NC–MS models with different ostium, sinus, and NC sizes were used to predict the RF using numerical and experimental modelling.	CFD and experimental models agreed well, but FEA and theoretical analyses differed significantly. As the ostium diameter increases from 3 to 9 mm, the resonance frequency increases by 2-fold.	Pourmehran et al. (2019) (Pourmehran et al., 2020)
MS	Fixed RF	CFD & Exp	A simplified NC-MS model was used to evaluate the effect of droplet density and size on ADD efficiency.	The efficiency of ADD to MS decreases with an increase in the size or density of particles. This decrease is due to an increase in the acoustic Stokes number.	Pourmehran et al. (2020)
MS	Fixed RF	CFD & Exp	simplified NC-MS model was used to evaluate the efficacy of drug delivery as affected by acoustic wave characteristics.	A critical parameter in ADD to the MS was the air plug oscillation amplitude, which occurred at the resonance frequency of the MS	Pourmehran et al. (2020)
MS	Fixed RF	CFD & Exp	The effect of acoustic wave characteristics on drug delivery efficiency was investigated using a 3D printed NC-MS model. 2.5 wt% NaF used as a drug tracer. CFD simulation was also carried out.	Drug delivery efficiency of ADD increased more than 45-fold over non-acoustic delivery.	Pourmehran et al. (2021)
MS	Fixed 45 Hz, 100 Hz	*in-vitro*	A nasal cast was evaluated for aerosol deposition in the sinuses using NaF, tobramycin, ^{99m}Tc-DTPA, and two commercial nebulizers, PARI SINUS and NL11SN ATOMISOR.	Using the PARI SINUS resulted in higher aerosol deposition within the sinuses than the NL11SN ATOMISOR. Therefore, choosing the right nebulizer technology is crucial.	Leclerc et al. (2023)
MS	Sweep 150–800 Hz	CFD & Exp	A 3-D model of an individual's healthy nose using CFD and a modified HR formula have been developed for predicting resonance frequency of MS.	Using the Helmholtz formula, the resonance frequency was overpredicted by 50%. The modified HR formula could predict the RF better. Limitation applies.	Pourmehran et al. (2022)
MS	Sweep 45–800 Hz	*in-vitro*	Aerosolized drug penetration into MS was analyzed using a nasal replica made from CT scans through 3D printing and with NaF and gentamicin as markers.	The right MS accumulates 2.5 times more aerosol than the left MS when the acoustic sweep frequency range is doubled	El-Merhie et al. (2016)
MS	Sweep 100–850 Hz	*in-vitro*	Utilizing a sweep acoustic airflow nebulization technique to maximize drug delivery to MS. Models were cast in enhanced resin using MATLAB® and 3D printing. 2.5 wt% NaF and gentamicin with a MAD of 2.8 μm was used as a drug tracer.	A shorter sweep cycle duration increases NaF deposition. Sweep cycle durations of 1 s, 80 dB intensity, and frequency ranges of 100–850 Hz produced the highest intrasinus depositions.	Moghadam et al. (2018)

RF: resonance frequency; MS: maxillary sinus; PS: paranasal sinuses; NC: nasal cavity.

Writing – review & editing. **Peter-John Wormald:** Supervision, Formal analysis, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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