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Recent advancements in nasal vaccine delivery

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Abstract
Mucosal administration, more especially the nasal route, is a viable and alternate method of delivering medications and vaccines. Mucosal channels are selectively used for a variety of illnesses because to their many benefits. Many attempts are currently being undertaken to create innovative nasal delivery systems and efficient medication compositions. This alternate path might help with a lot of unresolved medical problems and make long-term chronic treatments or mass vaccination campaigns easier and less expensive. Currently, the field of nasal delivery of medications and vaccinations is expanding fastly, supported by advancements in nanotechnology. It is anticipated that the number of medications authorized for nasal delivery would rise noticeably. Recently nasal vaccine against coronavirus is launched, because they provide protection exactly where it is needed. Nasal route is a effective delivery method and adjuvants being researched for the creation of nasal vaccinations are included in this review.

Keywords: Mucosal, nasal route, vaccines, delivery, nanotechnology

Introduction

Nasal vaccine delivery is a budding idea for local and systemic treatment of many infections. Vaccine delivery through nasal mucosa is one of the painless method and may also avoid the spread of infectious agents via contaminated syringes. Nasal vaccines provide better systemic bioavailability and protection from gastric enzymes compared with parenteral and oral administration. Effectiveness of vaccine delivery depends upon to elicits potent immunoglobulin A (IgA) secretion. Major challenge in the field of nasal vaccine development is the rapid clearance of the vaccine by the nasal mucosal secretions. Nasal clearance may be overcome by the use of adjuvants to enhance their immunogenicity and delivery to the mucosal tissues. To improve the nasal retention and penetration via the nasal mucosal membrane the nanogel based vaccine formulation can be explored. Moreover, intranasal nanogels can also be used for the treatment of various CNS infections as drug transportation was via the olfactory nerve pathway resulting in rapid drug delivery to the brain. The application of nanogels as vaccine carriers also induced significant responses associated with protective immunity against selected bacterial and viral infections. The primary site of entry for many pathogens is the mucosal surfaces, and developing a vaccine that is both safe and stable in an appropriate dosage form is one of the main challenges. Nasal vaccinations delivered via micro- and nanocarrier-based delivery systems stimulate mucosal, cellular, and humoral immunity. In addition to providing immunity at several distant mucosal sites (oral, rectal, vaginal, and pulmonary), the nasal route of vaccination is thought to be a more straightforward, economical, and patient-friendly method of immunization [1]. The majority of nasal vaccine delivery systems, which include liposomes, nano-particulates, and micro particulates, are presently in the development stage and have demonstrated immunity in animal models [2]. Antibiotics are used to treat mucosal infections, and oral, parenteral, and nasal delivery methods are used to administer vaccinations. By eliciting mucosal immune responses and systemic immunity, a nasal vaccine improves defense against infectious agents [3]. However, it has proven difficult to date to create vaccine delivery systems that promote humoral and cell-mediated responses along with mucosal immunity. The nasal route is preferred over other mucosal routes, and various mucosal routes are being investigated using various delivery systems. Applications of Nasal vaccine delivery is summarised in Figure 1.

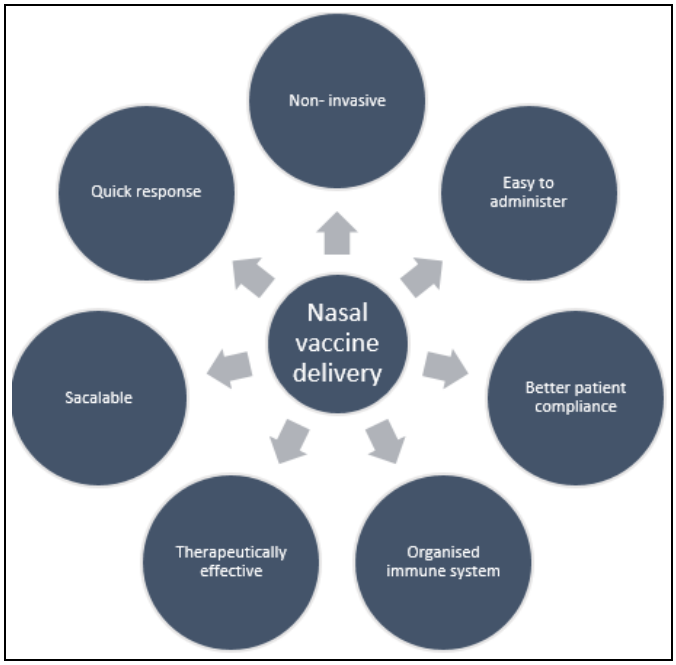

Fig 1: Applications of Nasal vaccine delivery

Anatomy and physiology of nasal route

An essential part of the human body for breathing is the nose. As a comprehensive system of defense against inhaled air and air conditioning, the nose plays a more intricate role. Nasal immunization against diseases of the upper respiratory mucosa is supported by the anatomical and physiological structure of the nasal cavity. The relationship between the nasal cavity's blood supply, olfactory region, mucosa, secretions, morphology, and physiology, and the vaccination administration route is discussed.

Anatomy

The human head's viscerocranium shields the nasal cavity. The median septum divides the human nose into two symmetrical halves, each of which extends posteriorly to the nasopharynx and opens to the face through the nostrils [4]. The anterior portion, which opens through the nostrils to the face, is made up of the nasal cavity and nasal vestibule. Between the vestibule and the respiratory region, the atrium is situated in an intermediary region. The respiratory region, also known as the nasal turbinates, occupies a greater portion of the nasal cavity. Its lateral walls divide it into three sections: the inferior nasal turbinate (inferior region), the middle region, and the superior nasal turbinate (superior region). Animals have a more complex turbinate-lateral wall attachment than do humans. These folds significantly increase the nasal cavity's surface area relative to its small volume.

Physiology

Particle filtration, as well as heating and humidifying inspired air prior to it entering the lungs, are the nose's primary jobs. Specialized ciliated olfactory nerve cells for the perception of smell are found in the olfactory region, which is located above the superior nasal turbinate. The human nasal cavity has a surface area of about 150 cm2 and a total volume of 15–20 mL, of which the respiratory region makes up about 85%. The nasal vestibule, turbinate (inferior, middle, and superior), olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of the ethmoid bone are just a few of the various regions that make up each nasal cavity. The nasal cavity, which is located in the nasopharynx, contains NALT. These nerve cells' central axon enters the olfactory bulb after passing through the ethmoid bone's cribriform plate. A stratified squamous epithelium with sebaceous glands makes up the anterior section of the nasal portion, while pseudo stratified columnar cells presenting microvilli make up the posterior section. The nasal respiratory mucosa, which consists of the basement membrane, lamina propria, and epithelium, is thought to be the most significant site for systemic drug delivery [5]. Mucous and serous glands, basal cells, goblet cells, and pseudo stratified columnar epithelial cells make up the nasal respiratory epithelium [6, 7]. The majority of epithelial cells have tiny projections known as cilia on their apical surface, and most have microvilli.

The lamina propria, basement membrane, and epithelium make up the nasal respiratory mucosa. Goblet cells, basal cells, mucous, serous glands, and pseudo stratified columnar epithelial cells are all found in the nasal respiratory epithelium. The cilia, which are tiny projections of microvilli on the apical surface of many epithelial cells, increase the respiratory surface area. Goblet cells and secretory glands secrete a thin layer of mucus that covers the nasal epithelium. Nasal mucus provides both physical and enzymatic protection and is in charge of a number of physiological processes, including warming and humidifying the air that is inhaled.

Goblet cells and submucosal glands are the primary sources of nasal secretions. 95 percent of mucus is composed of water, 2 percent glycoproteins, 1 percent inorganic salts, 1 percent albumin, immunoglobulins, lysozyme, lactoferrin, and other proteins, and less than 1 percent lipids [6]. 11 Because there are relatively few glycoproteins in mucus, it has unique viscoelastic properties. The mucus layer is divided into two layers: a lower layer with a higher viscosity that is roughly 5-10 μm thick and an upper layer that is roughly 0.5-5 μm thick. The pH of a human nose ranges from 5 to 8, with 6.3 being the reference point.

Significance of nasal vaccine delivery

One of the better options to traditional multiple injectable vaccines, which involve painful procedures and run the risk of infectious organisms spreading through tainted syringes, is the mucosal method of vaccine delivery. The field of developing mucosal vaccines has flourished, and numerous vaccine delivery systems have been created for application through the ocular, nasal, oral, rectal, and vaginal channels. The oral and nasal routes of mucosal immunization are the most widely used and convenient of all the available methods. Intranasal administration of cocaine, tobacco snuff, and other hallucinogenic and psychotropic substances has been used for many years [7]. Similar to this, synthetic medications (such as nonpeptide medicines, antibiotics, and antihistamines) have been given intranasally for a long time due to their local impact on the mucosa [8]. Following its 2001 release, the first nasal influenza vaccine was taken off the market because of possible toxicity issues. In 2003, Flumist, an additional intranasal vaccination, was introduced and was delivered via syringe sprayer. A vaccine's effectiveness is dependent on both the mode of administration and the mode of delivery; for instance, nasal immunization causes the respiratory system to secrete a significant amount of immunoglobulin A (IgA) [9]. Compared to parenteral and oral delivery, nasal vaccinations have been demonstrated to produce superior systemic bioavailability and protection against gastrointestinal enzymes. Vaccines administered via the nose function as a "first entry block," preventing pathogen entry while causing localized immune responses specific to the invaded microbe, so boosting overall efficacy.

Because it is the most suitable form of vaccination, it induces both mucosal and systemic adaptive immune responses specific to the antigen and is abundant in T, B, and plasma cells. Because of the needle-free delivery, patients comply with it better.

Nasal vaccine delivery strategies

As an alternative to the current parenteral immunization, there are several mucosal routes of immunization, including oral, nasal, pulmonary, vaginal, and rectal. There are various reasons why the nasal route is more appealing. When using widely available commercial devices for self-administration, it is a practical site for simple self-administration [10] 39. Generally speaking, nasal immunization requires far lower doses of antigen than oral or occasionally parenteral administration. Antigens are not exposed to low pH or digestive enzymes such as nuclease and protease during

nasal immunization, and mucus acts as a barrier to prevent antigens from penetrating the mucosal epithelium.

Liposomes

Liposomes are synthetic vesicles that encapsulate antigens and are composed of bilayer lipid molecules like cholesterol and phospholipid. Liposomes' biocompatibility, size, and ampiphilic nature make them a promising delivery system. Additionally, liposomes have the ability to function as an adjuvant [11], eliciting a possible immune response with a minimal antigen payload. They can also change substances that are not immunogenic into forms that are (for example, by making soluble substances particulate in nature). Macrophages and M cells absorb liposomes and use them to process antigens and/or present them to other lymphoid cells for the purpose of triggering immune responses. Additionally, they have the ability to directly expose lymphoid cells to antigens in order to trigger immune responses. When liposomes containing bacterial polysaccharide antigens were applied nasally to BALB/c mice, it was discovered that the mice's pulmonary secretions showed improved immune responses following liposomal antigen immunization as compared to antigen alone and oral immunization [12].

The Swiss Serum Institute (Berne, Switzerland) has launched a nasal influenza vaccine in Europe that is based on a liposome (Virosomal) formulation of influenza virus subunits. Liposomes may present a viable nasal vaccine delivery method.

Micro-and Nano particulate Systems

In order to deliver antigens to a particular location within the body, particulate carriers have garnered a great deal of interest as antigen carriers. The size range of nanoparticles is 1–1000 nm (1 μm), whereas the size range of microparticles is 1–1000 μm; the smaller particle size facilitates faster adsorption. A more stable system that defends against the harsh nasal mucosa environment, prolonged release, bioadhesion qualities, and the ability to significantly boost immunity at a lower dosage are some additional benefits [13]. Microparticles and nanoparticles can be prepared with varying properties and release characteristics depending on the preparation method used. Biomolecules like proteins, peptides, polynucleotides, and polysaccharides, as well as synthetic polymers like polylactide-polyglycolide copolymers, polyacrylates, poly-ε-caprolacton, and N-trimethyl chitosan-poly(γ-glutamic acid) are among the polymers used for the particulate system [14, 15]. To elicit strong and enduring immune responses, nano- and microsized particulate carriers are prepared with the antigenic molecule and transport it to the intended site of action [16].

Immune Stimulating Complexes (ISC)

A spherical open cage-like structure (usually 30–40 nm in diameter), known as an ISC, is a highly adaptable and efficient antigen presentation system. It is formed spontaneously when cholesterol, a lipid (such as phosphatidyl choline), and the mixture of saponins that make up Quillaja saponins A are mixed together [17]. 85 Additionally, Quillaja saponin, which is enveloped in antigen, functions as a potent natural adjuvant. The possibility of inducing immune responses through immunization with ISCs containing viral and bacterial membrane glycoproteins was demonstrated by Morein and colleagues in 1984. ISCs are powerful inducers of cellular (mediated by T cells) as well as humoral (mediated by antibodies) immune responses. Antigens presented in unison with the ISCs matrix facilitate processing through both endogenous and exogenous pathways, stimulating CD4+ and CD8+ T cells [18]. Furthermore, the Quil A moiety's adjuvant action triggers durable immune responses. It is discovered that the antibody levels induced by ISCs are comparable to those following immunization with traditional adjuvants like alum or complete Freund's adjuvant [19]. According to certain research, ISC immunization elicits a broad spectrum of immune responses, including all IgG subclasses and cell-mediated immune responses like *in vitro* cytokine production, antigen-specific proliferative responses, and delayed-type hypersensitivity (DTH) *in vivo* [20, 21, 22]. Hence ISC-based delivery systems may be suitable for nasal vaccine administration.

Virus-Like Particles (VLPs)

Virus-Like Particles are a viable option for administering vaccines to the nasal site because of their large surface area, low proteolytic activity, high vascularization, self-adjuvanting, and high immunostimulatory properties. With a 20–100 nm self-assembled empty capsid protein that resembles a virus in size and shape and lacks DNA or RNA, VLPs are inert [23]. After nasal immunization, which produces systemic immunity as well as both local and distal mucosal immunity via the common mucosal immune system (CMIS), VLPs are effectively absorbed by DCs and powerfully stimulate immune responses. When it comes to inducing IgA at distal mucosal sites, it is even more effective than parenteral administration. Mammalian cells, insect cells, yeast, bacteria, and even plants can all produce the VLPs. These characteristics allow VLPs to be used as a vehicle for a variety of protein and peptide antigens. VLPs as a protein antigen delivery system are still constrained by the relatively complex genetic modification on protein fusion and the consequently needed structural integrity characterization, despite their successful use and strong immunity. For a long time, VLP technology has been in use. Recombinant hepatitis B surface antigen (HBsAg), which is made in the yeasts Saccharomyces cerevisiae or Pichia pastoris, is one example [24].

Bioadhesive delivery system: The antigen carrier system in a bioadhesive delivery system sticks to biological tissue for a considerable amount of time. Nasal mucosa bioadhesion lengthens the antigen's retention period and shields it from mucosal enzymes. Nasal vaccines based on bioadhesives are recommended to address nasal clearance issues, aid in absorption, and provide longer-lasting antigen delivery. By slowing mucocilliary clearance, bioadhesive polymers can be used to extend the nasal residence time. This allows for longer absorption with the nasal mucosa, leading to an increase in absorption. The formulations contain a variety of bioadhesive polymers, including sodium alginate, sodium carboxy methylcellulose, xanthan gum, carrageenan, hydroxypropyl methylcellulose (HPMC), K15M and E5, and polyvinyl pyrrolidone (PVP) [22, 25]. Between polymer–mucin chains, bioadhesion happens via hydrogen, hydrophobic, van der Waals, through the induction of IgG and IgA responses, nasal immunization with various antigens, including tetanus toxoid, influenza, pertussis, and

diphtheria, after encapsulation and administration using various bioadhesive polymers, such as pluronic F127, chitosan and its combination, and PEG-coated polylactic acid, demonstrates enhanced immune response. In human clinical trials, the chitosan-based influenza nasal vaccine elicited a potent immune response [26-28]. Nasal immunization could potentially benefit from the extended antigen delivery provided by bioadhesive drug delivery systems.

Micro-and Nanoemulsion

Over the past 20 years, the potential of micro-and nanoemulsion for different administration routes has been continuously investigated [29]. Emulsions are a popular choice for a delivery system to improve uptake across nasal mucosa because of their lipophilic nature and small globule size. There are several different kinds of emulsions, such as water-in-oil (W/O) and oil-in-water (O/W). Emulsions like incomplete Freund's adjuvant, adjuvant, montanide, and MF59 comprise the majority of novel adjuvants [30, 31]. Emulsions are low viscosity, transparent, isotropic, thermodynamically stable colloidal dispersions that are stabilized by a film of alternating surfactant and cosurfactant molecules interfering at the interface. One of the main benefits over alternative drug delivery methods like solid dispersion, liposomes, and particulate delivery systems is ease of administration and scalability.

Several inactive ingredients are included in emulsion formulations, including oil (soybean, sesame, isopropyl myristate, etc.), cosurfactant (ethanol, propanol, PEG, etc.), surfactant (Tweens, Span80, chromophores, PEG, lecithin, cetrimide, etc.), and aqueous phase. Mucoadhesive polymers, like sodium alginate, pluronics, and various grades of carbopol (974P/971P/980P), are typically added to emulsions in order to extend the time that antigens are released. When it comes to nasal vaccine delivery, micro- and nanoemulsion offers superior spray ability over alternative particulate delivery methods. When preparing a formulation, it is important to take into account various factors such as the type and concentration of oil, surfactant, cosurfactant, and aqueous phase; the ratio of oil to surfactant to cosurfactant; and the environmental temperature and pH. When developing emulsion vaccines, dilatability, particle size, pH, zeta potential, viscosity, and freeze/thaw cycling are important factors to consider. Nasal nanoemulsion vaccines have been investigated for a number of illnesses, including influenza, HIV, and hepatitis B [32]. According to certain studies, the nasal vaccine immunization produced high levels of IgG and IgA antibodies, much like vaccines based on alum adjuvant. For low-cost nasal vaccine immunization of developing and underdeveloped populations, the emulsion-based delivery strategy shows promise.

Techniques to enhance nasal bioavailability

Strategies for the exploitation of absorption enhancers for the improvement of nasal administration are discussed, including use of surfactants, cyclodextrins, protease inhibitors, and tight junction modulators, as well as application of carriers such as liposomes and nanoparticles. The most common permeation enhancers investigated for nasal drug administration and their classification are listed in Table 1.

Table 1: The most common permeation enhancers investigated for nasal drug administration and their classification.

Penetration enhancer	Type	Examples
Surfactants	Bile salts	Sodium taurocholate Sodium deoxycholate sodium Glycodeoxycholate
	Fatty acids and derivatives	Palmitic acid Palmitoleic acid Stearic acid Oleyl alcohol Oleic acid Capric acid DHA, EPA
	Phospholipids	Dipalmitoyl phophatidyl choline, soybean lecithin, phosphatidylcholine
Cationic polymers	polymer	Chitosan and their derivatives
Enzyme inhibitors		Human neutrophil elastase inhibitor (ER143)
Cyclodextrins		Beta-Cyclodextrin
Tight junction modulators	Claudine modulator	Clostridium perfringens enterotoxin
	Zo modulator	Zonula Occludens toxin (ZOT)

Conclusions

Nasal vaccination delivery has been evaluated as a substitute delivery route and proven to be on par with or better than other mucosal delivery methods, such as parenteral. It increases patient compliance and reduces the possibility of spreading illnesses like HIV, hepatitis B, and other agents through sloppy injection techniques. By inducing a systemic and mucosal immune response, the intranasal vaccine delivery system prevents pathogen entry through all mucosal routes. A variety of delivery methods are being investigated (in both the clinical and development stages), which may pave the way for the actual development of nasal vaccine delivery systems.

Declaration of interest

The authors were addressing no conflicts of interest.

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