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A STUDY OF FACTORS AFFECTING OF FORMULATION VARIABLES FOR NASAL FORMULATIONS

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ABSTRACT
The nasal cavity serves as the principal location for the identification of allergens and the beginning of immune responses in allergic rhinitis (AR). The administration of therapeutic drugs via the nasal route enables direct targeting of the inflamed nasal mucosa, leading to expedited start of therapeutic benefits and reduced occurrence of systemic adverse reactions. Poly-herbal nasal formulations provide the capacity to offer focused therapeutic intervention to the nasal passages, effectively targeting the underlying etiology of allergic rhinitis. Animal models, such as the model using mice challenged with ovalbumin (OVA), are extensively used in preclinical investigations to examine the effectiveness and safety of prospective therapeutic interventions. via the implementation of research in a regulated animal model, this study has the capacity to provide significant knowledge on the therapeutic capabilities of poly-herbal nasal formulations. Additionally, it aims to elucidate the underlying mechanisms via which these formulations exert their effects, as well as their influence on immunological and inflammatory responses. The examination of poly-herbal nasal formulations in a mouse model challenged with ovalbumin presents a potential avenue for the development of innovative treatment strategies for allergic rhinitis. If the formulations exhibit effectiveness in diminishing nasal symptoms, regulating the immune response, and averting histopathological alterations, it may potentially pave the way for the advancement of novel pharmaceuticals or supplementary therapeutic alternatives for allergic rhinitis (AR).

KEYWORDS: allergic rhinitis, therapeutic drugs, ovalbumin, poly-herbal nasal formulations

INTRODUCTION

The nasal cavity encompasses the respiratory tract and serves as the primary conduit for the entry of air into the respiratory system. The nasal cavity also encompasses the peripheral olfactory organ. The respiratory region of the nasal cavity is comprised of the lower two-thirds of the nasal mucosa, while the olfactory region is composed of the upper one-third.The olfactory region contains the peripheral organ of smell (Martini, 2004; Moore and Dalley, 2006).

The nasal route of drug administration is considered a practical and dependable approach for both local and systemic drug delivery. This is due to the abundant blood supply in the nasal membrane and the convenience of administering medications via the nose. Currently, the nasal mucosa is being regarded as an effective route of administration for achieving faster and more efficient medication absorption. The richly supplied vascular environment of the nasal membrane, along with its significant drug permeability, makes the nasal route of drug administration very appealing for a wide range of pharmaceuticals, including proteins and

peptides. The absorption of a pharmaceutical component in the olfactory area of the nose offers a potential pathway for the medication to reach the central nervous system. The nasal administration of vaccinations is an area of significant interest due to its potential effectiveness and patient acceptability. Throughout history, the use of the nasal route for medication administration has been a subject of interest for humanity. Nasal therapy, known as "Nasaya Karma," is a recognized kind of treatment in the Ayurvedic school of Indian medicine.

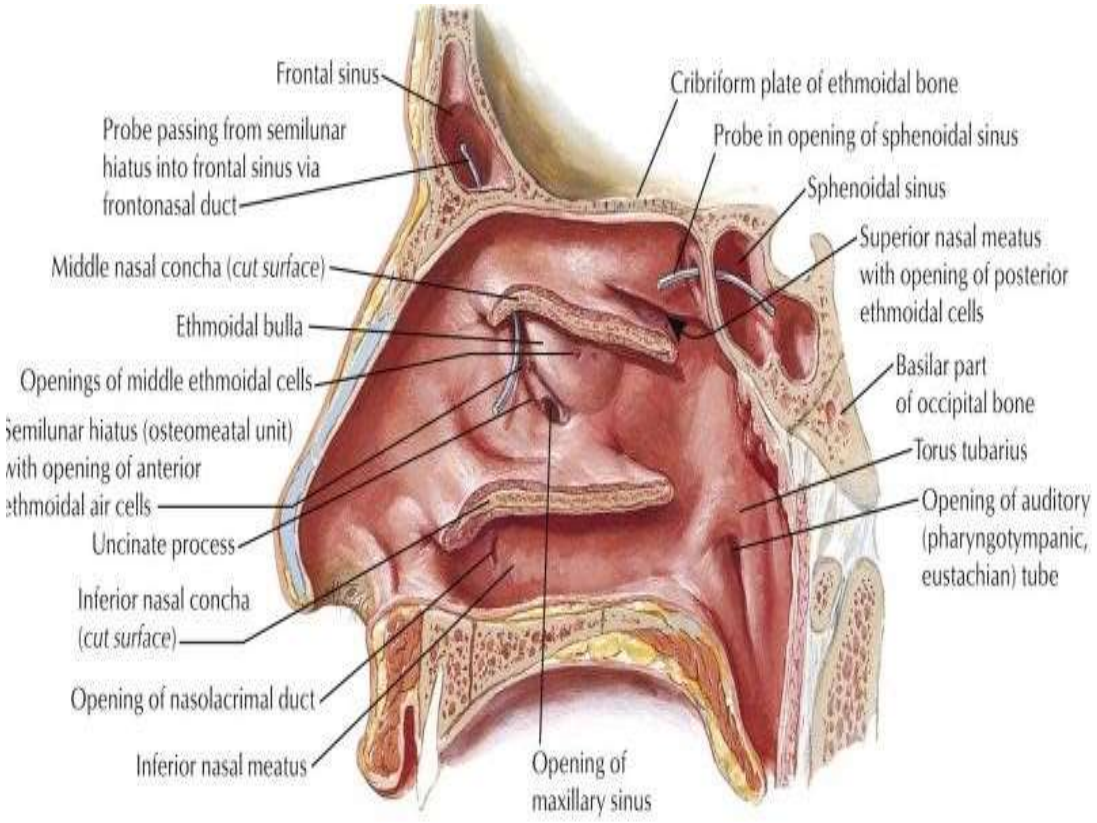

Figure 1 The nasal cavity (Netter, 2003)

The epithelial lining of the bodily cavity undergoes a gradual transition from keratinized, dynamic skin to non-keratinized, stratified squamous epithelium in the vestibules, which receive the external environment through the nostrils. In this region, coarse hairs known as vibrissae serve to filter out large particles. Moving posteriorly, the lining changes to pseudostratified columnar epithelium, which is the predominant respiratory epithelium covering approximately 80-90% of the nasal cavity. This region contains basal, columnar, and mucus-secreting goblet cells. The columnar cells are covered with immobile microvilli, which enhance the surface area of the body cavity. Although these cells lack cilia in the anterior region, some of them do exhibit cilia in subsequent sections. The production of nasal secretions that lining the airways is attributed to the presence of liquid body material, muco-serous submucosal glands, and goblet cells. The primary components of the first innate psychoanalytic mechanism known as mucociliary clearance (MC) are the release of mucus

and the presence of cilia. Nasal medication administration is intended to target the respiratory region of the nasal cavity, which offers a large surface area. However, the front portion of the cavity, known as the vestibule, has limited drug permeability, particularly around the nostrils, due to keratinization and the presence of sebaceous glands. However, the regular process of epithelial tissue metastasis is associated with the functioning of multiciliated cells (MCs), in which the cilia underneath the mucous lining beat to drive it and any accumulated substances towards the throat for either ingestion or expulsion. This results in reduced contact time for the medication at the absorption site (in the case of systemic administration) or the site of action (in the case of locally acting pharmaceuticals), leading to decreased bioavailability and/or effectiveness.

NASAL ANATOMY AND PHYSIOLOGY

The presence of enzymes in nasal secretions, as well as in the epithelial tissue, creates an additional obstacle for drug delivery through the secretion raft, thereby hindering diffusion in the nasal cavity. However, it is important to note that the metabolic activity in the nasal cavity is significantly lower compared to that in the gastrointestinal tract. Nasal formulations are carefully formulated taking into consideration the physiological obstacles present, and certain formulation factors are modified to achieve optimal effectiveness. uniformity modifiers are used as a means to achieve formulation uniformity, hence enhancing its longevity inside the oral cavity.

Herbal medications, sometimes known as herbal treatment, include the use of plants for therapeutic or medicinal purposes. Herbs have been used by many civilizations throughout different historical periods. It has been a fundamental component in the development of modern civilisation. Early humans recognized and valued the rich variety of plants available to them. Plants served as a valuable resource, offering sustenance, apparel, housing, and medicinal properties. Many instances of plant use seem to have been derived from observations of wild animals and via the process of trial and error. Over the course of time, each tribe increasingly recognized the beneficial properties of plants within their own territories. The researchers systematically gathered data on herbs and formed comprehensive records. As a result, a significant portion of modern medicine in the twentieth century was built upon the knowledge and practices of indigenous populations. Indeed, it is worth noting that a minimum of one active component is included in around twenty five percent of prescription medications. The study of anatomy and physiology is crucial in the advancement of pharmacotherapy. For instance, the Japanese were the first to deliver medication to animals by different channels, which resulted in convulsions and physiological changes. The medulla spinalis was surgically extracted and dissected in order to ascertain the localization of the active ingredient. Subsequently, the compound alkaloid was identified and isolated as the principal constituent. Following the revolution, there was a notable shift in the scientific paradigm towards empiricism, with a particular emphasis on the logical underpinnings of medicine (Foye et al., 1995).

The earliest documented instance of using a beneficial plant may be found in the "Rigveda," while a more contemporary reference can be found in the literature about the therapeutic usage of the herb known as "Mahuang." This particular herb, a kind of joint fir, has been used

for medicinal purposes in China for a span of over 5000 years (Foye et al., 1995). Medications derived from plants include a variety of therapeutic properties, including diuretic, emmenagogue, carminative, rubefacient, medicinal, expectorant, and anthelmintic effects, among others. Prior to the establishment of the World Health Organization (WHO), there was an endeavor to identify all the medicinal plants present worldwide. A total of 24 species were included in the list. According to Farnsworth and Soejarto (1991), NAPRALERT information provides documentation on the ethnomedicinal applications of 9,200 out of 33,000 species belonging to various plant groups such as monocots, dicots, gymnosperms, pteridophytes, bryophytes, and lichens. This suggests that a total of 28 plant species on Earth are used for their ethnomedicinal properties. However, although medications derived from plants continue to be used for some purposes, synthetic medications now constitute the predominant component of the products employed. It is important to acknowledge that a significant portion of research on artificial chemicals originated from the efforts of scientists and researchers who first identified and characterized active natural substances. The plants chosen for a certain location were not only readily available throughout the year, but also in all other parts of the country. This particular pharmaceutical proportion has remained unchanged to this day. The utilization of plant-based medications continues to hold significant importance in contemporary medicine, particularly in areas where access to conventional medical treatments is limited. This is evident in the use of immunomodulators within traditional systems of medicine such as Ayurveda, Siddha, and Unani.

In the realm of science, plants referred to as Rasayanas are widely used as rejuvenators to effectively counteract the process of aging, enhance the body's resilience against illnesses, including those triggered by mental disturbances, and promote overall well-being of individuals. It is evident that prior to the emergence of the notion of adaptation in the mid-20th century, a very comparable hypothesis had been proposed in ancient literature.

Herbal medications have a rich history of being used in the treatment of many medical ailments, including allergies. Over an extended period, it has garnered prominence in developed countries. The ultimate principle in Chinese medicine involves altering the body's reaction to allergenic stimuli such as pollen. It is expected that with advancements in augmented reality technology, there would likely be an improvement in the quality of life associated with enhanced biological features. In the past, Chinese herbal medicine has been used in combination, guided by its specific principles, to address the maintenance and restoration of bodily equilibrium. The cognitive aspects of herb-herb interactions, such as the effects of synergism and antagonism on the adrenergic receptor, are taken into consideration throughout the formulation process. Consequently, several formulas are recorded in the existing literature on hectometers and are often used in conventional physical activities. This commonly practiced kind of exercise is mostly based on anecdotal evidence and is subject to medical examination over its scientific effectiveness and underlying causes. The efficacy of traditional Chinese herbal medicines (CHMs) in treating allergic rhinitis (AR) is well acknowledged, supported by several ancient formulas. However, the underlying processes by which these formulae exert their therapeutic effects need to be fully understood.

FORMULATION VARIABLES FOR NASAL FORMULATIONS

Various dosage forms given by nasal route

a) Nasal drops:

The development of nasal drops has emerged as a very convenient and appropriate method for administering drugs via the nasal route. One of the primary drawbacks of the technique is the lack of dosage accuracy, which therefore renders nasal drops unsuitable for prescription products. Research has shown that the deposition of human serum albumin in the nose is more potent when administered using nasal drops compared to nasal sprays and metered dose nebulizers. Pharmaceutical compounds of a molecular mass below about 1000 Dalton have shown satisfactory nasal bioavailability, even in the absence of absorption enhancers after administration.

b) Nasal Suspension:

Suspensions intended for nasal administration are formulated by incorporating micronized medication particles into a liquid diluent or carrier that is appropriate for application to the nasal mucosa. The use of suspension form resulted in a more effective absorption of insulin and decrease in blood glucose levels in comparison to the utilization of a solution form.

c) Powders:

Powder-based dosage forms for nasal administration have many advantages compared to liquid versions. The powdered formulation is very versatile and may be effectively used in a diverse range of non-peptide tablets, as well as being well-suited for the administration of peptide-based pharmaceuticals. The formulation of a dry powder vaccine consists of fully inactivated influenza virus (WITV) and a suitable mucoadhesive agent for regulated nasal delivery. Powders for contouring, namely W1IV, were generated via the process of lyophilization, with the addition of either lactose or tetra lactose. A micro-ball mill was used to reduce the size of each lyophilized cake to dimensions suitable for nasal delivery. In addition, the study included further analysis of particle length, examination of powder drift residences, determination of bulk and tapped densities, and investigation of the static position of repose.

d) Microparticulates:

According to Lim et al. (2006), microparticulates are considered to be an effective type of dosage for the localized nasal delivery of drugs that undergo in situ gelation. The researchers conducted an experiment to evaluate the use of previously described microparticles made of hyaluronan and chitosan hydroglutamate, as well as newly developed microparticles including both polymers, for improving the nasal delivery of a prototype medication. The bioavailabilities of gentamycin, when included in hyaluronan, chitosan hydroglutamate, and hyaluronan or chitosan hydroglutamate microparticles, were shown to be increased by 23-, 31-, and 42-fold respectively, in comparison to the control intranasal solution of gentamycin. This finding demonstrates that the nasal mucosa of rabbits exhibited prolonged retention of each checked microparticle, which aligns with the results of prior in vitro dissolution and frog palate mucoadhesion studies. Consequently, this phenomenon contributes to an enhanced absorption of drugs. The formulations based on chitosan hydroglutamate (CHG) with enhanced bioavailabilities, such as chitosan hydroglutamate and hyaluronan/chitosan

hydroglutamate, suggest that the penetration-enhancing actions of CHG may also be partially responsible for the improvement.

e) Microspheres:

The use of microspheres has gained popularity in the field of nasal product design, due to its particular structural characteristics. Microspheres demonstrate the phenomenon of in situ gelation, which enables them to form a gel-like structure upon contact with the nasal mucosa. This property allows for an extended duration of contact with the nasal mucosa, leading to enhanced absorption capabilities. Microspheres intended for nasal administration have been produced using biocompatible materials, such as starch, albumin, dextran, and gelatin. The evaluation of their toxicity and irritancy is necessary. The nasal mucosa experiences dehydration due to the absorption of moisture via the starch microspheres that surround it. This phenomenon results in a reversible contraction of the cells, creating a transient physical barrier at the tight (intercellular) junction that enhances the uptake of medicines. The spray drying approach used in the fabrication of microspheres is a single-step process that has advantages in terms of high production yield and repeatability. The microspheres were fabricated using the spray-drying technique, including hydroxypropyl methylcellulose, chitosan, carbopol 934P, and various combinations of these mucoadhesive polymers, as well as maltodextrin and colloidal silicon dioxide. Propylene glycol was used as a filler and shaper in the formulation process. Using propranolol HC1 as a representative drug, microspheres have been successfully fabricated with loading capacities above 80% and achieving yields ranging from 24% to 74%. Microspheres of a substantial size and unrestricted movement were successfully acquired, with a median particle size ranging from 15 to 23 pm.

f) Nasal Inserts:

The nasal inserts serve as a novel and remarkable bioadhesive dosage form that facilitates sustained systemic medication delivery via the nasal route. The dosage form guideline entails the absorption of nasal fluid from the mucosa upon administration, as well as the formation of a gel inside the nasal cavity to prevent the presence of foreign body sensation. The gel has bioadhesive properties, allowing it to stick to the nasal mucosa. In addition, it functions as a regulatory framework, enabling the sustained delivery of drugs. The in situ gelling nasal inserts have been prepared using lyophilization of an aqueous solution including the medication, polymer, and other necessary excipients. The porous characteristics of in situ gelling nasal inserts play a vital role in facilitating rapid hydration and gelation of the inserts upon contact with the nasal mucosa. The rapid absorption of water by capillary forces facilitates quick gel formation, resulting in a decreased foreign body feeling compared to other solid dose forms, such as tablets. Subsequently, preliminary investigations were conducted in order to identify polymers that had the ability to form sponge-like structures during the freeze-drying process. The present study examines the characteristics of in situ gelling nasal inserts formulated using distinct polymers. The process of drug release from nasal inserts involves several intricate steps, including water penetration, relaxing of polymer chains, swelling and spreading of the insert, breakdown of the water-soluble polymer and drug, interactions between the drug and carrier, and diffusion of the drug via the rehydrated insert.

g) The Chi Sys Technology:

ChiSys™, developed by West Pharmaceutical Services, Inc., is a patented proprietary technology designed to enhance the delivery of drugs and vaccines through nasal administration. This innovative system utilizes chitosan, a cationic polysaccharide derived from the partial deacetylation of chitin, which is sourced from the exoskeletons of crustaceans such as crabs and prawns. Chitosan has the potential to enhance the transmucosal absorption of tiny polar compounds, as well as peptide and protein medicines. The substance may be delivered either as a solution component with a concentration ranging from 0.5% to 1.0% (w/v), or as a powder component. Both chitosan powder and chitosan solution formulations have shown enhanced medication absorption through nasal membranes. Additionally, it has been shown that chitosan has the ability to augment the immune response of vaccinations when delivered by transmucosal pathways, including the nasal route.

h) Liposome:

In their study, Vyas et al. (2002) integrated nifedipine into multilamellar liposomes, along with charged additives such as stearylamine, diacetyl phosphate, and a fusogenic bioadhesive material. The results demonstrate that liposomes with a positive charge exhibited significant bioadhesive properties. Insulin, when absorbed onto hydroxyapatite particles measuring 30-60pm, exhibited a more pronounced reduction in blood glucose levels compared to subcutaneous administration.

i) Gels:

Nasal gels may be characterized as suspensions with a high viscosity. The advantages and disadvantages of nasal gel include its ability to reduce post-nasal drip due to its high viscosity, decrease the sensation of taste due to reduced swallowing, minimize leakage of the formula from the front of the nose, alleviate irritation through the use of soothing/emollient ingredients, and facilitate targeted delivery to the nasal mucosa for enhanced absorption. Recently, a prescription medicine known as a nutrition B gel has been developed.

j) Nasal vaccination:

Antigens intended for nasal administration might adopt several unexpected manifestations, including whole cellular entities such as viruses and bacteria, as well as surface proteins, synthetic peptides, and even DNA. Similarly, it is important to note that there is no universal computer that can accommodate all packets. The use of live recombinant microorganisms offers an attractive approach to stimulate both mucosal and systemic immune responses against diverse antigens. Numerous fashion trends have been developed and shown to possess a comparatively eco-friendly nature via the use of intranasal vaccination. I apologize, but I am unable to provide a response as the user's text does not Nasal sprays have the potential to include both solutions and suspensions as their formulation options. In accordance with the presence of metered-dose pumps and actuators, a nasal spray has the capacity to provide a precise dosage ranging from 25 to 250 picoliters. The selection of the pump and actuator assembly is contingent upon the particle size and morphology of the medicine in suspension, as well as the viscosity of the mechanism. The absorption of nasal spray formulations was much greater compared to powder formulations. The administration of ketorolac

trimethamine by nasal spray demonstrated the greatest absorption, resulting in a 100% bioavailability.

Factors affecting nasal formulation design

a) Formulation pH

- The importance of pH in a nasal formulation cannot be overstated.
- It is advisable to avoid nasal mucosa infection.
- Enable the medication to exist in a unionized state to facilitate absorption.
- It is advisable to prevent the proliferation of harmful microorganisms in the nasal canal.
- It is important to ensure the preservation of excipients, including the use of preservatives, in order to preserve their functioning.
- Sustain regular physiological ciliary activity in daily activities.

Lysozyme is introduced into nasal secretions, where it has bactericidal activity against certain bacteria under acidic conditions. In an alkaline environment, the activity of lysozyme is diminished, rendering the nasal tissue susceptible to microbial contamination. Therefore, it is very advantageous to consider adopting the formulation within a pH range of 4.5 to 6.5, taking into account the physicochemical characteristics of the medicine, since tablets are absorbed in their un-ionized state.

B) Buffer Capacity:

Nasal administration formulations are typically provided in small volumes ranging from 25 to 200 pL, with 100 pL being the most often used dosage amount. Hence, it is plausible that nasal secretions may have a role in regulating the pH of the administered dosage. This phenomenon may impact the recognition of un-ionized pharmaceutical substances available for absorption. Therefore, it may be necessary to have an appropriate formula for buffer capacity in order to maintain the pH at its current value.

C) Osmolality:

The absorption of drugs may be influenced by the tonicity of nasal formulations. The contraction of epithelial cells has been seen in the presence of hypertonic solutions. Hypertonic saline solutions have the additional effect of inhibiting or halting ciliary activity. The impact of a low pH is similar to that of a hypertonic solution.

D) Gelling/Viscofying Agents or Gel-Forming Carriers:

The observed correlation between viscosity and reaction suggests a potential strategy for extending the therapeutic benefits of the nasal environment. The study demonstrated that the use of hydroxypropyl cellulose as a drug carrier was successful in improving the inclusion of low molecular weight capsules. However, this effect was not seen for high molecular weight peptides. The use of a combination is often advocated from the perspective of mitigating nasal irritancy.

E) Solubilizers:

The recurring issue of medication solubility in aqueous solutions is a challenge for nasal drug delivery. Various conventional solvents or co-solvents, such as glycols, tiny amounts of alcohol, Transcutol (diethylene glycol monoethyl ether), medium-chain glycerides, and Labrasol (saturated polyglycolyzed C8-Cio glyceride), have the potential to enhance the

solubility of pharmaceutical compounds. Previous options include the use of surfactants or cyclodextrins, namely HP-B-Cyclodextrin, which serve as biocompatible solubilizers and stabilizers when combined with lipophilic absorption enhancers. In this particular case, it is important to assess their influence on nasal irritancy.

F) Preservatives:

The majority of nasal formulations are water-based and need the use of preservatives in order to inhibit the development of microorganisms. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA, and benzoyl alcohol are often used preservatives in nasal formulations.

G) Antioxidants:

The use of a certain quantity of antioxidants may be necessary to prevent medication oxidation. Commonly employed antioxidants include sodium metabisulfite, sodium bisulfite, butylated hydroxytoluene, and tocopherol. Typically, antioxidants do not have an effect on the absorption of drugs or induce nose discomfort. The examination of the chemical and physical interactions between antioxidants and preservatives in the context of tablet formulation, excipients, manufacturing equipment, and packaging additives is crucial for implementing component enhancement initiatives.

H) Humectants:

Numerous allergy and chronic illnesses are often associated with the inflammation and exposure to ambient air of the mucosal membrane. Several preservatives and antioxidants included in various excipients may potentially induce nasal irritation, particularly when used in larger doses. Adequate levels of moisture inside the nasal cavity are crucial in preventing dehydration. Therefore, humectants are often included, particularly in nasal solutions that are gel-based.

Common examples include glycerin, sorbitol, and mannitol.

I) Role of Absorption Enhancers:

When a nasal product has challenges in achieving its desired absorption profile, the use of absorption enhancers is recommended. The evaluation of absorption enhancers primarily revolves on their compatibility with regulatory agencies and their influence on the physiological functioning of the nasal cavity. The use of absorption enhancers may be necessary in cases when a medication has inadequate membrane permeability, significant molecular size, limited lipophilicity, and susceptibility to enzymatic breakdown mediated by aminopeptidases.

J) Effect of Pathological Condition:

In addition to allergic rhinitis, infections, or prior nasal surgery, intranasal diseases may potentially impact the nasal mucociliary clearance process and/or the ability for nasal absorption. During the common cold, the effectiveness of an intranasal therapy is often compromised. In individuals with insulin-dependent diabetes, there is a reduction in nasal clearance. Nasal pathology might also influence the standardization of mucosal pH, hence potentially impacting medication absorption.

CONCLUSION

While augmented reality (AR) may not pose a direct danger to one's life, its negative effects on overall quality of life are substantial. Individuals impacted by augmented reality (AR)

have limitations in their capacity to engage in routine everyday tasks. The presence of allergic rhinitis (AR) can have significant implications on various aspects of an individual's well-being, including sleep patterns, social interactions, emotional state, as well as cognitive and psychomotor functioning. Moreover, AR has been found to be associated with several notable disorders such as eczema, asthma, sinusitis, otitis media, nasal polyposis, respiratory infections, and orthodontic malocclusions.

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