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A Review on Recent Trends in Nasal Drug Delivery System

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ABSTRACT

Intranasal administration of antihistamines, antibiotics, vasoconstrictors, and decongestants has been used for many years to induce a local effect on the mucosa. These medications have the advantage of systemic bioavailability when self-medicated When compared to oral delivery, nasal administration is more effective. Traditional nasal drug delivery systems, being superior to oral or injection administration, challenge limitations that maximize their efficacy and applicability. The intranasal route has gained popularity as a method for systemic administration of vaccines, hormones, peptides, and other medicines. Intranasal medication delivery, once limited to the treatment of rhinitis and nasal congestion, is increasingly obtaining popularity for the administration of a vast range of medications. Nasal drug delivery alternatives are being considered as feasible alternatives to established systemic drug administration routes. This is due to the nasal epithelium's high permeability, which allows for a greater molecular mass around 1000 Da, as well as the quick rate of drug absorption is often like that of intravenous injections, alongwithplasma drug profiles that are almost identical.

Keywords:-Vasoconstriction; Nasal drug delivery; Bioavailability;Congestion;Absorption rate.

Introduction

The nasal route was introduced as a viable systemic drug distribution substitute to other conventional drug distribution routes in the early ‘1980s.This Nasal delivery route has been given a new lease, on life after being used for thousands of years[1].It's a good way to

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administer drugs like proteins and peptides, which are active at low dosages and have little oral bioavailability[2].The nasal mucosa is permeable to more chemicals than the intestinal tract due to lack of pancreas,stomachenzymatic activity,less degradation by gastric contents,andneutral pH of the nasal mucus. It has been proposed as a possible approach for achieving higher and faster levels of medication absorption[3].Nasal therapy is also known as "NASAYA KARMA" in Ayurvedic schools of Indian medicine is an approved kind of treatment[4].The nasal deliverycan be useful,for systemic pharmaceutical administration as well as for local effects. Researchers are still working on developing an appropriate nasal drug delivery method[5].Many steps have been taken in the past years to increase the retention time of medication formulation in the olfactory region in enhancing nasal drug absorption. The nasal mucosa's high vascularization and permeability stimulated researchers' interest in employing it as a method for systemic medication delivery[6].To ensure a local or systemic action, the drug to be administered must be adjusted to particle size, concentration, and chemical form depending on the desired site of drug action. Bypassing the first-pass metabolism, this pathway providesaporous endothelium membrane, broad surface area, high blood flow, and easy accessibility[7].Nasal preparations include nasal sprays,nasal drops, nasal ointments, nasal creams, and nasal aerosols according to the marketed formulations of nasal products. Due to their extended retention duration, nasal ointments and creams are primarily used in the treatment of nasal bacterial infections andthecure of nasal blockage or congestion[8]
.

The benefits and constraints of nasal therapies, as well as the physiology of the nasal passage, are briefly discussed in this systematic review. Advantages, nasal absorption mechanism, nasal absorption obstacles Nasal drug absorption factors and techniques, nasal drug administration applications.

Morphology and Physiology of Nose

The nose channel travels from the nasalvestibuleto the nasopharynx which is 12-14 cm long. It is divided into three sections: respiratory, olfactory,and vestibular(Figure 1). The nasal area is 16-19 cm^3 in volume and 180 cm^2 in surface area, having two chambers (nostrils) divided by the septum of the nose[9].The vestibular area, which filters particles from breathed air, is positioned at the front aperture of the nasal passages. In this region, however, drug administration and absorption are of the utmost importance.Hairs cover this area, filtering the air and preventing airborne pollutants from entering the respiratory system[10].The respiratory region has a surface area of around 130 cm^2 which is big and vascularized. Most medication

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absorption takes place in this area. it is covered with pseudostratified epithelium and coated with sticky mucus that flows towards the posterior passages of the nasal cavity due to cilia rhythmic motions[11]**.** The olfactory pathwaycovers a total surface area of around 15 cm^2, which is vital for delivering drugs to the cerebral-spinal fluidand brain. It's made up of lamina propriaa and thick connective tissue[12].Nasal mucosa thickness varies between 2-4 mm.The sticky mucus layer 5 m protects the epithelial cells that line the nose canal, trapping foreign particles. Water accounts for 95% of mucous secretion, mucin for 2%, salts for 1%, proteins such as immunoglobulin, albumin,lactoferrin, lysozymefor 1%, and lipids for 1%.Mucus secretion also contains IgA, IgE, and IgG antibodies[13]**.**The nasal secretion's pH ranges from 5 to 6.5.Ciliary stimulation clears the mucous membrane in the nose canal, and mucus is produced 4 to 6 times every hour. Mucus passes through the nose at a rate of 5-6 mm/min[14].

Nasal Mucosa

The nasal lining is made up of the same pseudostratified ciliated epithelium as most of the respiratory system. Each cell has up to 200 cilia, the tips of which are found in the superficial gel layer[15]**.**In the anterior portion of the superior and middle eustachian tubes, where there is the most contact with the inspired air, tumor growth with cuboidal cells without cilia can occur[16].

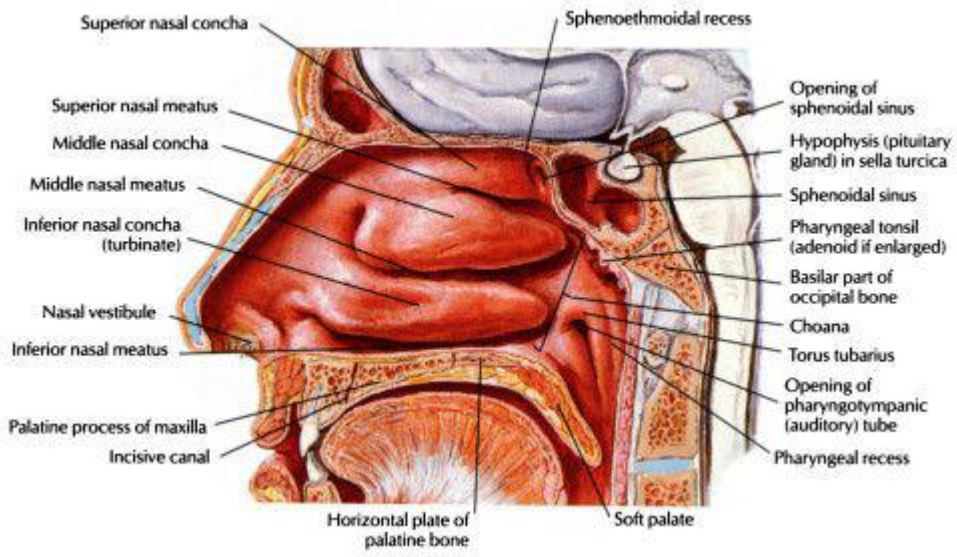

Figure 1:Structure of nasal mucosa

Table 1: Characteristics of the Nasal Mucosa

Parameters	Nasal Mucosa
Surface area	150-180 cm^2

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Thickness	1-2 mm
Endothelial basement membrane	The porous and thin structure of the endothelial basement membrane possesses no restriction to the entry of thedrug molecule into the systemic circulation
PermeabilityEpithelium	The nasal mucosa possesses porous epithelium
Vascularity	Arterial supply:External and internal carotid artery,maxillary artery via a sphenopalatine artery

Advantages

1. Self-medication is easier with easy access and needle-free drug delivery without any requirement for skilled people, which promotes patient compliance as compared with parenteral approaches[17].

2. Drugs having low molecular weight, especially lipophilic drugs, penetrate the nasal mucosa[18].

3. Because of the relatively high vascularization and wide absorption surface, the drug absorbs quickly and has a quick onset of effect. The Tmax of fentanyl following nasal delivery was less than or comparable to 7 minutes as compared to intravenous [i.v] administration. As an alternative to parenteral administration, intranasal delivery of a relevant medicine would be beneficial in emergency therapy[3].

4. Avoid the gastrointestinal tract's harsh environmental conditions (drug chemical and enzymatic degradation) [20].

5. Nasal medication delivery avoids hepatic first-pass degradation, allowing for a dose reduction when compared to oral drug delivery [21].

6. Opportunity for drug delivery to the nervous system directly through the olfactory epithelium, bypassing the blood-brain barrier[22].

7.Nasal administration is an alternative to parenteral administration, particularly for proteins and peptides [23].

8. The vaccine is delivered directly to lymphatic vessels, and secretion immune reaction is induced at a proximal mucosal site [24].

9. Case convenience and compliance is bettered

10. The mucous membrane allows for good penetration of low molecular weight medications, especially lipophilic ones.

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Mechanism of Drug Absorption

The mucus is the principal mechanism in the transport and permeation of a drug via the nasal passage. Mucin which is a protein derived from mucus, can adhere to solutes and so influence the rate of diffusion. The mucus layer must pass through the absorbed medications from the nasal cavity[25].

There are two mechanisms:

Paracellular- It contains the paracellular route, which is an aqueous transport mechanism, but which is inactive and slow. Molecular weight for water-soluble compounds and intranasal absorptionhas an inverse log association. Bioavailability is low for drugs having a molecular weight greater than 1000 Daltons[26].

Transcellular- It involves lipoidal transport, also termed as the transcellular process, and is responsible for the distribution of lipophilic drugswiththe rate depending on their lipophilicity, Drugs can also be delivered through the cellular membrane via a carrier-mediated route or by causing tight junctions to open[27].

Barriers to nasal absorption

The nasal medication delivery system is thought to be a cost-effectiveandoption for formulations experts as it provides easy and simple formulation procedures. The therapeutic effectiveness,safety and toxicities of intra-nasally delivered medicinal products are affected by a variety of circumstances[28].

Factors related to barriers for drug absorption

Bioavailability: The bioavailability of polarized Drugs is often low, ranging from roughly 10% of low molecular weight pharmaceuticals to less than 1% with peptides like insulin and calcitonin[29].The low permeability of cell membrane has been the most important factor restricting the nasal intake of polar medications, specifically big molecular mass polar pharmaceuticals like peptides and proteins. Drugs can penetrate through the epithelial cellular membrane in one of three ways: receptor-mediated or vesicular via receptors, transcellular by simple gradient of concentration, and paracellularly via tight connections between cells.Polar medicines with molecular weights less than 1000 Da are more likely to get through the membrane via the latter pathway[30].

Despite tight junctionsthatconstituteadynamic system that expandsand also close to a degree as required, the average size of these pathways is on the order, of tens of nanometers, preventing the transport of bigger molecules. Endocytosis transport allows proteins and larger peptides to pass through the nasal cell wall, but only in small numbers.Coadministration of

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absorption-enhancing medications with such polar medicines can considerably improve nasal absorption[31] .Agents mainly used for trans nasalinvolvementarebile salts and bile salt derivatives (sodium deoxycholate, sodium taurodihydrofusidate,sodiumglycocholate), Surfactants(laureth9,sodiumlaurylsulfate),phospholipids(DDPC,lysophosphatidylcholine),fatty acids and fatty acid derivatives (linoleic acid) andvarious cyclodextrins (dimethyl-cyclodextrin) ,chitosan and derivatives like poly-L-arginine, poly-L-lysine. These enhancers work in a number ofwaysbut most of them work by changing the permeability of the epithelial cell layer by modifying phospholipid bilayers, leaching proteins from the membrane, or even removing the mucosa's outer layer. Some of these enhancers also have an effect on tight junctions and/or act as an inhibitor of enzymatic degradation[32].

Low transfer through the membrane:Theimportant feature is poor cellular membrane transport which refers to the mucociliaryallowancemechanism's general quick removal of supplied formulation, from nasal passage. This is especially true for medications that are difficult to absorb via the nasal membrane[33]**.**Non-mucoadhesive solution and powder formulations have been proven to have a clearance half-life of 15–20 minutes.Deposition of the formulation in the anterior section of the nasal pathway, as opposed to depositingfurtherposterior in the nasal passage, has been suggested to reduce clarity and improve absorption. In comparison to nasal drops, which are administered to a broader region further behind in the nasal route, most of the nasal sprays of different brands have been proven to transport the formulations to a restricted area in the anterior section of the nasal pathway[34].To combat the fast mucociliary clearness, bioadhesive substances are used for the formulations. By depositing the formulation in the forward, less ciliated portionof the nasal pathway, the clarity can be minimized, resulting in good absorption[35]**.**

Enzymatic Degradation:

Another component that contributes to peptide and protein bioavailability over the mucosa of the nose, but is typically overlooked, is the likelihood of enzymaticbreakdown of the molecule, in the nasal cavity lumen or during transit through the epithelial layer[36]**.**Exopeptidases like mono and diaminopeptidases could cleave peptides at their C and N terminaland endopeptidases like cysteine and serine can attack inner peptide bonds at both sites. Enzyme inhibitors and enzyme overload could be used to break through this barrier. In conclusion, the nose has distinct advantages as a medication administration site. Low permeability for high molecular weight and polar medications, quick clearness of the delivery system from the nasal cavity, and probable biological drug breakdown in the nostrils may all

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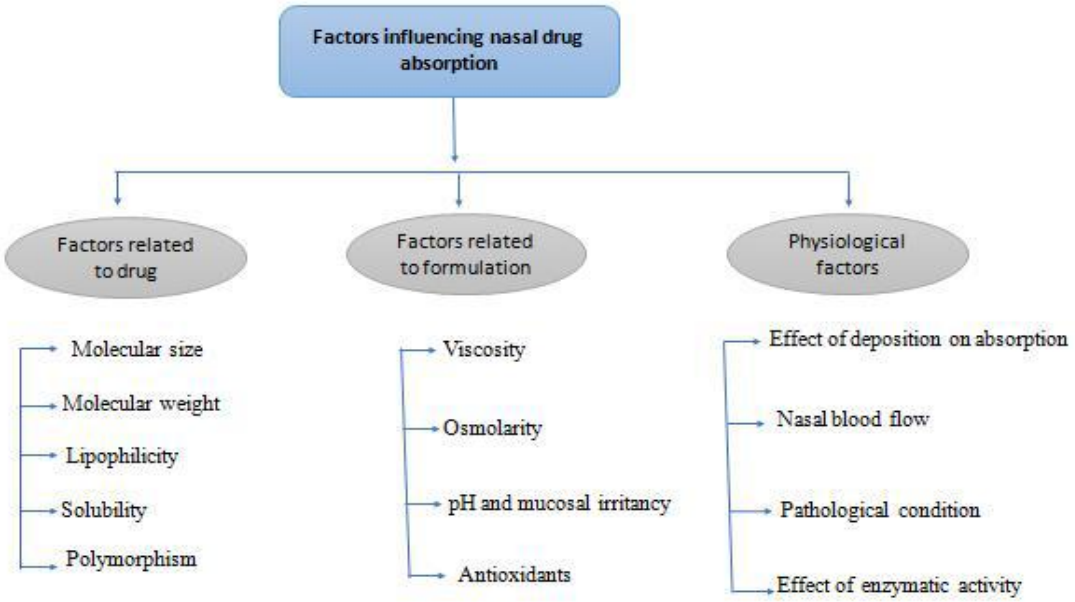
be issues. Various techniques, like as the use of absorption enhancers and bioadhesive systems, can be used foraddressing these issues[37] .

Factorsinfluencingdrugabsorption through nasal cavity



Factors related to drug

Molecular Size:

The drug's molecular size seems to have had an impact on its absorption through to the nose. The molecular weight and the drug penetration are directly related in lipophilic medicines, but to the contrary is true for water-soluble substances. For molecules with MW 300 Daltons, the rate of permeation is dependent upon the size of the molecules [38].

Molecular weight:

A linear inverse relationship between medication distribution and molecular weight has been documented up to 300 Da. Unless distribution enhancers are used, absorption reduces dramatically when the molecular weight exceeds 1000 Da. The shape is also important,Linearparticles absorb less energy than cyclic-shaped particles[39].

Lipophilicity:

The penetration of the chemical via the mucosa of the nose increases as the lipophilicity of the particles increases. Despite, the fact that the mucosa of the nose has some hydrophilic

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properties it appears that these mucosa are largely lipophilic in nature with the lipid domain playing an essential part in the barriers function is based on these membranes. In one study, lipophilic compounds alprenolol and propranolol were found to be well absorbed from the mucosal surface, in contrast to the hydrophilic drug metoprolol, because lipophilic substances can divide into the lipid layer of the endothelium membrane and permeate into and pass the cells in the cytoplasm, they can easily cross biological membranes through the transcellular route[40].

Solubility:

The molecularly dispersed form of medication at the absorption site may cross the biomembranes, drug dissolution is a prerequisite for any drug absorption. As a result, before nasal absorption, the medicine must be dissolved in the nasal cavity's watery fluids. As a result, the optimum aqueous drug solubility is critical for adequate contact with the nasal mucosa and posterior absorption. Drug solubility, on the other hand, has an impact on the absorption profile. As a result, medications that are poorly soluble in water and/or require high doses may be a concern. This can be overcome by increasing the water solubility of the medication[41].

Polymorphism:

In nasal drug release and product design, determining the polymer form of medication is a crucial part to consider. Different polymorphs have an impact on medication breakdown and absorption through the nasal pathway. various polymorphic versions of medication have various levels of nasal mucus membrane penetration. The stability and purity of polymorphic forms must be considered in the nasal compositions. The drug's delivery to the brain is regulated by the nasal mucosa's pH and the drug itself. For the avoidance of nose irritation, bacterial growth, and mucosal damage, the formulation's optimal pH should be between 4.60 and 6.50. Only a portion of the medicine that is not ionized can pass through the nasal mucosa [42].

Factors Related to formulations

Viscosity:

The viscosity of the nasal spray affects spray characteristics such as spray geometry and droplet size as well as nasal deposition.When compared to viscous formulations, nasal formulation along with reduced viscosity tends to settle posterior to the nose. Furthermore, increased viscosity was linked to narrower plume angleand larger droplet size, resulting in a small spray region. The permeability of medications is altered when more viscous

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preparationsinvolvetypical activities such as mucociliaryclearanceor ciliary beating[43].

Osmolarity:

The isotonic solution of formulations can affect drug administration. In presence of hypertonic solutions, epithelial cell shrinkage has been reported[44] .Hypertonic saline solutions decrease or cease ciliary function as well. A hypotonic solution has thesameeffect as low pH solutions[44].

pH and mucosal irritancy:

The penetration of medicine is influenced by the pH of the formulation as well as the pH of the nasal surface. The pH of the nasal formulation should be adjusted to 4.5–6.5 to avoid nasal discomfort. It results in effective drug permeation and prevents the formation of microorganisms, in addition to minimizing discomfort[45].

Antioxidants:

Antioxidants rarely cause nose irritation or interfere with medicine absorption. Antioxidants includesodium bisulfite, sodium metabisulfite, butylated hydroxyl toluene, and tocopherol[46] .

Physiological Factors

Effect of Deposition on Absorption:

The formulations are deposited in the front section of the nostril, which allows for a longer length of nasal resident duration. The front region of the nostril has low permeability, but the posterior area of the nose has a shorter resident time and higher permeability[47].

Nasal Blood flow:

The flow of blood to the mucous layer of the nose is abundant. Nasal drug administration is affected by blood flowsince,nasal relaxationandcongestionregulate the fall and rise in drug penetrated amount, respectively. As a result, it's possible to deduce that parasympathetic activation causes greater permeability [48].

Pathological conditions:

The condition which influences the efficacy and speed of mucociliaryclearness, nasal secretions, and irritation in the nasal mucosa such as the commonrhinitis,cold,nasal polyposis, and atrophic rhinitiscan alter the Drug absorption profile[49].

Effect on Enzymatic activity:

Nasal absorption of drugs avoids the hepatic first-pass metabolism and gastrointestinal impact. Due to the availability of a wide spectrum of biochemical enzymes in nasal cells, they may be considerably digested in the nasal passage lumens or during passing over the nasal epithelial barrier. Pharmaceuticals such as nicotine,cocaine,alcohols, progesterone, and

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decongestants are metabolized by oxidative phase I enzymes (e.g., Cytochrome P450 isoenzymes[50] .Distinct species have different populations and/or activity of nasalenzymes. However, based on the quantity of tissue involved, the degree of activity for nasal enzymes appears to be lower than for those in the gastrointestinal tract or liver[51] .

Effectof pathological condition:

Nasal pathological diseases include rhinitis (allergic and non-allergic), nasal polyps and cancer, and ordinary colds can all affect permeation from the nasal passage in variousways.Bleeding, increased mucus flow, nasal blockage, and crusting are all symptoms of nasal conditions. A rhinovirus infection has been shown to cause epithelial cell sloughing and epithelial layer damage in vitro. A nasally delivered medicine may be washed away by excessive nasal discharge before it can be absorbed[52].

Strategies To Improve Nasal Absorption

Various measures have been used to increase the drug's bioavailability in the nasal mucosa, including

1. To increase the resident time the nasal cavity
2. To improve absorption by the nose
3. To change the physicochemical qualities of medication by changing its structure.

4.To enhance the absorption and bioavailability of the formulation any one or a combination of the above procedures can be applied. Several ways have been used to enhance drug administration through the nose, including:

Mucociliary clearance:

Mucociliary clearance is the process of removing foreign materials and substances as rapidly as possible from the nasal mucosa. One method for delaying clearance is to apply the medicine to the anterior region of the nasal cavity, which is largely controlled by the sort of dosage form used[15] .The preparation could alternatively be made with polymers like methylcellulose, hydroxypropyl methylcellulose, or polyacrylic acid, which enhances viscosity and functions as a bioadhesive with mucus. Increased residence time does not always imply increased absorption; this principle can be shown using an insulin solution containing carbopol and carboxymethyl cellulose of similar viscosity (CMC). Carbopol improves insulin absorption, whereas CMC solution does not enhance the administration of insulin. In the case of Carbopol, it increases distribution via opening intracellular connections. Using biodegradable microspheres as a drug delivery carrier is another potential option to extend nasal resistance duration. In the presence of water, biodegradable

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microspheres swell, increasing the viscosity. As a result of this event, the nasal residence time increases[53].

Permeation enhancers:

Permeation enhancers are mainly used to increase the active ingredient's absorption... Penetration enhancers work by the following mechanisms: Reduce mucociliary clearance; Open tight junctions; Reduce mucus elasticity or viscosity and Solubilize or stabilise the medication. Absorption enhancers work by enhancing the rate at which the medicine passes via the nasal mucosa. Different enhancers work by, changing the composition of epithelial cells, they must do so without harming or permanently modifying the nasal mucosa[54] **.**

The following are the general requirements for an ideal penetration enhancer:[55]

1 It should result in a significant increase in drug permeation.

2. There should be no permanent injury or alteration to the tissues.

3. It should not be harmful and irritatetheskin.

4. It should be helpful even when taken in little quantities.

5. When absorbing is required, the impact should occur

6. The effect shouldtransientandreversible.

Prodrugs:

The bulk of intranasal medications is given as solutions or powders that must be digested before they may be absorbed. Although lipophilic drugs are not water-soluble, they are easily transported across biomembranes.In order to make an aqueous nasal formulation with a sufficient concentration, they need tobe supplied as a prodrug with a more hydrophilic character. As soon as prodrug enterstheblоodstream. It must be transformed back to the original medication.synthesisedseveralL-dopa drug candidates and observed that their solubility was much increased over the parent drug, permitting the production of effective nasal formulations[56] .Testosterone which is also a water-soluble produced a similar result. Polar medicines that are extremely hydrophilic, on the other hand, may not beable to cross the blood-brain barrier. As a result, membrane penetration may be boosted if they are supplied as a prodrug with a better lipophilic character[57] **.**

Co-Solvents:

Cosolvents can be used as an alternative to prodrugs to increase medication solubility. The most widely used co-solvents in the intranasal formulation are ethanol,glycerol,polyethyleneglycol,andpropylene glycol andthey may be very essential since they are pharmaceutically acceptable,non-toxic and nonirritant to the nasal pathway[58] .

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Nasal enzyme inhibitors: Drug metabolism in the nose can be slowed alongwiththe use of enzyme inhibitors. In the production of peptideand proteins compounds, enzyme inhibitors such as proteasesandpeptidases are routinely used. Fusidicacidand Salts derivatives, for example, block enzymes as a result increasedbioavailabilityandmedication absorption. Additional enzyme inhibitors such as aprotinin,tripsin,amastatin, bestatin,borovaline and boroleucin are commonly used for enzymatic activity[59].

Structural modification:

The most profitable method to promote nasal permeation is to improve the structure of a drug without changing pharmacological effectiveness. By modifying the physicochemical qualities of treatment, such as molecular weight, molecular size and solubility, chemical modification of drug molecules andPka has been widely employed to increase medication absorption by the nose.. When salmon calcitonin was chemically changed to ecatonin (where the C-N link replaced the S-S bond), ecatonin had a good bioavailability other than salmon calcitonin[60] .

Applications of Nasal Delivery

Nasal decongestant:

The nose is used to treat localised problems with low therapeutic doses and minimal systemic side effects. Local pathological problems in the nose are treated with low molecular weight water-soluble or hydrophobic medicines. Nasal decongestants, such as xylometazoline, are also used to treat colds through the nose[61].

Systemic Effects:

When a quick response is required, like in the treatment of migraine, nostril administration is suitable for acids labile medicines, peptides,and proteins[62] .Because of their higher molecular weight and polarity, peptideandproteinmedicines have less bioavailability (1–2%), resulting in poor permeation via the nasal mucosal membrane. Progesterone and propranolol bioavailability via nasal epithelium, on the other hand, is comparable to parenteral delivery[63] .Less bioavailability can be increased by including permeation enhancers in the formulation and utilising bioadhesive agents to extend the drug's contact time with the mucosal membranes. In rats, utilising 0.1 percent N-succinyl chitosan as a permeation enhancer resulted in a considerable increase in the higher relative bioavailability of isosorbide dinitrate (69.85 percent) then the control groups (43.32 percent)andthe 0.5 percent chitosan (55.36 %) [64].

Vaccine Delivery:

Vaccines and their use in the treatment of respiratory illnesses via the nose have been studied. Because immune system moleculesare located in the mucosal surface, the respiratory system is the body's initial line of defence against infections. Lymphocytic tissue enriches the nasal mucosa. It boosts system levels of particular nasal secretory immunoglobulin A andimmunoglobulin G as well as local immune cells, giving you more resistant to microbial invasion[65].

References

[1]. Jaiswal, P. L., Darekar, A. B., & Saudagar, R. B. (2017). A recent review on nasal microemulsion for treatment of cns disorder. *International Journal of Current Pharmaceutical Research*, *9*(4), 5..DOI:10.22159/ijcpr.2017v9i4.20963

[2]. Ferrante, M., Andreeta, A., & Landoni, M. F. (2010). Effect of different penetration enhancers on diclofenac permeation across horse skin. *The Veterinary Journal*, *186*(3), 312-315.. 2010 Dec 1;186(3):312-5.doi: 10.1016/j.tvjl.2009.09.010.

[3]. Ghadiri, M., Young, P. M., & Traini, D. (2019). Strategies to enhance drug absorption via nasal and pulmonary routes. *Pharmaceutics*, *11*(3), 113.10.3390/pharmaceutics11030113

[4]. Singh, S. K., Swami, P., & Rajoria, K. (2020). Effects of medicated enema and nasal drops using Triphaladi oil in the management of obesity-A pilot study. *Journal of Ayurveda and integrative medicine*, *11*(2), 173-176. doi: 10.1016/j.jaim.2020.02.001

[5]. Keller, L. A., Merkel, O., & Popp, A. (2021). Intranasal drug delivery: Opportunities and toxicologic challenges during drug development. *Drug Delivery and Translational Research*, 1-23..DOI: https://doi.org/10.1007/s13346-020-00891-5

[6]. Al Asmari, A. K., Ullah, Z., Tariq, M., & Fatani, A. (2016). Preparation, characterization, and in vivo evaluation of intranasally administered liposomal formulation of donepezil. *Drug design, development and therapy*, *10*, 205.doi: 10.2147/DDDT.S93937

[7]. Alnasser, S. (2019). A review on nasal drug delivery system and its contribution in therapeutic management. *Asian Journal of Pharmaceutical and clinical research*, *12*, 40-45..DOI: https://doi.org/10.22159/ajpcr.2019.v12i1.29443

[8]. Gao, M., Shen, X., & Mao, S. (2020). Factors influencing drug deposition in the nasal cavity upon delivery via nasal sprays. *Journal of Pharmaceutical Investigation*, *50*(3),

251-259..https://doi.org/10.1007/s40005-020-00482-z

[9]. Tai, J., Lee, K., & Kim, T. H. (2021). Current Perspective on Nasal Delivery Systems for Chronic Rhinosinusitis. *Pharmaceutics*, *13*(2), 246..doi: 10.3390/pharmaceutics13020246.

[10]. Harkema, J. R., Plopper, C. G., & Pinkerton, K. E. (2000). Comparative structure of the respiratory tract: airway architecture in humans and animals. In *Pulmonary immunotoxicology* (pp. 1-59). Springer, Boston, MA.

[11]. Shang, Y., Inthavong, K., Qiu, D., Singh, N., He, F., & Tu, J. (2021). Prediction of nasal spray drug absorption influenced by mucociliary clearance. *PLoS One*, *16*(1), e0246007..https://doi.org/10.1371/journal.pone.0246007

[12]. Gänger, S., & Schindowski, K. (2018). Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. *Pharmaceutics*, *10*(3), 116..doi: 10.3390/pharmaceutics10030116.

[13]. Leal, J., Smyth, H. D., & Ghosh, D. (2017). Physicochemical properties of mucus and their impact on transmucosal drug delivery. *International journal of pharmaceutics*, *532*(1), 555-572.doi: 10.1016/j.ijpharm.2017.09.018.

[14]. Morawska-Kochman, M., Jermakow, K., Nelke, K., Zub, K., Pawlak, W., Dudek, K., &Bochnia, M. (2019). The pH Value as a Factor Modifying Bacterial Colonization of Sinonasal Mucosa in Healthy Persons. *Annals of Otology, Rhinology & Laryngology*, *128*(9), 819-828..doi: 10.1177/0003489419843143.

[15]. Bustamante-Marin, X. M., & Ostrowski, L. E. (2017). Cilia and mucociliary clearance. *Cold Spring Harbor perspectives in biology*, *9*(4), a028241..doi: 10.1101/cshperspect.a028241.

[16]. Bustamante-Marin, X. M., & Ostrowski, L. E. (2017). Cilia and mucociliary clearance. *Cold Spring Harbor perspectives in biology*, *9*(4), a028241.doi: 10.1158/0008-5472.CAN-05-1705.

[17]. Giroux, V., & Rustgi, A. K. (2017). Metaplasia: tissue injury adaptation and a precursor to the dysplasia–cancer sequence. *Nature Reviews Cancer*, *17*(10), 594-604..doi: 10.1038/nrc.2017.68. Epub 2017 Sep 1.

[18]. Chenthamara, D., Subramaniam, S., Ramakrishnan, S. G., Krishnaswamy, S., Essa, M. M., Lin, F. H., & Qoronfleh, M. W. (2019). Therapeutic efficacy of nanoparticles and routes of administration. *Biomaterials research*, *23*(1), 1-29..doi: 10.1186/s40824-019-0166-x.

[19]. Froelich, A., Osmałek, T., Jadach, B., Puri, V., & Michniak-Kohn, B. (2021). Microemulsion-based media in nose-to-brain drug delivery. *Pharmaceutics*, *13*(2), 201.doi: 10.3390/pharmaceutics13020201

[20]. Hua, S. (2020). Advances in oral drug delivery for regional targeting in the gastrointestinal tract-influence of physiological, pathophysiological and pharmaceutical factors. *Frontiers in pharmacology*, *11*, 524..doi: 10.3389/fphar.2020.00524.

[21]. Xu, J., Tao, J., & Wang, J. (2020). Design and application in delivery system of intranasal antidepressants. *Frontiers in Bioengineering and Biotechnology*, 1450..doi: 10.3389/fbioe.2020.626882.

[22]. Miyake, M. M., & Bleier, B. S. (2015). The blood-brain barrier and nasal drug delivery to the central nervous system. *American journal of rhinology & allergy*, *29*(2), 124-127..doi: 10.2500/ajra.2015.29.4149.

[23]. Miyake, M. M., & Bleier, B. S. (2015). The blood-brain barrier and nasal drug delivery to the central nervous system. *American journal of rhinology & allergy*, *29*(2), 124-127..doi: 10.47391/JPMA.759.

[24]. Russell, M. W., Moldoveanu, Z., Ogra, P. L., & Mestecky, J. (2020). Mucosal immunity in COVID-19: a neglected but critical aspect of SARS-CoV-2 infection. *Frontiers in Immunology*, 3221.doi: 10.3389/fimmu.2020.611337

[25]. Clementino, A. R., Pellegrini, G., Banella, S., Colombo, G., Cantù, L., Sonvico, F., & Del Favero, E. (2021). Structure and fate of nanoparticles designed for the nasal delivery of poorly soluble drugs. *Molecular Pharmaceutics*, *18*(8), 3132-3146..doi: 10.1021/acs.molpharmaceut.1c00366.

[26]. Vigani, B., Rossi, S., Sandri, G., Bonferoni, M. C., Caramella, C. M., & Ferrari, F. (2020). Recent advances in the development of in situ gelling drug delivery systems for non-parenteral administration routes. *Pharmaceutics*, *12*(9), 859.doi: 10.3390/pharmaceutics12090859.

[27]. Marx, D., Williams, G., & Birkhoff, M. (2015). Intranasal drug administration—an attractive delivery route for some drugs. *Drug Discov Dev*, 299-320.DOI: 10.5772/59468

[28]. Brayden, D. J., Hill, T. A., Fairlie, D. P., Maher, S., & Mrsny, R. J. (2020). Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches. *Advanced drug delivery reviews*, *157*, 2-36..doi: 10.1016/j.addr.2020.05.007.

[29]. Laddha, U. D., & Tagalpallewar, A. A. (2021). Physicochemical, biopharmaceutical, and

practical considerations for efficient nose-to-brain drug delivery. In *Direct Nose-to-Brain Drug Delivery* (pp. 39-54). Academic Press..doi: 10.2174/138920112803341752.

[30]. Dong, X. (2018). Current strategies for brain drug delivery. *Theranostics*, *8*(6), 1481..doi: 10.7150/thno.21254. eCollection 2018.

[31]. Costantino, H., & Li, C. Y. (2006). *U.S. Patent Application No. 11/246,450*.

[32]. Quay, S., Kleppe, M., & Costantino, H. (2006). *U.S. Patent Application No. 11/293,676*.

[33]. Nižić Nodilo, L., Ugrina, I., Špoljarić, D., Amidžić Klarić, D., Jakobušić Brala, C., Perkušić, M., ... & Hafner, A. (2021). A Dry Powder Platform for Nose-to-Brain Delivery of Dexamethasone: Formulation Development and Nasal Deposition Studies. *Pharmaceutics*, *13*(6), 795..doi: 10.3390/pharmaceutics13060795.

[34]. Kaur, P., Garg, T., Rath, G., & Goyal, A. K. (2016). In situ nasal gel drug delivery: A novel approach for brain targeting through the mucosal membrane. *Artificial cells, nanomedicine, and biotechnology*, *44*(4), 1167-1176..doi: 10.3109/21691401.2015.1012260.

[35]. Gan, L., Cookson, M. R., Petrucelli, L., & La Spada, A. R. (2018). Converging pathways in neurodegeneration, from genetics to mechanisms. *Nature neuroscience*, *21*(10), 1300-1309..doi: 10.1038/s41593-018-0237-7.

[36]. Wu-Pong, S., & Rojanasakul, Y. (Eds.). (2010). *Biopharmaceutical drug design and development*. Springer Science & Business Media.DOI:10.1007/978-1-59745-532-9.

[37]. Miyamoto, M., Natsume, H., Iwata, S., Ohtake, K., Yamaguchi, M., Kobayashi, D., ... & Morimoto, Y. (2001). Improved nasal absorption of drugs using poly-l-arginine: effects of concentration and molecular weight of poly-l-arginine on the nasal absorption of fluorescein isothiocyanate–dextran in rats. *European Journal of pharmaceutics and biopharmaceutics*, *52*(1), 21-30..doi.org/10.1016/S0939-6411(01)00149-7

[38]. Akhtar, N., Singh, V., Yusuf, M., & Khan, R. A. (2020). Non-invasive drug delivery technology: Development and current status of transdermal drug delivery devices, techniques and biomedical applications. *Biomedical Engineering/Biomedizinische Technik*, *65*(3), 243-272..https://doi.org/10.1515/bmt-2019-0019

[39]. Thorat, S. (2016). Formulation and product development of nasal spray: an overview. *Scholars journal of applied medical sciences*, *4*(8D), 2976-2985.

[40]. Pires, A., Fortuna, A., Alves, G., & Falcão, A. (2009). Intranasal drug delivery: how, why and what for?. *Journal of Pharmacy & Pharmaceutical Sciences*, *12*(3), 288-311..DOI:10.18433/J3NC79

[41]. Chaturvedi, M., Kumar, M., & Pathak, K. (2011). A review on mucoadhesive polymer

used in nasal drug delivery system. *Journal of Advanced Pharmaceutical Technology & Research*, *2*(4), 215..DOI:10.4103/2231-4040.9087

[42]. Sosnowski, T. R., Rapiejko, P., Sova, J., & Dobrowolska, K. (2020). Impact of physicochemical properties of nasal spray products on drug deposition and transport in the pediatric nasal cavity model. *International Journal of Pharmaceutics*, *574*, 118911..DOI: 10.1016/j.xphs.2016.03.033

[43]. Hareesh Reddy, M., Sambasivarao, K., & Rao Baru, C. (2016). Methods of adjusting tonicity and pH values of some drugs and substances. *Int J Adv Res Biol Sci*, *3*, 207-12.DOI**:** 10.4103/jpbs.JPBS_210_19

[44]. Haumann, R., Videira, J. C., Kaspers, G. J., van Vuurden, D. G., & Hulleman, E. (2020). Overview of current drug delivery methods across the blood–brain barrier for the treatment of primary brain tumors. *CNS drugs*, *34*(11), 1121-1131..DOI:10.1007/s40263-020-00766-w

[45]. Dhakar, R. C., Maurya, S. D., Tilak, V. K., & Gupta, A. K. (2011). A review on factors affecting the design of nasal drug delivery system. *Int J Drug Deliv*, *3*(2), 94-208.

[46]. Maaz, A., Blagbrough, I. S., & De Bank, P. A. (2021). In Vitro Evaluation of Nasal Aerosol Depositions: An Insight for Direct Nose to Brain Drug Delivery. *Pharmaceutics*, *13*(7), 1079..DOI: 10.3390/pharmaceutics13071079

[47]. Watts, A. M., Cripps, A. W., West, N. P., & Cox, A. J. (2019). Modulation of allergic inflammation in the nasal mucosa of allergic rhinitis sufferers with topical pharmaceutical agents. *Frontiers in pharmacology*, *10*, 294..https://doi.org/10.3389/fphar.2019.00294

[48]. Cingi, C., Bayar Muluk, N., Mitsias, D. I., Papadopoulos, N. G., Klimek, L., Laulajainen-Hongisto, A., ... & Scadding, G. K. (2021). The Nose as a Route for Therapy: Part 1. Pharmacotherapy. *Frontiers in Allergy*, 1..DOI:10.3389/falgy.2021.638136

[49]. Illum, L. (2003). Nasal drug delivery—possibilities, problems and solutions. *Journal of controlled release*, *87*(1-3), 187-198..DOI: 10.1016/s0168-3659(02)00363-2

[50]. Ni, W., Yang, X., Yang, D., Bao, J., Li, R., Xiao, Y., ... & Gao, Z. (2020). Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Critical Care*, *24*(1), 1-10..DOI: 10.23750/abm.v91i4.10159

[51]. Stenner, M., & Rudack, C. (2014). Diseases of the nose and paranasal sinuses in child. *GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery*, *13*.DOI:10.1055/s-0033-1363211

[52]. Shaikh, R., Singh, T. R. R., Garland, M. J., Woolfson, A. D., & Donnelly, R. F. (2011). Mucoadhesive drug delivery systems. *Journal of pharmacy and Bioallied Sciences*, *3*(1), 89.DOI: 10.4103/0110-5558.76436

[53]. Algin-Yapar, E. (2014). Nasal inserts for drug delivery: an overview. *Tropical Journal of Pharmaceutical Research*, *13*(3), 459-467.DOI:10.4314/tjpr.v13i3.22

[54]. Songkro, S. (2009). An overview of skin penetration enhancers: penetration enhancing activity, skin irritation potential and mechanism of action. *Songklanakarin Journal of Science & Technology*, *31*(3).Corpus ID: 55695438

[55]. Kushwaha, S. K., Keshari, R. K., & Rai, A. K. (2011). Advances in nasal trans-mucosal drug delivery. *Journal of applied pharmaceutical science*, *1*(7), 21. 1;1(7):21.

[56]. Bennion, B. J., Be, N. A., McNerney, M. W., Lao, V., Carlson, E. M., Valdez, C. A., ... & Carpenter, T. S. (2017). Predicting a drug's membrane permeability: A computational model validated with in vitro permeability assay data. *The journal of physical chemistry B*, *121*(20), 5228-5237..DOI: 10.1021/acs.jcim.8b00648

[57]. Ansari, M. J. (2019). An overview of techniques for multifold enhancement in solubility of poorly soluble drugs. *Current Issues in Pharmacy and Medical Sciences*, *32*(4), 203-209.DOI: 10.3390/molecules21010042

[58]. Kaur, P., Garg, T., Rath, G., & Goyal, A. K. (2016). In situ nasal gel drug delivery: A novel approach for brain targeting through the mucosal membrane. *Artificial cells, nanomedicine, and biotechnology*, *44*(4), 1167-1176. DOI https://doi.org/10.22270/jddt.v10i2-s.4029

[59]. Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021). Engineering precision nanoparticles for drug delivery. *Nature Reviews Drug Discovery*, *20*(2), 101-124..https://doi.org/10.1038/s41573-020-0090-8

[60]. Deckx, L., De Sutter, A. I., Guo, L., Mir, N. A., & van Driel, M. L. (2016). Nasal decongestants in monotherapy for the common cold. *Cochrane Database of Systematic Reviews*, (10).2016(10).doi: 10.1002/14651858.CD009612.pub2.

[61]. Bajracharya, R., Song, J. G., Back, S. Y., & Han, H. K. (2019). Recent advancements in non-invasive formulations for protein drug delivery. *Computational and structural biotechnology journal*, *17*, 1290-1308.doi: 10.1016/j.csbj.2019.09.004.

[62]. Meredith, M. E., Salameh, T. S., & Banks, W. A. (2015). Intranasal delivery of proteins and peptides in the treatment of neurodegenerative diseases. *The AAPS journal*, *17*(4), 780-787.doi: 10.1208/s12248-015-9719-7.

[63]. Peterson, B., Weyers, M., Steenekamp, J. H., Steyn, J. D., Gouws, C., & Hamman, J. H.

(2019). Drug bioavailability enhancing agents of natural origin (bioenhancers) that modulate drug membrane permeation and pre-systemic metabolism. *Pharmaceutics*, *11*(1), 33..doi: 10.3390/pharmaceutics11010033.

[64]. Kyriakidis, N. C., López-Cortés, A., González, E. V., Grimaldos, A. B., & Prado, E. O. (2021). SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. *npj Vaccines*, *6*(1), 1-17.doi: 10.1038/s41541-021-00292-w.

[65]. Hellfritzsch, M., & Scherließ, R. (2019). Mucosal vaccination via the respiratory tract. *Pharmaceutics*, *11*(8), 375.https://doi.org/10.3390/pharmaceutics11080375.