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MODERN ENCROACHMENT AND PROVOCATION IN NASAL DRUG DELIVERY SYSTEM

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ABSTRACT: Nasal drug delivery has occupied an important place in the field of drug delivery technology. Transmucosal nasal delivery is a promising drug delivery option where common drug administration's (e.g. intravenous, intramuscular, and oral) are inapplicable. This route is also advisable for drugs undergoing extensive first pass effect. The physiology of the nose presents obstacles, but offers a promising route for non-invasive systemic delivery of numerous therapies and debatably drug delivery route to the brain. Nasal route is easily accessible for self-administration without the help of health professionals and no needle stick hazards are associated with nasal administration. To overcome these problems in nasal drug delivery, deep understanding and study of the various factors affecting nasal delivery is muust. Thus present review focuses on various aspects of nasal drug delivery with special emphasis on various formulations available, obstacles, advancement and future prospects in nasal drug delivery.

INTRODUCTION: Oral drug delivery is the most desirable route for the drug administration. Whenever systemic effects are indented but oral bioavailability of some compounds has promoted the search of more effective route for the systemic delivery. Transmucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) peroral administration for systemic administration, nasal mucosa is the major route of administration to achieve faster and higher level of drug absorption. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route, this is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism and readily accessibility.

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The high permeability, high vasculature and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules. The non-invasiveness and self-administrative nature of nasal also attracts the formulation scientists to deliver protein and peptides compounds. Majority of products available are used for treatment of allergic rhinitis, migraine, cold, pain etc. The various formulations given by nasal route includes nasal gel, spray, powders etc. Thus nasal route is the promising alternative for other drug delivery systems.

Anatomy and physiology of Nose [4-8]: The human nasal cavity has a total volume of about 16 to 19 ml and total surface area of about 180cm^2. It is divided into two nasal cavities via the septum. Some of the regions are described as follows.

The Respiratory region: The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption.

The Vestibular region: It is located at the opening of nasal passages and is responsible for filtering out the air borne particles. It is considered to be the least important of the three regions with regards to drug absorption.

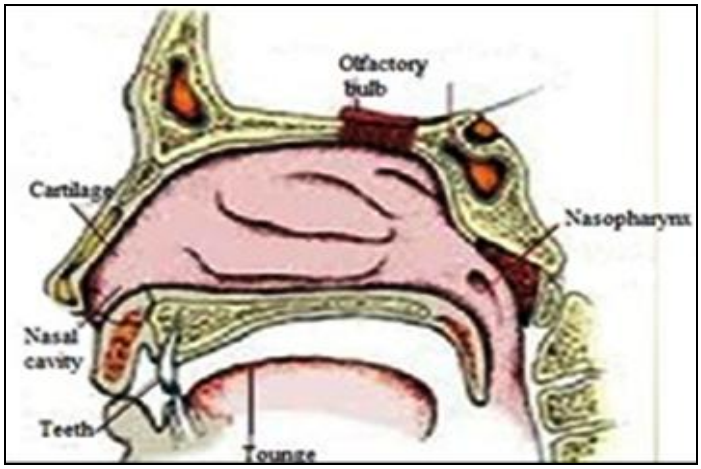


FIG. 1: ANATOMY AND PHYSIOLOGY OF NOSE

The olfactory region: It is of about 10 cm^2 in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. Human olfactory region comprises of thick connective tissue lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, bowans bundle and blood vessels whereas epithelium consists of three different cells i.e. basal cells, supporting cells and olfactory receptor cells etc. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendritic and extending from the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium.

The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10 to 15 minutes the pH of the mucosal secretions ranges from 5.5 to 6.5 in adults. Numerous enzymes for instance, Cytochrome P-450, Carboxylesterases and Glutathione S-transferase are present in nasal cavity.

Advantages and disadvantages of Nasal Drug Delivery System [9]:

Advantages:

1. Self-administration is possible.
2. User friendly.
3. Improved patient compliance.
4. Non-invasive.
5. No first pass metabolism.
6. Rapid drug absorption.
7. Higher bioavailability.
8. Quick onset of action.

Disadvantages:

1. All drugs cannot be given by nasal route.
2. Frequent use of this routes leads to nasal mucosal damage.
3. Drug cannot be withdrawal if once administered.
4. Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailability.

Opportunities in Nasal Drug Delivery [10]:

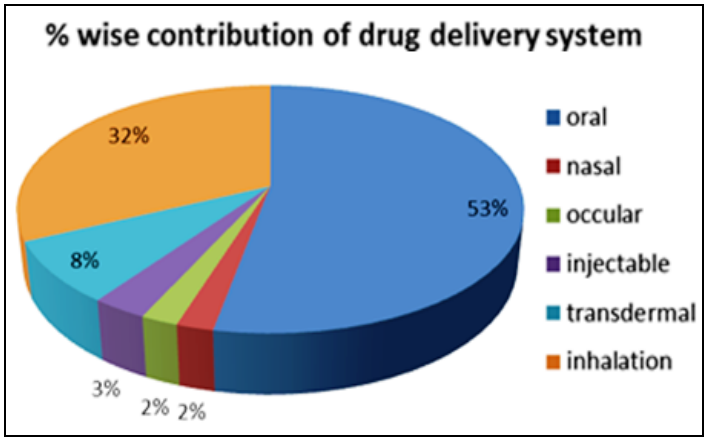


FIG. 2: % WISE CONTRIBUTION OF DRUG DELIVERY SYSTEM

As per the information of percentage wise distribution of drug delivery systems, it is revealed that the major contribution of oral (58%) drug delivery than that of inhalation (38%) than transdermal (8%), Injectable (3%), ocular (2%) and finally nasal (2%). Nasal routes contribute only by 2% in drug delivery which also gives new hopes for researchers to work in this field. New researcher can step in this field and can bring new nasal formulation with greater bioavailability and less toxic effect.

Factors influencing Nasal Drug Absorption [11-13]:

a) **Factors Related to Drug:**

1. **Molecular Weight:** Based on the reports by Fisher et al it can be concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug.

2. **Chemical Form:** Chemical form is the important parameter in drug absorption because conversions of the drug into a salt or ester form and may alter its absorption.

3. **Polymorphism:** Polymorphism is known to affect the dissolution rate and solubility of drugs thus their absorption through biological membranes. So it is of prime importance that polymorphic stability and purity of drugs for nasal powders and/or suspensions should study.

4. **Solubility & Dissolution Rate:** For better absorption drug should get dissolve .If particles are present it is somewhat difficult for absorption.

5. **Lipophilicity:** From literature study it has been revealed that as lipophilicity goes on increasing it increases permeation through the nasal mucosa. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Drug like testosterone has been absorbed nasally already prove in animal models.

6. **Partition Coefficient and pKa:** As pH partition theory states that unionised species are absorbed well as compared with ionized hence it is same in the case of nasal absorption also.

b) **Factors related to Formulation**:

1. **pH:** The pH of the formulation, as well as that of nasal surface can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5

2. **Osmolarity:** Optimum osmolarity should maintain as it causes shrinkage of the nasal epithelial mucosa and alters the permeation of drugs.

3. **Viscosity:** A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

4. **Buffer Capacity:** Nasal formulations are generally administered in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administrated dose. This can affects the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH *in-situ*.

5. **Drug Concentration, Dose & Dose Volume:** Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.

c) **Physiological factors**:

1. **Effect of Deposition on Absorption:** Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability while posterior portion of the nose where the drug permeability is generally higher, provides shorter residence time.

2. **Nasal blood flow:** Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

3. **Effect of Enzymatic Activity:** Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino-peptidase at the mucosal membrane.

The level of amino-peptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin (Igs) in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.

4. **Effect of Mucociliary Clearance:** The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered.

5. **Effect of Pathological Condition:** Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption.

How to overcome these factors???

Methods to improve Nasal Absorption [14-18]: Followings are some approaches which have been used successfully for the improvement of nasal drug absorption.

1. **Permeation enhancers:** Various types of permeation enhancers have been investigated to improve the nasal absorption like fatty acids, bile salts, phospholipids, surfactants, cyclodextrins etc.

2. **Prodrug approach:** Prodrugs are the inactive chemical moiety which becomes active at the target site. This approach is mainly used to improve the physicochemical properties such as taste, solubility, stability etc of formulation.

3. ***In situ* gel:** These formulations generally controlled the problems of administration along with conversion into gel by the influence of stimuli includes temperature, pH and ionic concentration etc.

4. **Nasal enzymes inhibitors:** Enzymes inhibitor like protease and peptidase are used as inhibitors for the formulation of peptide and protein molecules.

5. **Structural modification:** Drug structure can be modified without changing the pharmacological activity to improve the nasal absorption. Chemical modifications are mainly used to modify the drug structure.

6. **Mucoadhesion:** Mucoadhesion can be defining as the state in which two materials held together for long period. Mucoadhesive polymers make intimate contact with biological membrane, after the establishment of contact and penetrate into the tissue surface.

a. **Natural mucoadhesive polymers:** Availability of natural polymers can be easily ensured by natural sources which is an environmental friendly processing with low cost. Some examples which include Potato starch, Rice starch, Maize starch, Wheat starch, Gaur gum, Tragacanth, Xanthan gum etc.

b. **Synthetic mucoadhesive polymers:** Synthetic polymers produce environmental pollution during synthesis and have a high cost of production. These polymers include methyl cellulose, Poly ethylene oxide, Poly vinyl alcohol Ethyl cellulose, Hydroxyl propyl methyl cellulose etc.

Formulation and Active agents that have been utilized in Nasal Drug Delivery [19-21]:

TABLE 1: FORMULATION AND ACTIVE AGENT THAT HAVE BEEN UTILIZED IN NASAL DRUG DELIVERY

Sr. no.	Formulation	Active agent
1	*In-situ* nasal gel	Midazolam, Insulin, Triptans , Diltiazem
2	Nasal inserts	Chlorpromazine, Albuterol
3	Microspheres	Beta-amyloid fibril, Starch microspheres, Dextran Gentamicin, Insulin , Desmopressin
4	Microparticles	Serum albumin, Thiolated chitosan microparticles
5	Dry powder	Zolmitriptan
6	Nasal gel	Oxytocin, Metoclopramide Hydrochloride

Challenges for Nasal Delivery Systems [22]:

TABLE 2: CHALLENGES FOR NASAL DELIVERY SYSTEMS

Problem	Challenge	Solution
Enzymatic degradation	Inhibit nasal enzymes	Enzyme inhibitor, prodrugs
Mucociliary clearance	Overcome it	Deposit formulation in anterior cavity
Less permeation	Enhance drug permeation, modify the membrane	Permeation enhancer, Prodrugs
Poor physic-chemical properties of drug	Improve it	Prodrugs, cosolvents

Advancement in Nasal Dosage Form [23-31]:

1. **Nasal Drops:** Nasal drops are one of the most simple and convenient systems developed for nasal delivery. Due to ease of self-administration it is becoming more popular. The main disadvantage of this system is the lack of dose precision.

FIG. 3: NASAL DROP

2. **Nasal Sprays:** Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose. These are preferred over powder sprays because powder results in mucosal irritation.

FIG. 4: NASAL SPRAY

3. **Nasal Powders:** These formulations are developed when there is problem with stability. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug.

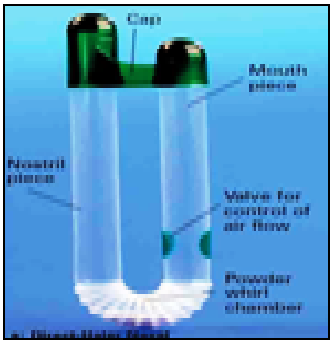


FIG. 5: NASAL POWDER

4. **Nasal Gels:** The nasal gel showed growing interest due to reduction of post-nasal drip, high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption.

FIG. 6: NASAL GEL

5. **Nasal Inserts:** Nasal inserts are novel, bioadhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to imbibe nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.

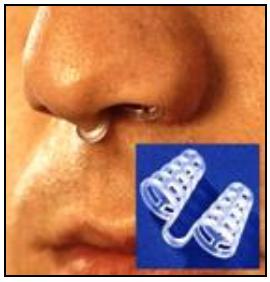
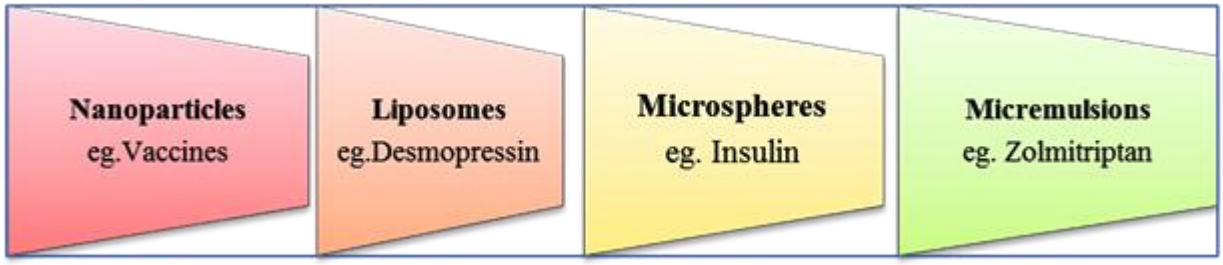


FIG. 7: NASAL INSERT

Novel Nasal Drug Formulations [32-33]: This includes the following formulations enlisted as;



Available Nasal Products [34-35]:

TABLE 3: AVAILABLE NASAL PRODUCTS

Drug	Brand	Supplier	Main indication
Azelastine	Asteline	Meda pharma	Rhinosinusitis
Beclomethasone	Beconase	GlaxoSmithKline	Rhinosinusitis
Budesonide	Rhinocort	AstraZeneca	Rhinosinusitis
Buserelin	Suprefact	Sanofi-Aventis	Treatment of prostate cancer
Cynocobalamine	Nascobal	Strativa pharma	Vit B12 deficiency
Desmopressin	Desmospray	Ferring pharma.	Control of dehydration in diabetes insipidus
Estradio	Aerodiol	Servier lab.	HRT
Fentanyl	Instany	Nycomed Pharma	Pain management
Levocabastin	Livostin	Jansen-Cilag	Rhinosinusitis
Mometazone	Nasonex	Scharing-plough	Scharing-plough
Mupirocine	Bactroban	GlaxoSmithKline	Eradication of nasal Staphylococci
Nafarelin	Synarel	Roche Laboratories	Management of endometriosis
Nicotine	Nicotrol NS	Pfizer	Smoking cessation
Olapatadine	Patanase	Alcon-lab.	Rhinosinusitis
Oxytocine	Syntocinone	Novartis	Lactation stimulation
Sodium cromoglycate	Nasalcrom	Sanofi-Aventis	Rhinosinusitis
Triamcinolone acetonide	Nasacort	Sanofi-Aventis	Rhinosinusitis

Characterisation of Nasal Formulations [36-43]:

TABLE 4: CHARACTERISATION OF NASAL FORMULATIONS

Formulation/ Parameters	Particle size analysis	Scanning electron microscopy (SEM)	Differential scanning calorimetry (DSC)	Mucoadhesive property	Viscosity	pH	Spreadability
In-situ nasal gel	✓	✓	✓	✓	✓	✓	✓
Nasal inserts	----	✓	✓	----	----	----	----
Micro-spheres	✓	✓	✓	✓	✓	✓	----
Micro-particles	✓	✓	✓	✓	✓	✓	
Dry powder	✓	✓	✓	----	----	----	----
Nasal gel	✓	✓	✓	✓	✓	✓	✓

CONCLUSION: This review is nut shell in the field of nasal drug delivery system which focuses on the modern advancement in nasal drug delivery system along with the challenges as well as it gives new hopes and opportunities for the researchers having interest in this field. This review also gives deep insight of requirements in upcoming future prospectus.

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