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Review Article

NOVEL DRUG DELIVERY SYSTEM THROUGH NASAL (NON-INVASIVE)

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ABSTRACT

Intranasal route is the best method for high absorption and direct delivery to the brain. The interests and importance, of this route, are that the systemic effects of drugs when administered through the nasal route, have expanded over recent decades and it used for therapeutic and recreational purposes. In comparison with the parenteral route of drug administration, intra-nasal administration of drugs offers an interesting alternative for achieving systemic therapeutic effects of drugs. The oral administration of the drug produces low drug bioavailability, and this can be minimized using this nasal route. Moreover, the advantage of this route is that it can bypass the first-pass metabolism. Therefore, it is important to understand the potential and limitations of various nasal drug delivery systems. The aim of this review article is to discuss the various pharmaceutical dosage forms that have the potential to be utilized for local or systemic drug administration. It is assumingly expected that this review will help to understand about this route and also to develop suitable intra-nasal formulations to achieve specific therapeutic objectives. The different types of nasal drug formulations that can be used are nasal drops, nasal sprays, nasal gels, nasal suspensions and emulsion, and nasal powders.

Keywords: Intranasal, First-pass metabolism, Mucoadhesion, Bioavailability.

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INTRODUCTION

Nasal cavity is one of the best methods for delivering the drug because it has faster and higher drug absorption. By this method, we can avoid first-pass metabolism and also drug absorption from the nasal site is higher permission when compared to the gastrointestinal tract (GIT). Many drugs are gastro liable, so we can overcome that problem by intranasal system. Nasal therapy is also ancient therapy, and we can call it as "NASAYA KARMA" [1].

Drawback of the system is mucociliary clearance due to mucociliary clearance bioavailability is reduced and main advantage is it is of self-medication. By animal model, many nasal drug deliveries have been tested. Nowadays, nasal delivery comprised systemic and local therapeutic effect and used to treat.

1. Hay fever
2. Allergic rhinitis
3. Anaphylactic shock.

For systemic actions, many researches are going on, and the available pharmaceutical dosage forms such as gel, solution, and liposomes and this is designed for quick response to the drug which administered through nasal, for example, oxymetazoline [2]. In our system highly lipid soluble drugs can be easily distribute well [3]. Intranasal administration of a drug has advantages; it directly acts to brain without entering into systemic circulation. By nasal delivery process, many drugs were discovered, and human nasal is regulated by tight junctions especially paracellular pathway. Paracellular plays important role for nasal mucosa drug administering way [4].

TIGHT JUNCTIONAL FORMATIONS

Tight junctions are formed by internal membranes various proteins, tricellin, occluding, lipo-lysis stimulated lipoprotein receptor, and junctional adhesion molecule and these tight junctions are worked under cytokines (IL, TNF) interleukins, tuber necrotizing factor by transduction pathways [4].

ANATOMY AND PHYSIOLOGY OF NOSE

By anatomically respiratory system is divided into two types:

1. Upper respiratory tract
   a. Nose
   b. Pharynx
   c. Larynx.
2. Lower respiratory tract
   a. Trachea
   b. Tracheobranchial
   c. Bronchioles.

Air primarily enters by the nose through external nares and secondarily into pharynx finally to posterior nares [5]. The total surface area of the nose is 160cm^2, and it has volume about 16–19 ml [6]. Warm, humid air enters into nose which also provides filtration of the inspired air and the unwanted particles get adhesive by the mucoadhesive process. Physiologically nose has (1) vestibular, (2) turbinate, and (3) olfactory [7] (Figs. 1 and 2).

Vestibular part is starting point of nose which is anterior and very narrow stiff hair inside the nostrils which protect from the environmental particles and is capable of filtering size about 10 μm as it has stratified squamous epithelium [8].

The turbinate is highly blood perfusion area comprises three regions superior, middle, and inferior (Fig. 1) and turbinate is lined by pseudostriated columnar epithelium, and it is made by mucus-secreting ciliated and non-movable microvillus which is highly responsible for increasing surface area due to non-movable response. The drug absorption is moderate. Ciliates are covered with motile cilia, and they are responsible for mucus transport of a drug that binds with mucociliary area as they could be expelled out and thus limited absorption only could occur [9-11]. The turbinate part consists of the following parts (a) vestibule, (b) atrium, (c1) inferior turbinate, (c2) middle turbinate, (c3) posterior turbinate, (d) olfactory bulb, and (e) nasopharynx [12].

Moreover, finally olfactory region and it's important for transporting the drug to brain and cerebrospinal fluid it comprises 8% of the total surface area it is made by non-ciliated, pseudo striated columnar epithelium and a mucus layer is present which traps unwanted particle and mucus

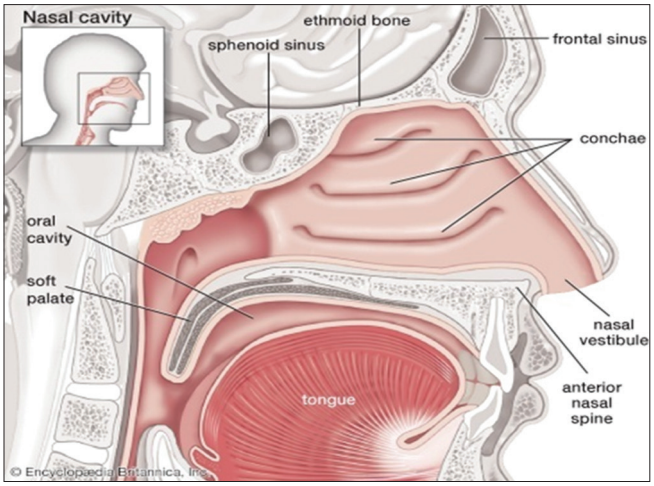

Fig. 1: Taken from Google

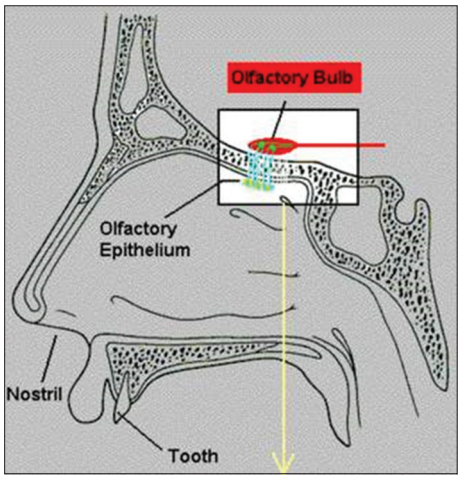

Fig. 2: Physiological diagram nose

secretion consists of salts, water, protein, albumin, immunoglobulins, and lysosomes [13]. pH of nasal secretions is about 5.9-6.5 [6,14].

Cells of nasal epithelium with covering mucus layer (a) ciliated cell, (b) non-ciliated cell, (c) corbel cell, (d) mucous gel layer, (e) sol layer, (f) basal layer, and (g) basement membrane [12].

DRUG FORMULATION CONSIDERATIONS

Nose has a higher surface area, which is potentially used drug delivery. The pharmaceutical development has a higher task for therapeutic objectives which is used for

- Local
- Systemic
- Single-repetitive dose loading
- By knowing the above status, it will be better for development of nasal delivery system is appropriate [15-17].

By knowing the factors that can affect drug absorption, disposition it can easy for making the novel, various pathological conditions and anatomical and physiological are also considered and in UK various nasal formations given in Table 1 [14].

ENHANCEMENT OF DRUG

Permission enhancer is added to the formulation which highly water-soluble [27]. The exact mechanism of absorption and permission is not known and the permission enhancer will induce the epithelial barrier modifications so that the drug entry becomes easy [26]. Above the given Table 2, different type of permission enhancer absorption is listed with the mechanism.

NASAL DRUG DELIVERY ROUTE ADVANTAGES AND LIMITATIONS

1. While comparing other routes such as parental, oral nasal has high potential, it directly delivers the drug to brain (through olfactory nerve), so the nasal route is much attractive when compared to other [30]. Brain is a delicate and highly perfused organ it has a lot of functions (sensory and collection processing and integrity finally motor actions). It is protected from the environmental factors, tight junctions surrounding the brain is called blood–brain barrier (BBB). It has a great transendothelial resistance which also blocks drug transport the delivery to brain by nose has many drug transport system such as (1) paracellular and (2) transcellular and/or neuronal pathway [31].
2. The presence of olfactory pathway it efficiently bypasses the BBB [32]. Nasal route is better alternative route for drug absorption and also in patient with problems such as GIT infections and GI route (or) parental route is inconvenient Example: Patient with Zollinger-Ellison syndrome, vomiting patient unable to swallow (achalasia), difficulties in children and old aged persons [33]. The important limitation of the nasal route is not applicable for all drugs. To increase the drug half-life, we must know about the physiochemical properties such as acid base disassociation constant (pk), partition coefficient, molecular weight, and drug solubility [34].
3. Many drugs formulations are solution type. They are very difficult to absorb due to polar and low solubility as these cause poor membrane permeability, instant clearance, and enzymatic degradation within nasal canal [6].
4. Drug or fillers which cause the local irritation to the nasal mucosa [35].
5. Formulation factors also have a great impact and type of formulation such as solid, liquid, gel, powder, and pH also included [36].
6. Physical conditions of the nose like nasal atrophic rhinitis which can reduce the nasal drug absorption and may also physiological condition such as blood flow, mucociliary clearance also plays an important role for reducing the nasal drug absorption [33,37].
7. Presence of nasal mucous which also takes time for drug absorption and also reduces the contact time [38]. To overcome from the mucosa clearance by adding the mucoadhesive polymers in it (or) encapsulate with formulations so that bioavailability could be increased [39]. The drug absorption is distributed by major barriers is mucociliary and conditions like coryza, hay fever can change the mucociliary clearance, and some drugs may bind with mucins and decrease bioavailability of a drug [40-42].

MECHANISM OF ACTION THROUGH NASAL ROUTE

Mucous is the first step drug which has to pass through mucous layer tiny particles which may enter quickly and easily but larger particles have difficulties to enter [43]. Mucin is a protein substance present in mucous which has the potency to bind with drugs, and it alters the permeation process a structural modification of the mucus layer exists, so the result physiological changes occur [44]. The given drug that passes through mucous follows many mechanisms for drug absorption.

1. Paracellular
2. Transcellular
3. Transcytosis.

However, the paracellular and transcellular are major route [45].

Paracellular

It refers to the transfer of substances across an epithelium by passing through the intracellular spaces between the cells [46]. There is a direct correlation of a drug particle size and drug absorption because higher molecular weight does not cross well just bioavailability of the drug decreases [43].

Table 1: Current formulations of nasal drug delivery system [14]

Indication	Active pharmaceutical ingredient	Formulation
Acute treatment of migraine	1. Sumatriptan	Nasal spray sol
	2. Zolmitriptan	Nasal spray sol
Analgesic	1. Fentanyl citrate	Powder and diluents for reconstituent aqueous spray nasal spray sol
	2. Diamorphine HCL	
Endometriosis	Nafarelin acetate	Nasal spray sol
Nasal congestion, allergies	1. Xylometazoline HCL	Nasal spray, nasal drops
	2. Oxymetazoline HCL	Nasal spray, solution
	3. Azelastine HCL	Nasal spray
	4. Ephedrine	Nasal drops
	5. Ipratropium bromide	Nasal sprays sol
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	1. Budesonide	Spray suspension
	2. Beclomethasone, dipropionate	Spray suspension
	3. Mometasone furoate	Spray suspension
	4. Fluticasone furoate	Spray suspension
	5. Fluticasone with azelastine HCL	Spray suspension
	6. Sodium cromoglycate	Spray solution
Prostatic carcinoma	Buserelin acetate	Nasal spray
		Nasal solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	1. Neomycin sulphate	Nasal cream
	2. Chlorhexidine dihydrochloride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal spray solution
Nocturia with multiple sclerosis, sensitive cranial diabetes insipidus	Desmopressin acetate	Nasal spray solution
Vaccination	Flu-vaccination	Nasal spray suspension

Table 2: Nasal drug absorption enhancers

Class of compound	Example	Possible action	References
Fatty acid	Lysophosphotidyl choline	Membrane disruption	[18]
Surfactants	SLS, saponin, polyoxyethylene	Membrane disruption	[19-22]
Bile salts	Sodium glycolate, sodium deoxycholate, sodium taurodihydrofusidate	Enzyme inhibition, open tight junctions, mucolytic activity	[23-25]
Bio-adhesive material	Carbopol, starch microsphere, chitosan	Reduce nasal clearance, open tight junctions	[26]
Enzyme inhibition	Amastatia	Enzyme inhibition	[27]
Cyclodextrins derivatives		Open tight junctions, membrane disruption	[28,29]

SLS: Sodium laryl sulfate

Transcellular
It is achieved with passive diffusion or transport mechanism [46]. Moreover, it also called lipoidal route it highly depends on lipophilicity of the drug, drug cross the membrane by active process using carrier [45].

Transcytosis
Drugs and macromolecules which are transported across the interior of the cell it forms a vesicle and transported to other side [46].

NASAL DRUG DIFFERENT TYPES OF FORMULATIONS

Nasal drops and sprays
Nasal drops by squeezing the bottle the nasal drops are used for local areas for local areas and also for mucociliary dysfunction [36,47]. Nasal delivery is easiest and simplest method for administration and also for formulations, and the major drawback of the system is contamination may occur during using periods and the exact and accurate amount of the drug administering also difficult [48]. The delivery is as follows:

Nasal sprays contain a three parts
i. Chamber
ii. Piston
iii. Operating actuator.

Advantages of nasal spray are more accurate than nasal drops measured dose can expel out [36]. Nasal spray shown a consistent dose of reproducible plume geometry the droplet size and dose accuracy can be depended on formulation properties such as surface tension, viscosity, and thixotropy [49-52]. The design of the pump and orifice size can affect the nasal disposition sprays [17,48].

Nasal gel
By its characteristics, it is soft semisolid in nature and the semisolid characteristics can be two dynamic mechanical properties (i) elastic module G and (ii) viscous module G [34]. The flow properties of the nasal gel depends on vicious concentration and type of polymer for good results of biopharmaceutics bio-adhesive polymers plays a high role and these results a good improvement of patient complains [53,54]. A long time contact of a drug at the absorption site can increase the bioavailability because of slowing the mucociliary movement [55]. The mechanism of the mucoadhesive was explained by various theories, but the mechanism is generally based on two keys (i) contact and (ii) consolidation a long contact of polymer can diffuse with mucus [48]. Various non-harmful and biologically degradable polymers are discovered for mucoadhesive system Example-Polyvinyl alcohol [56]. Mucoadhesive gels for nasal administration have been studied for different antibiotics such as ciprofloxacin [30], mometasone [57], carvedilol [58], and vaccines and proteins [59,60]. Some of the gels behave pseudoplasticity and their flow properties cannot be used for nasal delivery for this purpose gelation is used for overcome form that problem [61]. In polymeric formulations, the drug has to be solution form but after reaching into the body it should converted into gelation to the form of gel in a body depends on temp., pH, and ions in a body [62].

Nasal suspension and emulsion

Nasal suspension formulations are rare nowadays and the relativity of marked aqueous eye drops is preparing example - sodium carboxymethylcellulose and loteprednol etabonate [63]. The preparation of nasal suspension of insulin was studied by Ando *et al*. 1998 [64]. The absorption enhancers were used for nasal suspension such as soybean steryl glycoside and sterol mixture and their pharmacological actions about 6.7% and 11.3% have been achieved [65-68]. For nasal formulations, emulsions are better chosen over suspensions because emulsions will enhance the rate and extend of a drug of poorly soluble drugs so that low solubility drugs have been encapsulated or formulated with emulsions for drug solubility example-diazepam [69]. Nasal-suspensions ranging from 1 to 500 nm for brain targeting and it crosses the BBB and researches going on nasal-emulsions [70-72].

Nasal powders

Nasal powder dosage forms are simply formulated by active pharmaceutical ingredients with fillers [73,74]. There are two types of drying spray drying and freeze drying [75-77]. The insulin is mixed with water-insoluble derivatives such as cellulose and Carbopol 934p and that was administered nasal way once the drug took by water it swells and gives the pharmacological action and glucose level got reduced by one-third using IV-insulin dose [78]. Bioadhesive polymers of nasal delivery were formulated by dry powders and nasal delivery of proteins and peptides it was first established by Nagai and Thogersen 1984 [79]. Beclomethasone dipropionate was coated with bioadhesive molecule and hydroxylpropyl used for carrier and it enhances the nasal resident time compared with nasal solution [80]. Indeed of highest bioavailability of the insulin was markedly decreased for the repeated administration of powder formulation [81]. The delivery drug has not been cleared from the nasal cavity because of physical barrier. Therefore it inhibits the drug penetration of inorganic substance such as calcium phosphate to enhance the drug absorption. This was demonstrated in rats for nasal absorption retardation at the site of administration which was proposed [74].

CONCLUSION

Nasal drug delivery system is one of the best potential and versatile routes for past many decades. It has a unique characteristic of drug release. It has bypassed the first-pass metabolism and also the drug has been directly delivered to brain so it has high potential of bioavailability. Various pharmaceutical dosage forms related to nasal utilized for the local or systemic drug has been discussed in this article intuitively, this review article will help for further new developed intranasal formulations to achieve the proper bioavailability practical and technical issue were discudded in this article a problem or difficulty to overcome for full potential to be realized.

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