

Nasal Drug Delivery with Special Focus on *In-situ* Mucoadhesive Gel: A Review

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Abstract: From the past few decades nasal route become an important area of interest for researcher due to some important characteristics like highly porous endothelial membrane, large surface area, vascularized epithelium, high perfusion rate, avoidance of hepatic first pass metabolism. Beside these properties, the nasal route also has some major limitations like administration of drug from its dosage form and mucociliary clearance retard the proper absorption of drug; the effect of such limitations can be overcome by using an approach namely *in-situ* mucoadhesive gel. Basically *in-situ* means the formulation is found sol type in nature (storage conditions) but when administered to the nasal cavity, the transitions of phase occurs and get converted to the gel form; so this property facilitate the administration of dosage form. The gelation occurs by the effect of temperature, change in pH etc. In another side mucoadhesive nature of gel retain the dosage form against mucociliary clearance; so enhance the absorption as well as bioavailability of dosage form. In the present study we are discussing about various basic properties, advantages, disadvantages, anatomy and physiology of nasal route. In this study, we also discussing about various kinds of dosage form with special emphasizing on *in-situ* mucoadhesive dosage form for nasal drug delivery. The present study also covers some research and patents on nasal drug delivery.

Key words: Nasal Gel • Thermoreversible • Mucoadhesive • *In-Situ* • Mucociliary Clearance Etc

INTRODUCTION

Now days there are various kinds of dosage forms available for administration of drug via various routes. Each and every route is important as per the requirement of therapy. Bioavailability of drug is generally affected by the selection of route. From the past few decades nasal route become an area of interest for researchers for drug administration as systemic therapy [1] Nasal route possesses some important properties of nasal route like highly porous endothelial membrane, large surface area, vascularized epithelium, high perfusion rate, avoidance of hepatic first pass metabolism which makes it more important and suitable route in designing a dosage form [2]. From ancient time, the nasal route is continuously used for the relief from local infection/ disease such as rhinitis and nasal congestion. The drugs having low oral bioavailability can be administered through nasal route; effective brain targeting can also be done by using nasal route. Small molecules, peptides and proteins can be

administered more efficiently as compared to other routes except of I.V. route [3,4]. Due to the selective absorption nature of the nasal mucosa, it has limited permeability to various pharmaceutical compounds in comparison to the gastro intestinal tract. In nasal mucosa less enzymatic activity is observed compared to gastro-intestinal tract [5,6] The olfactory region of the nasal cavity is directly in contact with the central nervous system, which allows the drug to cross blood brain barrier [7,8] The mucosal lining of the nasal cavity is impermeable to the particles having molecular weight greater than 100 Daltons [9] that's the reason why most of the hydrophilic drugs and macromolecular compounds like insulin are not absorbed through this route [10]. Another most important property of nasal mucosa is the mucociliary clearance which causes the removal of the any foreign particles or compounds before they reach to the systemic circulation [11]. To overcome such problems various techniques have been used such as use of salt form, surfactants, phospholipids and fusidate derivatives. These all act as the permeation

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enhancers and help the drug to cross mucosal barrier, which results in the drug transfer to the systemic circulation [12-16]. However, before using the permeation enhancers their detailed studies should be conducted for certain toxicity levels. Because they can cause damage to the nasal mucosa, which cannot be healed later [17]. There are many aspects which form challenges for the nasal drug delivery to use it over the conventional techniques. Now many researches are going to formulate and develop new preparations which can show better effect over the conventional products and it is expected that they will replace conventional products in the future.

Advantages:

- Prevents the drug degradation from enzymatic action of the gastro intestinal tract.
- Prevents the drug degradation by hepatic first pass metabolism.
- Limits the risk of over dose.
- Show quick onset of action.
- Self medication is possible.
- This route offers the greater bioavailability, which reduces the dosing frequency.
- Using this delivery system brain targeting is possible via the olfactory region of nasal mucosa.

Limitations

Low Bioavailability: The polar drugs have low bioavailability i.e. the drugs having lower molecular weight have bioavailability less than 10%, peptides like insulin and calcitonin have less than 1%. [18] The absorption of large molecular sized polar drug particles in the nasal cavity is limited due to low membrane permeability and as a result large sized peptide and protein molecules cannot be absorbed through the nasal cavity, the absorption can only be possible in the cavity for some of the large sized peptide and proteins particles by endocytosis [19].

Mucociliary Clearance: It is a defensive mechanism of the nose, by which the irritating substances are removed out from the nasal cavity. Due to this the drug does not get time to cross the nasal mucus membrane and it is expelled out. This happens mainly when the drug cannot be absorbed to the mucus membrane. The half life of the liquid and powders for clearance is about 15-30 minutes which are not bioadhesive in nature [20,21] To get rid of the clearance problem the bioadhesive/ mucoadhesive

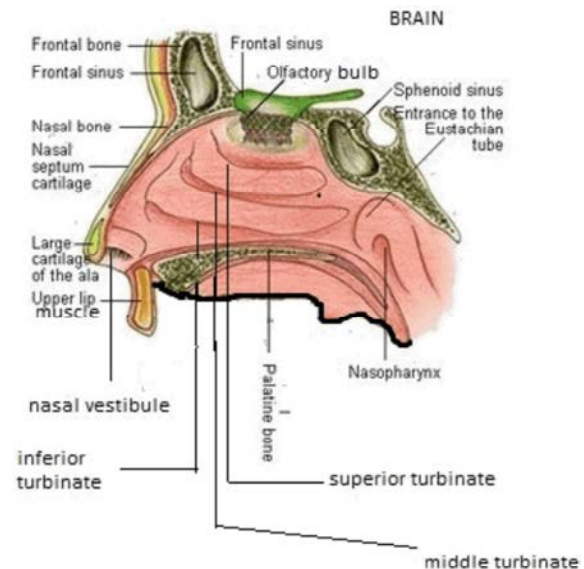


Fig. 1: Anatomy of human nose

agents are used in the formulation, which adhere the formulation to the ciliated part of the nasal cavity and protect it from being cleared [22,23]

Enzymatic Degradation: Variety of the enzymes are present in the nasal cavity which degrade the peptides. Exopeptidases like mono and diamino peptidases are present in the nasal cavities which cleave the bonds at N and C terminal leading to breakage of the internal peptide linkage. Enzyme inhibitors are used to overcome such problems [24,25].

Nasal Anatomy and Physiology: Nose is the important part of the human body; it is located in the middle of face. Nose is the starting point of the respiratory system. The septum divides the nose into two cavities. These together form the nasal cavity. Nasal cavity is further divided into three main regions, these are:

- Nasal vestibule
- Olfactory region
- Respiratory region

The surface area and volume of nasal cavity is approximately about 150 cm² and 15 ml respectively. Anatomy of the nasal cavity is given in Figure 1.

The olfactory and non olfactory epithelium divides the nasal cavity covered with the mucous membrane into two. The nasal vestibule lies in the non olfactory region. Among all the regions the respiratory region is very

important for drug delivery to the systemic circulation. The respiratory region comprises of three parts; a) inferior turbinate, b) middle turbinate, c) superior turbinate. The epithelium lining of the respiratory region consists of basal cells, ciliated columnar cells, non ciliated columnar cells and goblet cells containing mucous. A wave like channel of cilia is present for the transportation of the particles to the pharynx region.²⁶ About 300 microvilli are present in this region which provides a greater surface area for absorption. The lamina propria is present below the epithelium [27,28] In every 10 to 15 minutes mucus layering of nasal epithelium is renewed. The mucosal secretion pH varies among adults and children. In children pH lies between “5.0 - 6.7”, while in adults it is 5.5-6.7 [29].The mucus layer of the nasal cavity provides protection from the entry of the foreign particles by entrapping them. The clearance rate within the nose is 20 minutes and the movement of mucus through the nose occurs at the speed of 5 to 6mm/min [30] Many enzymes are present in the nasal cavity such as isoforms of cytochrome P450 (CYP1A, CYP2A and CYP2E), carboxylesterases, guthathione s-transferas [31,32]

Mechanism of Drug Absorption Through the Nasal Route: In the nasal cavity the absorption takes place through the mucus. The mucus layer is selectively permeable, which allow the small and uncharged particles to pass through it and resist the large and charged particles. Mucin is present in the mucus, exceptionally due to the change in the environmental factors like pH, temp etc. structural changes may be possible in the membrane.

There are several mechanisms by which the absorption takes place in the nasal cavity through the mucus membrane like simple diffusion, paracellular transport through the movement among the cells and vesicle carriers [33] Mainly problem arises with the drug absorption are reduced residence time and metabolism of the drug. There are two predominant mechanism of the drug absorption which is considered [34].

In the first mechanism the aqueous route of transport is involved. It is called as the paracellular route. But the absorption through this route is slow and passive. The intera nasal absorption and molecular weight are correlated with each other by inverse log. It was observed that the drugs having molecular weight less than 1000 daltons have poor bioavailability.

The transport through the lipoidal route is the second mechanism of the drug absorption via mucus membrane it is also called as the transcellular process. Through this mechanism the lipoidal drug are absorbed. This is an active transport means it is carrier-mediated transport.

Various Types of Nasal Formulation: Presently there are the different types of nasal formulations which available in the market presently. The selection of the dosage form depends upon the nature of the drug being used, patient requirement, acceptability, effect require and for the marketing purpose. Some types of nasal formulation available in the market are

- Liquid formulation.
- Powdered form.
- Pressurized MDIs (Metred dose inhalers).
- Gel form.

Liquid Formulation for Nasal: Liquid preparations are most commonly used today for the nasal administration. Most allergic and chronic disease are related with the crust and drying of the nasal mucosa. In such condition the humidifying effect of the liquid preparation is convenient and usefull, but there are some drawbacks of the aqueous based dosage form like microbial stability, nasal irritation and rhinitis. This occurs due to the amount of the excipients used in the formulation. The liquid based formulation does not able to retard effect of the mucociliary clearance on the drug [35]. Following are the some dosage form of the liquid formulation for nasal administration.

- Instillation and rhinyle catheter.
- Compressed air neubilizer.
- Squeezed bottle.
- Metered- dose pump sprays.

Powder Form: The powdered forms are not used in the nasal drug delivery commonly. They have some pros over the liquid preparation like use of fewer amounts of the excipients and the increased stability of the formulation because the powder can adhere to the nasal mucosa for grater period of the time and hence have increased retention time of formulation. Types of the powdered dosage form available in market for nasal administration.

- In sufflators.
- Dry powder inhalers.

Pressurized MDIs: Pressurized metered dose inhalers (MDI) are the devices, which deliver a specific amount of the drug directly into the lungs. This takes place by a short burst of the medicine which is inhaled by the patient through the aerosol dosage system. This type of the dosage form is commonly used in the treatment of the COPD i.e. chronic obstructive pulmonary disease, asthma and the other disease related to the respiratory tract [36].

Gel Form: These are the solution or suspension with the high viscosity. They are not commonly known today but have many of the advantages like post natal drip reduction due to high viscosity. Drug targeting can be done, anterior leakage can be prevented, reduction in the irritation to the nasal mucosa, greater retention time and the better absorption [37].

***In-Situ* Mucoadhesive Gel:**

***In-situ* Property:** In this property, the gel found in sol type nature but when administered, the body phase transition occurs and get converted to the semisolid gel form from the liquid phase. The gelation occurs by the effect of temperature, change in pH etc. ionic effect, gelation induced by ultraviolet radiation, gelation induced by solvent exchange [38]. Major constituting materials in the preparation of the *in-situ* gel are the polymers such as pluronics, poloxomar, tetronics, carbopol, carbomer etc. are the best examples of thermosensitive polymers

Various Approaches for *In-situ* Gel for Nasal Drug Delivery System [39]: More specifically following two approaches are used for conversion of a biomaterial into the *in-situ* gel form.

- Temperature based system
- pH based system
- Temperature based system: - In this the conversion in the state of matter of a biomaterial occurs with the influence of the body temperature i.e. no external source of the heat is applied for the transition of the phase or for gelation. This can be achieved in a drug delivery system by using of various thermosensitive polymers such as pluronics [40], tetronics and polyols. These types of gelling system are further classified into three parts positively thermosensitive,

negatively thermosensitive and thermo reversible gels. The thermoreversible gel is basically prepared by two major method one the simple method and second one is the cold method. Magnetic stirring is required in both of the methods but in the case of the cold method lyophilization can also be used.

- pH based system: - Second most common approach for the formation of *in-situ* gel is the pH based system. The formation of gel is based on the physical stimuli that occur due to the change in the pH. Every pH sensitive polymers have acidic or basic group which undergo in the protonic reaction in accordance to the change in the pH of the environment. The polyelectrolytes are the polymers having large ionisable group. Basically the polymers which are anionic pH sensitive are based on the poly acrylic acid (carbopol, carbomer) and their derivative. The combination of the poly ethyl glycol (PEG) and Poly Methacrylic are also used for the pH sensitive system to achieve the desired gelation.

Mucoadhesive Property: These are the matter's intermediate state which contains liquid as well as solid components that get adhered to the mucus membrane for increasing the bioavailability of the drug for a particular formulation and drug delivery system [39]. Chitosan, Carbopol, HPMC etc. are the best example of mucoadhesive polymer. The polymer which is best suited for the formulation is used. Mucoadhesive polymers are used to increase the bioavailability and retention time of the drug by resisting dosage form from mucociliary clearance.

Ideal Characteristic of Mucoadhesive Polymers Used for Nasal Drug Delivery:

- It should be non-toxic and compatible with the nasal pH.
- It should be non-irritating to the nasal mucosa.
- The adherence should be quick and site specific.
- The incorporation of the drug should be easy and does not cause any alteration with the effect of the drug.
- The shelf life of the polymer should be optimum it should not degrade during storage.
- The polymer should not be very expensive as it would make the preparation very costly.
- It should be available readily.

Theory of Mucoadhesion: There are various theories related to the mucoadhesion, some are explain below

Wetting Theory: This is the oldest theory of the mucoadhesion. This theory is used to calculate two parameters [39]

- The adhesion work.
- Contact angle.

Electrostatic Theory: This theory state that the electron transfer takes place through the mucoadhesive polymer and mucous membrane this transfer leads to the formation of interfacial electron double bond and the attractive forces in a series which causes the mucoadhesion [41].

Adsorption Theory: Due to the effect of the two or more secondary surfaces, force like Van der waal's forces, hydrogen bonding and hydrophobic bonding are responsible for the adherence of the mucoadhesive polymer to the mucin. Polar molecule and group causes interfacial re-orientation. The strong adhesion can cause chemisorption [41,42].

Diffusion Theory: The bioadhesive polymeric chain interpenetrates in the glycoprotein mucin chain by the effect of the concentration gradient and the semi permanent bond is formed within the opposite matrix by reaching an optimum depth. The diffusion depth depends upon the diffusion coefficient of the each phase. According to a report by the Reinhart and Peppas the diffusion coefficient effects the molecular weight and the diffusion coefficient is inversely proportional to the cross linking density [41].

Mechanical Theory: This theory states that the adhesion takes place by the interlocking of the many particles of an irregular adhesive on a rigid surface. Large surface area and the large contact between interfaces are provided by the surface roughness [42].

Fracture Theory: This theory describes about the force required for the separation of two surfaces after the adhesion. The maximum tensile strength produced during separation is calculated by dividing the force required for the separation by the total surface area of adhesion [43].

Factors Affecting Gel Formation [44]: Followings are the various factors which affect the thermoreversible gel formation.

Physiological Condition:

- Transport through the membrane.
- Tissue pH
- Mucociliary clearance.

Physicochemical Property of Polymer:

- Concentration of the polymer, which have thermo reversible property.
- Molecular weight of the thermo reversible polymer
- Transition temperature.
- Value of hydration.
- Morphology of the polymer.
- Behavior like phase separation of the polymer.
- Crystalline state and the polymorphism of the polymer.

Various Formulation Factors:

- Clarity
- pH of the formulation.
- Gelling capability.
- Spreadibility.
- Osmolarity.

Advantages of Thermoreversible Mucoadhesive Gel:

- Dose accuracy.
- Easy to administrate.
- Taste masking.
- Increased nasal residence time.
- Increased nasal bioavailability.
- Decreased irritation of the formulation.
- Prevent the leakage of drug interiorly.
- Drug targeting can be done.

Various polymers used in the preparation of thermoreversible *in-situ* gel are given in Table 1.

Various Researches on *In-situ* Nasal Gel:

- Majithiya *et al.* [46] developed nasal gel of drug sumitriptan by using polymers pluronics F127 and carbopol 934P. In his research work prepared gel shows greater residence time and better patient compliance.
- Hardikar Sharwaree *et al.* [47] developed nasal gel of Amitriptylline Hcl by using polymer pluronics F27 and HPMCK4. He found that the gel

Table 1: Various polymers used in the preparation of thermoreversible in-situ

S.no	Polymer	Mechanism of gelation
1	Methylcellulose	At lower temperature water molecule form cage like structure to acculmate the MC molecule. Then upon heating the structural confirmation of MC with water breaks and forms aggregates which cause gelation ⁴⁵
2	Poloxamer	With increase in temperature, the desolvation of hydrophilic chains occurs leading to breakage of hydrogen bonds, due to which gelation occurs ⁴⁵
3	Poly-(N-isopropylacrylamide) PNIPAM	The PNIPAM forms coil-to-globule transition state in water which is responsible for the gelation ^{45,46}
4	Poly(acrylic acid-co-acrylamide)	At 25°C the temperature, the combined effect between the hydrogen bond of between AAc and AAm units causes gelation. ⁴⁵
5	Poly(methyl vinyl ether) PMVE	Gelation takes place at the temperature 37°C. ⁴⁵

formed have 40 % greater bioavailability of the drug as compared to the oral route with the sustained effect

- Bhandwalkar *et al.* [48] worked on formation of nasal gel of Venlafaxine HCl by using polymers Lutrol F125(18 %) and 0.3 % PVP K30 and it was found that the prepared formulation was more effective as compared to the oral dosage form.
- Sharma *et al.* developed nanoparticles of levodopa for nasal drug delivery by using polymer pluronic PF127 and chitosan it was found that formulation formed shows better uptake of the levodopa as compared to the conventional dosage form which consist cabidopa is used. Hence avoid the use of carbidopa [49].
- Chaudhari *et al.* [50] developed mucoadhesive nasal *in-situ* gel of raloxifene HCl by using polymers pluronics F127 14% and 0.3% carbopol 934P. It was found that the formulation have the controlled effect and greater bioavailability (2%) as compared to the oral route.
- Abhirami *et al.* [51] developed nasal *in-situ* gel of celecoxib by using polymers Pluronic F127 and carbopol 934P. It was found that the developed formulation have sustained effect and increased bioavailability as compared to the oral route and better drug release i.e 100 % in 6 hours.
- Anjan de *et al.* [52] developed an *in-situ* nasal gel of ondansetron by using polymer PF 127, HPMC E15 and chitosan. He observed that the permeation rate as well as residence time of the preparation was increased.
- Kumar Ashok *et al.* [53] developed *in-situ* gel of domperidone of nasal drug delivery by using polymers pluronics F127 and carbopol 934P. The gel was prepared for controlled release action; it was found that the prepared formulation can give better patient compliance and good mucoadhesive strength.
- Inayat Bashir *et al.* [54] developed an intranasal *in-situ* gel of azelastine hydrochloride by using polymer gellan gum with HPMC E4M. It was concluded that the formulation have increased residence time and suitable for allergic rhinitis.
- Vardhan Jyoti *et al.* [55] worked on the *in-situ* gel of metoprolol succinate for nasal drug delivery by using polymers pluronics F127 and sodium alginate, In her research she found that the prepared formulation have longer residence time in the nasal cavity and have adequate mucoadhesion.
- Kumar Vijay *et al.* [56] developed *in-situ* gel of bromhexine hydrochloride (BHC) by using polymers poloxamer and HPMC. It was found that the prepared formulation have increased residence time.
- Mahakalkar *et al.* [57] formulated *in-situ* gel of zolmitriptan by using natural polymer extracted from the bark of *sterculia foetida linn* and pluronics F127. It was found in his research that the extracted polymer can be successfully used as the mucoadhesive polymer. And prepared formulation is beneficial in the treatment of migraine.
- Parmar Viram *et al.* [58] developed and evaluated ion dependent *in-situ* nasal gel of m etoclopramide hydrochloride for treatment of migraine by using polymers xanthum gum and gellan gum. it was observed that the prepared formulation shows *in vitro* sustained release effect for 8 hours.
- Kolsure Pramod Kumar *et al.* [59] prepared *in-situ* gel of zolmitriptan for nasal drug delivery by using polymers pluronics F127, pluronics F68 and sodium alginate. It was obtained that the prepared formulation is thermosensitive. It gels at the body temperature
- Utwar Shital developed nasal *in situ* gel of ondansetron by using polymer pluronics F127, pluronics 68, HPMC K4 and carbopol 934 P. it was founded that the prepared formulation gels at the body temperature and in evaluation the prepared formulation shows good physicochemical properties and *in-vitro* drug release [60].

Table 2: Various Patents on Nasal drug delivery

S.no	Applicant	Disease	Drugs	Patent No.	Year
1	Jiasheng TU <i>et al</i>	-	-	CN103705463(A)	2014.61
2	Wangfengqin <i>et al</i>	Allergic rhinitis	Ephedrine hydrochloride	CN103735496(A)	2014.62
3	Maes Paul Jose Pierre Marie(BE) <i>et al</i>	Hypogonadism	Testosterone	WO2014080282(A2)	2014.63
4	LI XIN <i>et al</i>	-	-	CN103169649(A)	2013.64
5	Xiang Tang <i>et al</i>	Attention diffict disorder	Citicoline sodium	CN102579320(A)	2012.65
6	Xiaorong Yang <i>et al</i>	-	Radix scutellariaextract	CN102349944(A)	2012.66
7	Siobhan fogarty <i>et al</i>	Low sexual libido, low sexual activity, low spermatogenesis	Testosterone	WO2012156822(A1)	2012.67
8	Liang Sun <i>et al</i>	-	Mometasonefuroate	CN102078612(A)	2011.68
9	Qiang Liu <i>et al</i>	Shaoyin headache, migraine	Angelica dihuricaextract, Ligusticumchuanxionghortoil, Asarumoil, borneol.	CN101933963(A)	2011.69
10	Song Chen <i>et al</i>	-	Cortical hormone	CN101810562(A)	2010.70
11	Vaisman <i>et al</i>	Pre mature ejaculation	Any drug of Anti depressant category	235918(INDIA)	2010.71
12	GaoliZheng (CN) <i>et al</i>	Osteoporosis	-	CN101337067(A)	2009.72
13	JinjunGuo	Allergic rhinitis	-	CN101590074(A)	2009.73
14	Patel RajniGulabdas <i>et al</i>	Nausea , vomiting	Ondansetron hydrochloride	209056(INDIA)	2007.74
15	M.W.Anderson <i>et al</i>	Dry nasal tissue	Water 50%-90%,	EP1450739A1	2004.75
16	Anwar A. Hussain <i>et al</i>	Angina pectoris, Arrhythmias, hypertension, migraine.	Propranol	US4394390A	1983.76

Note: Reference number 61-76 are of the patents which are mentioned in the table 2.

Various Patents on Nasal drug delivery are summarized in Table 2.

CONCLUSION

The initial requirement for making an effective drug delivery system is the patient compliance and acceptability. This is offered by the thermo reversible muco adhesive *in-situ* gel because of many of the advantages like mucoadhesion, increased residence time, more bioavailability of the drug as compared to the oral route. Due to the thermo sensitive nature and controlled targeted gelation time makes it compatible to administer via variety of the routes. This makes the thrm reversible mucoadhesive *in-situ* a promising approach for drug delivery system.

Future Prospects: *In-situ* gels can be prepared by using the wide variety of the biodegradable polymers. But there are many problems and difficulties associated with them like processibility, organic solvent needed for their preparation, burst effect and non reproducible drug kinetics. Natural polymers meet the requirement of an ideal polymer but the difficulty associated with them is batch to batch reproducibility, to overcome this synthetic polymers are used. Both physical and chemical methods are used for the improvement of effect of the both polymers. There are limited varieties of thermo reversible polymers is available and their performance is also not satisfactory.

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