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IN-SITU GEL FOR NASAL DRUG DELIVERY

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ABSTRACT

Oral drug delivery is one of the most desirable, preferred and convenient route for the administration of a drug, whenever systemic effects are intended, However, low oral bioavailability of some actives due to extensive hepatic first pass metabolism and gastrointestinal degradation has prompted the search for more effective routes for their systemic delivery. Transmucosal routes of drug delivery (the mucosal linings of the nasal, rectal, vaginal and buccal cavity), parenteral route and transdermal route offer distinct advantages over oral administration. These include possible bypass of firstpass effect, avoidance of pre-systemic elimination in gastrointestinal tract (GIT) and hence small dose of a particular drug is required. Reduction in dose will overcome the side effects and ultimately reduce the treatment cost. Intranasal drug delivery can be visualized as the promising route for administration of drugs as it has the potential to overcome some major limitations associated with other listed routes. It is an attractive approach for the systemic delivery of drugs because concentration time profile of drugs after nasal administration is often similar to that obtained after intravenous administration, with resultant rapid onset of pharmacological activity. In addition, intranasal delivery provides a convenient route for the delivery of drugs to central nervous system (CNS) as well as for the products with local activity. Intranasal administration offers several practical advantages from the patient's point of view (rapid onset of action, noninvasiveness, essentially painless, ease of delivery, favorable tolerability profile, improved patient compliance, ease of convenience, self-medication) and pharmaceutical industry viewpoint (no need of sterilization of nasal preparations).

KEYWORDS: Intranasal, Buccal, Transmucosal, CNS, GIT, Peroral, CSF, Olfactory, Bioavailability, Biodegradable, Polymers etc.

INTRODUCTION

The most desirable and convenient method of drug administration is the oral route because of their ease of administration. However, in many instances oral administration is not desirable when the drug undergoes degradation via first pass effect in liver. Hence, lack of systemic absorption through the gastrointestinal tract leds to research on different possible routes of drug delivery such as parenteral, intramuscular, subcutaneous, intranasal, transdermal.[1]

Nasal drug delivery has been recognised as a very promising route for delivery of therapeutic compound. In recent years there are many drugs which shows better systemic bioavailability through nasal route, due to large surface area and porus endothelial membrane and high blood flow.[2]

Nasal admistration is needle free and it is ideal alternative to parentral route for systemic drug delivery.TheDrug which is administered by nasal route is easy and convenient. Avoidance of hepatic first pass metabolism is the main advantage of nasal route.

Through nasal cavity drugs are administered by different dosage forms like solution, emulsion, and gel. But this formulation has certain drawbacks like

- Not easy to administer.
- Low dose accuracy.
- Irritant to nasal mucosa and give gritty feel.

To overcome such drawbacks in-situ gel are an alternative route of administration.

Gels: Gels are semisolid form which containsboth solid and liquid components. The solid components comprises a three dimensional network of interlinked molecules which immobilizes the liquid phase.[3]

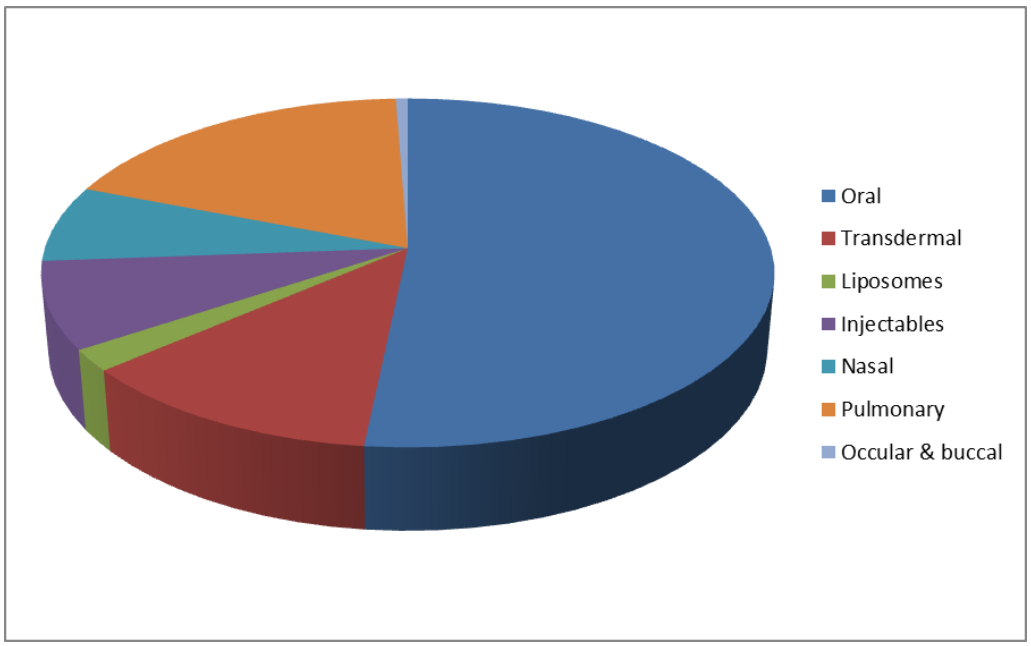
In-situ Gel Drug Delivery System

In-situ is a Latin word which means ‘In its original place or in position’. In this type of drug delivery system, the preparation is in a solution form before administration in body, but it converts into a gel form after administration.[4]

It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profile by intravenous injection with 100% bioavailability. Whereas absorption of hydrophilic drugs can be increased by means of absorption enhancer.[5]

The preparation of insitu gel using ionic polysaccharides has been disclosed in U.S. Pat. No. 5,958,443, which discloses compositions 270ehavior270ting a drug, a film forming polymer and a gel forming ionic polysaccharide (such as an alginate).[8,9]

Various routes: Oral, ocular, vaginal, rectal, IV, intraperitoneal



Advantage of in-situ gel system[6,7]

- Controlled and sustained release of the drug
- Ease of the drug administration
- It can be administered to unconscious patients
- More patient compliance and comfort
- Minimizing the dose frequency and drug toxicity
- Use of natural polymers provide biocompatibility and biodegradation
- Hepatic first – pass metabolism is absent.
- Rapid drug absorption
- Larger drug molecules have low bioavailability hence it can be improved by means of absorption enhancer or other approach

- Drugs which cannot be absorbed by oral route can be delivered to the systemic circulation through nasal drug delivery system
- Better nasal bioavailability for smaller drug molecules

Disadvantage of in-situ gel system[8]

- Histological toxicity of absorption enhancers which is used in nasal drug delivery system is not yet clearly established.
- Relatively difficult to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area as compare to GIT

Advantages of nasal In-situ gel over other nasal formulations[9]

- Reduction in post- nasal drip in to back of throat and therefore minimization of bad taste problem and loss of drug from nasal cavity.
- Reduction in anterior leakage of the drug from nasal cavity.
- Localization of formulation on the mucosa thereby providing a better chance for the drug to be absorbed.
- Gel can be afford to the use of soothing agent or emollients which may not be suitable for solutions, suspensions or powder dosage form so can reduce irritation potential.
- Can be developed for both systemic and local delivery.

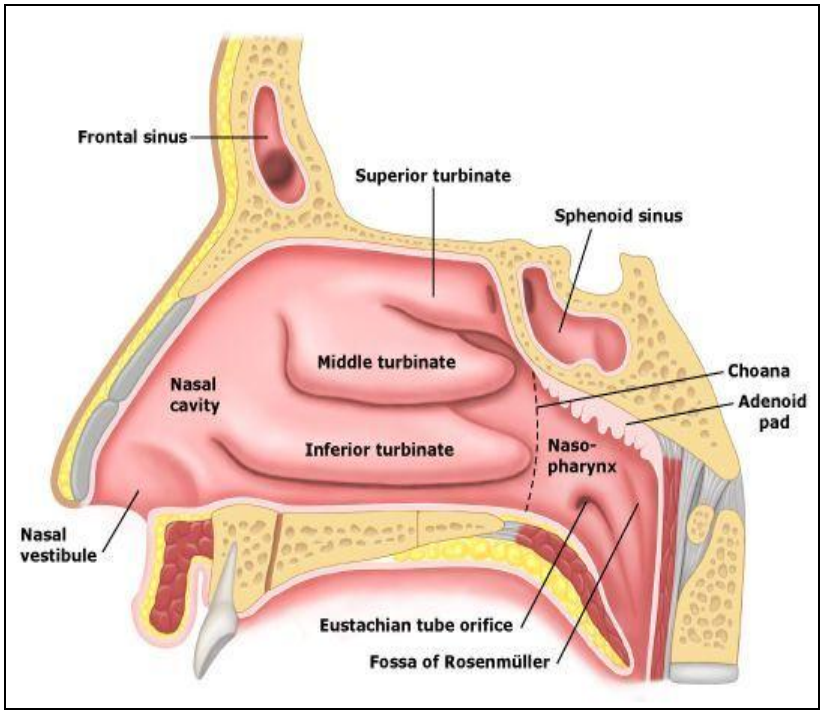
Profile of Ideal Drug Candidatesfor Nasal Delivery

Molecular weight ≤ 500 Da log P≤5
Aqueous solubility ≤ 500mg/ml
Dose potency≤ 5mg/dose/spray puff per nostril
Drug in solution: PH approximately 5.5 osmolarity ≤500 kg
No nasal irritation from drug
No toxic nasal metabolite

Volume 25 – 150 ul per nostril

Anatomy and Physiology of nose[10]

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril Breathing and olfaction are the major function of human nose. But also functioned as filtration and humidification of inhaled air before reaching in lowest airway. Nasal cavity has mucus layer and hairs, those helpful in filtration of particles trapped in inhaled air. Additionally metabolism of endogenous substances, mucociliary clearance also functions of nose. The human nasal cavity has a total volume of about 16-19ml and total surface area of about 180cm^2 and is divided into two nasal cavities via septum. The volume of each cavity is approximately 7.5ml having surface area around.



Three Distinguished Regions

1) The Respiratory region

The respiratory region isone the largest region with highest degree of vascularity andit is mainly responsible for systemic drug absorption. Itconsistsof respiratory epitheliumwhich is composed of four types of cells namely-non ciliated, ciliated columnar cells, basal cells, goblet cells. These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia.

2) 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. The olfactory region is located on the roof of the nasal cavities, just below the cribriform plate of the ethmoid bone, which separates the nasal cavities from the cranial Cavity. The olfactory tissue is mostly yellow in colour, in contrast to the surroundingpinktissue. The olfactory epithelial layer predominantly contains three types of cell: the olfactory neural cells, the subtentacular cells and the basal cells.

3) The Vestibular region

It is anterior part of nasal cavity. It has surface area about 0.6 $cm^{2.}$ Nasal portion is covered by a stratified squamous keratinized epithelial with sebaceous gland. It is located at the opening of nasal passages and is responsible for filtering out the air born particles. Here absorption of drugis very difficult but it afforded high resistance against toxic environment.

Table1. Structural features of various regions and their impact on the permeability of nasal cavity.[11]

Region	Structural Features	Permeability
Nasal vestibule	Nasal hairs (vibrissae) Epithelial cells are starified, squamous and keratinised sebaceous glands present	Least permeable due to the presence of keratinized cell, very resistant to hydration and can withstand insults from noxious substances of the environment
Atrium	Transepithelial region starified squamous cells present anteriorly and pseudostartified Cells with microvilli present posteriorly	Less permeable as it has a small surface area and stratified cells are present anteriorly
Respiratory region (inferior turbinate middle turbinate superior turbinate)	The narrowest region of the nasal cavity. Pseudostratified ciliated columnar cells with microvilli (300 per cell) large surface area Receives maximum nasal secretions due to the presence of seromucuous glands, nasolacrimal duct, and goblet cells	Most permeable region due to large surface area and rich vasculature
Olfactory region	Specialised ciliated olfactory nerve cells for smell perception. Receives ophthalmic and maxillary divisions of the trigennial nerve	Direct access to cerebrospinal fluid
Nasopharynx	The upper part contains ciliated cells, and the lower part contains squamous epithelium	Receives nasal cavity drainage

Composition of mucous

Nasal cavity is corved with a mucous membrane which contains goblet cell and secretes mucous. The composition of mucous is as follows. Airway mucus, Primary water (95%), mucus glycoprotein (2%), protein albumin, Immunoglobulin, lysozyme, inorganic salts & lipid, mucous glycoprotein.

Mechanismof Drug Absorption from Nasal Cavity

Two mechanisms have been considered predominantly out of several mechanisms that have been proposed.

The first involves an aqueous route of transport, which is also known as the paracellular route. Key feature of this mechanism involves

- This route is slow and passive.
- There is an inverse lop-log correlation between intranasal absorption and molecular weight of water soluble compounds.
- Poor bioavailability was observed for a drug with a molecular weight greater than 1000 Daltons

The second involves transport of drug through a lipoidal route and it is also known as the transcellular process and it isresponsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drugtransport

Barriers forNasal Drug Delivery[12]

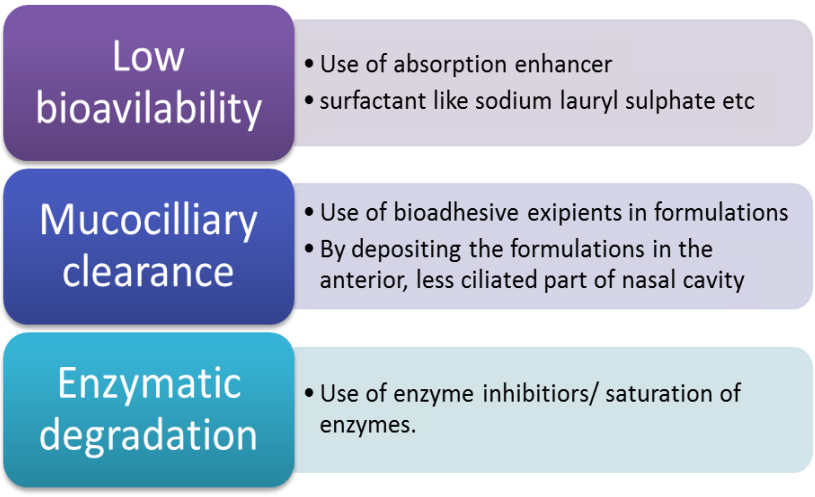


Figure 3: Barriers for Nasal Drug Delivery.

Factors affecting Nasal Drug Absorption[13,14]

Figure 4: Physiochemical properties affecting drug absorption.

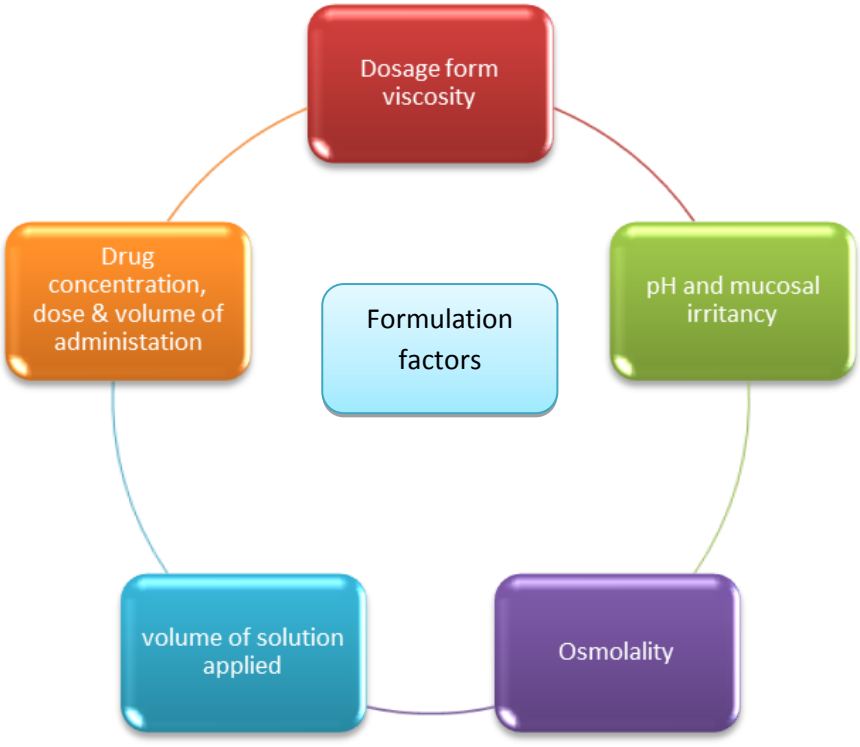


Figure 5: Formulation factors affecting drug absorption.

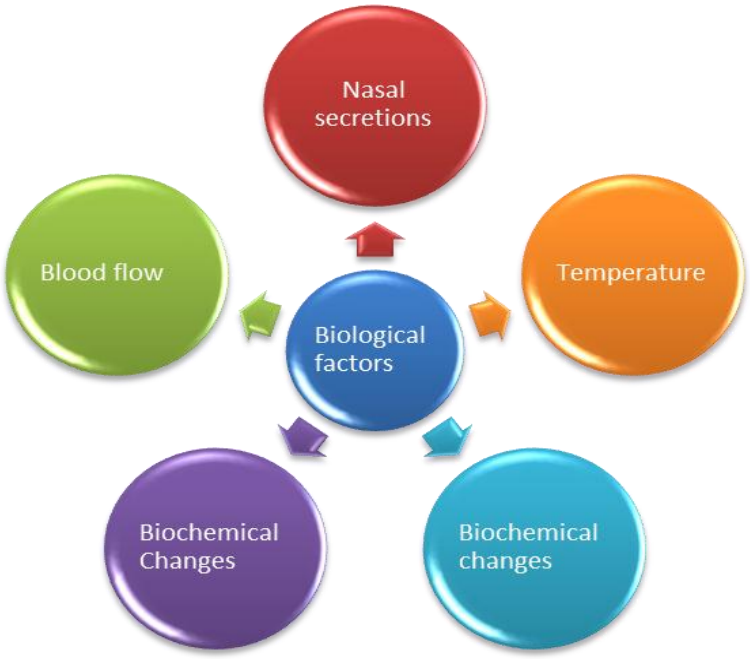


Figure 6: Biological factors affecting drug absorption.

Different Nasal Drug Delivery System[15,16,17]

1. Nasal Drops and spray

Nasal drops are one of the simplest and most beneficial delivery systems among all formulations. The limitation is the lack of precision in the administered dosage and the risk of contamination during use. Nasal drops can be delivered with a pipette or by a squeezy bottle. These formulations are usually recommended for the treatment of local conditions, but challenges include microbial growth, mucociliary dysfunction and nonspecific loss from the nose or down back the throat.

Nasal sprays contain both solution and suspension formulations. Nasal sprays deliver the exact dose (25-200 µl) by the availability of metered dose pumps and actuators.

2. Nasal Gel

A gel is a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in considerable quantity. The semi-solid 276ehavior of gels can be defined in terms of two dynamicmechanical properties: elastic modulus G' and viscous modulus G". The rheological properties of gels depend on the type of polymer, concentration and physical state of the gel. They can range from viscous solutions (e.g.methylcellulose, xanthan gum and chitosan) to very hard, brittle gels (e.g. gum, pectin and alginate). Bioadhesive polymers have shown good potential for nasal formulations and can control the

rate and extent of drug release resulting in decreased frequency of drug administration and improved patient compliance.

3. Nasal Powder

When both solution and suspension dosage forms cannot be developed then powder form is developed. The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation.

4. Microsphere

Microsphere has an important role in nasal drug delivery with enhancing absorption, sustained release, and also has great importance because it protects the drug from enzymatic degradation.

5. Nanoparticles

Nanoparticles are solid colloidal particles with diameters raging in between 1-1000 nm. Nanoparticles are also used for the targeting drug to brain via olfactory route. Nanoparticles may have the several advantages due to their small size; because only the smallest nanoparticles penetrate through the mucosal membrane and it also cross the tight junction of brain.

6. Liposomes

Liposomes are phospholipid vesicles composed by lipid bilayers enclosing one or more aqueous compartments wherein drugs and other substances can be include. Liposomal nasal formulation contain drug alone with combination of other excipients. Liposomal formulation are administered to the respiratory tract as an aerosol.

Evaluation of Nasal In-situ Gel[17]

1. Clarity

The clarity of formulated solution was determined by visual inspection against the black & white background.

2. Viscosity measurement

The viscosity and rheological properties of the polymeric formulation, either in solution or in gel made with artificial tissue fluid were determined with different viscometer like Brookfield viscometer. In situ gel formulation is placed in sample tube. Formulation is placed in sample

tube. It should have 5-1000mPas, before gelling & after ion gel technology by eye will have viscosity of from about 50-50,000mPas

3. Measurement of gel strength

This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. The gel which is present in a beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

4. pH of the Gel

The normal range of nasal mucosal Ph is 6.2 to 7.0 Ph. The advisable Ph of the nasal formulation is in the range of 5.5 to 7. Ph can be determined formulation is taken in beaker and 1ml NaOH added drop wise with continuous stirring. Ph is checked by using Ph meter

5. Invitro drug release study

The in situ gel formulations to be administered by many routes like oral, ocular and rectal the drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The formulation which is in sol form is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using different analytical technique. For injectable in situ gels, the formulation is placed into vials which contain a receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed.

6. Sol-Gel Transition Temperature and Gelling Time

For in situ gel forming systems, the sol-gel transition temperature and Ph should be determined. Gelling time is the time required for first detection of gelation of in situ gelling system. Thermo sensitive in –situ gel should be checked for in situ gelling at body temperature.

7. Drug polymer interaction study and thermal analysis

Interaction study may be determined with Fourier transform infrared (FTIR) spectroscopy. During gelation process, the nature of the interacting forces can be evaluated using the technique by employing KBr pellet method. Thermo gravimetric analysis (TGA) can be conducted for in-situ forming polymeric system to quantitate the percentage of water in hydro gel. Differential scanning calorimeter (DSC) conducted to observe if there are any changes in thermo gram as compared with pure active ingredients used for gelation

8. In vitro Permeation Study of Insitu Gel

The in-vitro permeation studies are performed by the diffusion studies in a diffusion cell made of glass which consists of a donor and receiver compartment. The nasal mucosa of the sheep is used in the diffusion studies**.**

Table 2: Marketed Nasal Drug Products.[18]

Drug Substance (Product name)	Indication	Dosage form	Status	Manufacturer
Salmon calcitonin (Karil 200 I.E.)	Osteoporosis	Solution (spray)	Marketed	Novartis Pharma
Desmopressin (Minirin Nasal spray)	Antidiuretic hormone	Solution (spray	Marketed	Ferring Arzneimitted
Buserelin (Profact nasal)	Buserelin	Solution (spray)	Marketed	Aventis Pharma
Nafarelin (Synarela)	Endometriosis	Solution (spray)	Marketed	Pharmacia
Oxytocin (Syntocinon)	Lactation induction	Solution (spray)	Marketed	Novartis Pharma
Protirelin (antepan* nasal) (Relefact* TRH nasal)	Thyroid diagnostics	Solution (spray)	Marketed	Aventis Pharma
Dihydroergotamin (Migranal* Nasal Spray)	Migraine	Solution (spray)	Marketed	Novartis Pharma
Estradiol (Aerodiol*)	Hormone replacement	Solution (spray)	Marketed	sarvier

CONCLUSION

Nasal drug delivery system is used to minimize the limitation of conventional dosage form. The nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption.Bioavailability of pharmaceutical and biopharmaceuticals can be improved with lesser side effects due to localized form of delivery formulations and it will minimize the painful condition and reduce the dependence of patient over technical staff for delivery of drug. The natural mucoadhesive polymer as a carrier for nasal drug delivery

can be used to improve the health of all living things and to minimize the unwanted effect of synthetic polymers. This review is gives deep insight of requirements inupcoming future prospectus. In situ gel, nasal inserts, microspheres, microparticles and nanoparticles are being used to bring novelty in nasal drugdelivery system

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