Review Article

In situ Nasal Drug Delivery

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Accepted on: 15-05-2015; **Finalized on:** 30-06-2015.

ABSTRACT

The oral route is most desirable and convenient route for drug administration and tablets, capsules are the most favoured dosage forms. However, although the oral route remains the most popular for systemic drug administration, low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery. Nasal drug delivery has attracted much attention as a promising alternative administration route, especially for peptide or protein drugs. The nasal route has many unique advantages such as relatively large absorptive surface area and high vascularity of the nasal mucosa and drugs that are active in low doses. Due to the advancement of biotechnology and genetic engineering, many new drugs are being developed. Many approaches can be used viz. temperature sensitive, pH sensitive for the delivery of drugs through nasal route. The objective of this review is to provide anatomy and physiology of nose, various approaches, contribution of nasal drug delivery, barriers, factors affecting, etc.

Keywords: Nasal Drug Delivery, *In situ* gel, Nasal mucosa, Bioavailability

INTRODUCTION

Nasal Drug Delivery System

The nasal route is an attractive alternative to drug administration and provides a direct access to the systemic circulation. In this, drugs are administered through nasal cavity by different dosage forms such as solution, emulsion, gel etc. and useful method for drugs having low dose and shows no or minimal oral bioavailability such as proteins and peptides. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism (Mahalaxmi R). Presently, commercially various nasal preparation is used for systemic absorption of drug in a different pathological conditions. Therapy through intranasal administration has been an accepted form of Treatment in the Ayurvedic system of Indian Medicine.[1,2]

Gels

Gels are semisolid systems containing both solid and liquid components. The liquid phase of the gel may be retained within a three-dimensional polymer matrix. Drugs can be suspended in the matrix or dissolved in the liquid phase. Gels combine the cohesive properties of solids and the diffusive transport characteristics of liquids.[3-5]

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[6,7]. An *in situ* gel is made of polymer materials that have a solution or semisolid state that responds to external stimuli at the administration site. These gels also have conformations that can undergo reversible conversion to form a semisolid or solid preparation.

The *in-situ* gelation compositions using ionic polysaccharides have been disclosed in U.S. Pat. No. 5,958,443, which discloses compositions comprising 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

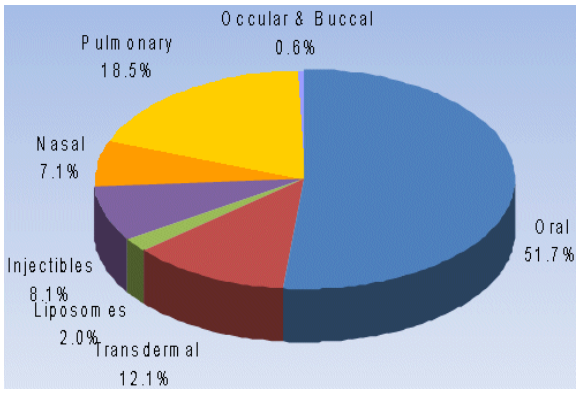

Figure 1: % Wise Contribution of Drug Delivery System

Merits[10]

- Improved local bioavailability
- Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
- Avoids degradation of drug through first pass metabolism
- Bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic side effects.

Limitations[11]

- Frequent use of this route leads to mucosal damage
- Drug delivery is expected to decrease with increasing molecular weight
- Some drugs may cause irritation to the nasal mucosa
- Nasal cavity provides smaller surface area as compared to GIT
- Drug cannot be withdrawn if once administered

Nasal Drug Delivery Sharing in Dosage Form Design[12]

Anatomy and Physiology of Nasal Cavity[21]

Researchers became interested in the nasal route for the systemic delivery of medication due to a high degree of vascularization and permeability of the nasal mucosa[13]. In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Passage of the nasal cavity which runs from nasal vestibule to nasopharynx has a depth of approximately 12-14cm. The total surface area of the nasal cavity in human adult is about 150 cm2 and total volume is about 15 ml[14]. Each of two nasal cavities can be subdivided into different regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone. The nasal cavity also contains the nasal associated lymphoid tissue (NALT), which is mainly situated in the nasopharynx. Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures[15]. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport[16]. Nasal cavity is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics[15].

Nasal Vestibule

Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm^2 [17]. Nasal hairs are present in this area, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands.

Atrium

Intermediate area between nasal vestibule and respiratory region is atrium. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by psudostratified columnar cells presenting microvilli.[18,19]

Respiratory Region

Largest part of the nasal cavity is respiratory region, also called conchae, is the cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands.[20] Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia.

Olfactory Region

Location of olfactory region is at the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuro-epithelium is the only part of the CNS that is directly exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception.[18,19]

Approaches for Nasal Drug Delivery[7,39,47,48]

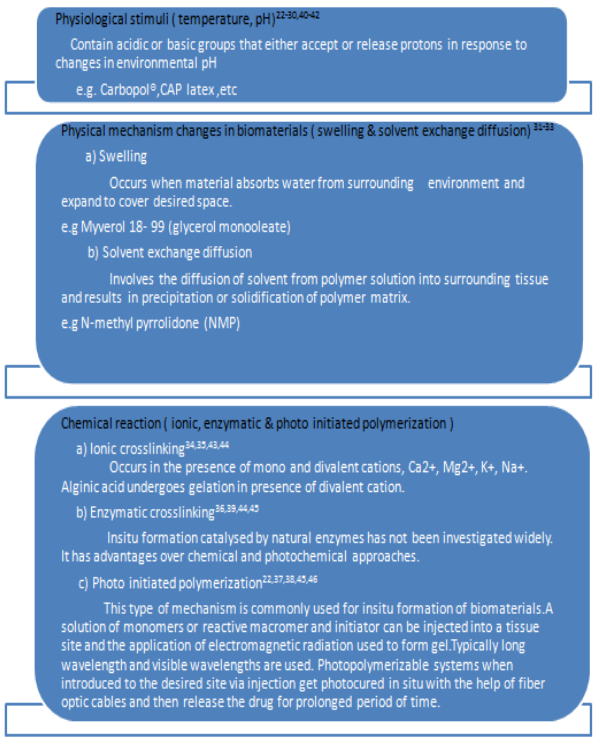

Figure 2: Approaches for nasal delivery

Barriers for Nasal Drug Delivery[15,49-53]

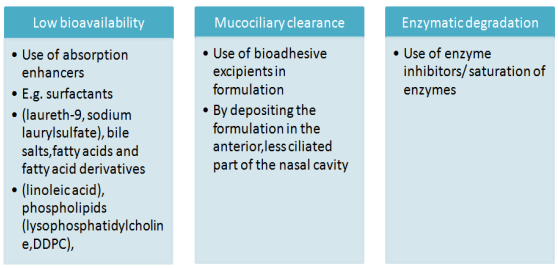

Figure 3: Barriers for Nasal Drug Delivery

Factors Affecting Nasal Drug Delivery System[54-66]

Figure 4: Physicochemical factors affecting nasal drug delivery

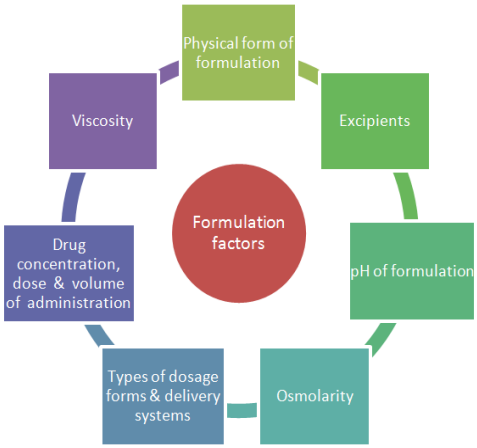

Figure 5: Formulation properties affecting nasal drug delivery

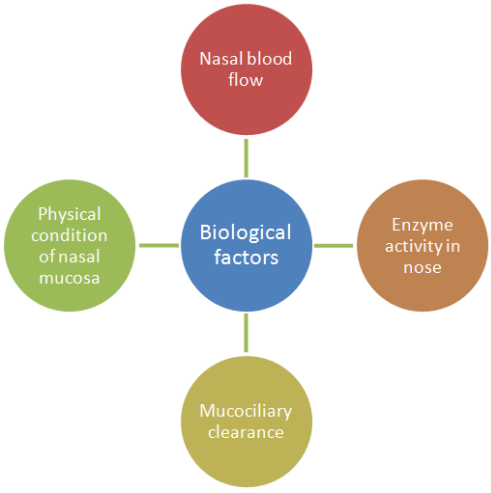

Figure 6: Biological factors affecting nasal drug delivery

Evaluation of Nasal *In Situ* Gel

Clarity[72]

The clarity of in situ gel was examined by visually under dark background[64].

pH of the Gel[72]

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 & 1ml NaOH added drop wise with continuous stirring. pH is checked by using pH meter[48].

Drug Content[61]

Formulation was taken in a volumetric flask and then it was diluted with distilled water then volume was adjusted. Pipette out appropriate quantity from this solution, again diluted with distilled water. After this absorbance of prepared solution was measured at particular wavelength of the drug by using U.V visible spectrophotometer.[65]

Viscosity Measurement[72]

The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas, before gelling & after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.[66,67]

Measurement of Gelation temperature: (For thermosensitive approach)

The gelation temperature was described by miller & Donovan technique. In this phase transition occurred from liquid phase to a gel phase. In this 2 ml *insitu* gel transferred to test tube and placed into water bath then the temperature of water bath increased slowly and constantly. Gel was allowed to equilibrate for 5 minute at each setting, then formulation was examined for gelation. When the meniscus would no longer move upon tilting to 90°, this is known as a gelation temperature.[72]

Measurement of Gel strength[59]

Formulated gels were placed in the test tubes and gelled in a thermostat at 37°C. The apparatus for measuring gel strength was then placed onto the in situ gel. The time taken by the apparatus to sink to a depth of 5 cm through the prepared gel was measured for each formulation.[69] Weights that detached the two vials using the following equation,

A. Stress is calculated by the formula[47]:

Detachment Stress (dyne/cm²) = $M * G / A$

Where,

M = wt required for detachment of two vials in gm

G = acceleration due to gravity

A = Area of tissue exposed.

In vitro Diffusion Study of *In situ* Gel[72]

In vitro release study of in situ gel solution is carried out by using Franz diffusion cell. The formulation is placed in donor compartment & freshly prepared simulated tear fluid in receptor compartment. Between receptor & donor compartment dialysis membrane is placed (0.22 µm pore size). The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37°C± 0.5°C. 1ml sample is withdrawn at predetermined time interval of 1hr for 6hrs the sample volume of fresh medium is replaced.

The withdrawn sample is diluted to 10ml in volumetric flask with respective solvent & analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using an equation generated from standard calibration curve. The percentage cumulative drug release (% CDR) calculated. The obtained data is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeyers peppas & Fickinian diffusion mechanism of their kinetics.[70]

In vitro Permeation Study Of *Insitu* Gel[73]

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.[70]

B. Permeability coefficient calculated from the slope of the graph:

$P = Slope * Vd/s$

Where,

Vd = volume of the donor solution

S = surface area of tissue

P = permeability coefficient.

Thermal Analysis[72]

Thermo gravimetric analysis can be conducted for in situ forming polymeric system to quantitative the percentage of water in hydrogel. Different scanning calorimetry is used to observed, if there are many changes in thermograms as compared with pure ingredients used thus indicating the interaction.[71]

Formulation Approaches

Nasal Gels[51]

Nasal gels are high viscosity thickened solutions or suspension. The deposition of the gel in the nasal cavity depends on the mode of administration. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market.[74]

Nasal Drops[51]

Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.[75]

Nasal Sprays[51]

Nasal sprays can be formulated from solution and suspension formulations. A nasal spray can deliver an exact dose anywhere from 25 to 200 µL. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation.[76]

Nasal Powder[51]

When 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.[77]

Liposomes[53]

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included.[78] Liposomal nasal formulation contain drug alone or with the combination of other excipients. Liposomal formulations are administered to the respiratory tract as an aerosol. The particles of the formulation have diameters of less than 50 microns.

Table 1: Patented Drugs for Nasal Drug Delivery

Patent	Issue date	Original Assignee	Title
US3874380	1975		Dual nozzle intranasal drug delivery
US4895559	Jan 23,1990		Nasal pack syringe
US6610271	Dec 15,2002	Intranasal Tech. Inc.(ITI)	The lorazepam nasal spray
US4767416	Aug 30,1988	Johnson & Johnson Patient Care. Inc.	Spray nozzle for syringe
US5064122	Nov 12,1991	Toko Yakuhin KogyoKabushii Kaisha	Disposable nasal adapter for intranasal spray containers
US5601077	Feb 11,1997	Becton Dickinson and Company	Nasal syringe sprayer with removable dose limiting structure
US8118780	Feb 21,2012	Liebel- Flarshiem Company	Hydraulic remote for a medical fluid injecto

Table 2: Marketed Nasal Drug Products[21,51,52,54,58,62,72,80,81]

Brand Name	Drug	Dose per nasal spray	Indication	Manufacturer
Miacalcin Nasal Spray	Calcitonin – Salmon	200 I.E.	Post – menopausal Osteoporosis	Novartis pharma
DDAVP Nasal Spray	Desmopressin acetate	0.1ml(10mcg)	Antidiuretic hormone	Ferring Arzneimitted
Stimate Nasal Spray	Desmopressin acetate	1.5mg/ml	Hemophilia A, von Willebrand's disease(type 1)	
Profact Nasal Spray	Buserelin	150mcg	Buserelin	Aventis Pharma
Synarela Nasal Spray	Nafarelin	200mcg	Endometriosis	Pharmacia
Syntocinon Nasal Spray	Oxytocin	30ml	Lactation induction	Novartis Pharma
Antepan Nasal Spray,Relefact*TRH Nasal Spray	Protirelin	1mg	Thyroid diagnostics	Aventis Pharma
Beconase AQ Nasal Spray	Beclomethasone dipropriate monohydrate	50 mcg	Seasonal and perennial allergic rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc
Vancenase AQ Nasal Spray	Beclomethasone dipropriate monohydrate	84 mcg	Seasonal and perennial allergic rhinitis	Schering Plough Corp
Rhinocort Nasal Spray	Budesonide	32 mcg	Seasonal and perennial allergic rhinitis and non-allergic perennial rhinitis	Astra USA Inc
Stadol NSO Nasal Spray	Butorphanol tartarate		Migraine headache pain	Bristol Myers Squibb
Nasalcrom Nasal Solution	Cromolyn sodium		Seasonal or perennial rhinitis	Fison's Corp
Decadron phosphate Turbinaire	Dexamethasone		Inflammatory nasal conditions or nasal polyps	Merck and Co.Inc
Nasalide Nasal Solution	Flunisonide		Seasonal or perennial rhinitis	Roche laboratories
Flunase Nasal Spray	Fluticasone proprionate	50 mcg	Seasonal or perennial rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc
Nasacort Nasal Inhaler	Triamcinolone acetonide	220 mcg	Seasonal or perennial allergic rhinitis	Rhone Poulenc Rorer
Asco*Top Nasal Spray	Zolmitriptan	5 mg	Migraine	Astra Zeneca
Imigran* Nasal Spray	Sumatriptan	20 mg	Migraine	Glaxo SmithKline
Migranal* Nasal Spray	Dihyfroergotamine	2 mg	Migraine	Novartis Pharma
Aerodiol* Nasal Spray	Estradiol	300 mcg	Hormone replacement	Servier

Microspheres[53]

Microsphere technology has been widely applied in designing formulations for nasal drug delivery.[79] Nasal microspheres have advantage that it provides prolonged contact with nasal mucosa. Microspheres swell in contact with nasal mucosa to form a gel. Thus it increases the absorption & bioavailability by adhering to nasal mucosa and increase the nasal residence time of drug. The ideal microsphere particle size is 10 to 50µm.

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. Route of administration often influences the bioavailability and therapeutic effectiveness of drugs. 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 also gives deep insight of requirements in upcoming future prospectus. In situ gel, nasal inserts, microspheres, microparticles and nanoparticles are being used to bring novelty in nasal drug delivery system.

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Source of Support: Nil, **Conflict of Interest:** None.