**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 administration4-7. 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

- 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

Anatomy and Physiology of Nasal Cavity

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. 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. 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 cribiform plate of ethmoid bone. The nasal cavity a 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 that are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this nonolfactory 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. 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.

Nasal Vestibule

Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm². 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 pseudostratified columnar cells presenting microvilli.

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, goblet cells, basal cells and mucous and serous glands. 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.

Approaches for Nasal Drug Delivery

Physiological stimuli (temperature, pH)

Chemical reactions (enzymatic & photo initiated polymerization)

Figure 2: Approaches for nasal delivery
Evaluation of Nasal In Situ Gel

Clarity

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

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

Drug Content

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.

Viscosity Measurement

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.

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.

Measurement of Gel strength

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.

Weights that detached the two vials using the following equation,

A. Stress is calculated by the formula:

\[ \text{Detachment Stress (dyne/cm}^2\) = M \times 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

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 data. The drug content calculated using an equation generated spectrophotometer at respective nm using reagent blank.

Table 1: Patented Drugs for Nasal Drug Delivery

<table>
<thead>
<tr>
<th>Patent</th>
<th>Issue date</th>
<th>Original Assignee</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>US3874380</td>
<td>1975</td>
<td></td>
<td>Dual nozzle intranasal drug delivery</td>
</tr>
<tr>
<td>US4895559</td>
<td>Jan 23,1990</td>
<td></td>
<td>Nasal pack syringe</td>
</tr>
<tr>
<td>US5064122</td>
<td>Nov 12,1991</td>
<td>Toko Yakuhin KogyoKabushii Kaisha</td>
<td>Disposable nasal adapter for intranasal spray containers</td>
</tr>
<tr>
<td>US5601077</td>
<td>Feb 11,1997</td>
<td>Becton Dickinson and Company</td>
<td>Nasal syringe sprayer with removable dose limiting structure</td>
</tr>
<tr>
<td>US8118780</td>
<td>Feb 21,2012</td>
<td>Liebel- Flarshiem Company</td>
<td>Hydraulic remote for a medical fluid injecto</td>
</tr>
</tbody>
</table>

Formulation Approaches

Nasal Gels

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.

Nasal Drops

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.

Nasal Sprays

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.

Nasal Powder

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.

Liposomes

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. 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.
Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Nasal microspheres have advantage that it provides prolonged contact with 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, 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.

REFERENCES


Table 2: Marketed Nasal Drug Products

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Dose per nasal spray</th>
<th>Indication</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Miacalcin Nasal Spray</td>
<td>Calcitonin – Salmon</td>
<td>200 I.E.</td>
<td>Post – menopausal Osteoporosis</td>
<td>Novartis pharma</td>
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<tr>
<td>DDAVP Nasal Spray</td>
<td>Desmopressin acetate</td>
<td>0.1ml(10mcg)</td>
<td>Antidiuretic hormone</td>
<td>Ferring Arzneimittet</td>
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<tr>
<td>Stimate Nasal Spray</td>
<td>Desmopressin acetate</td>
<td>1.5mg/ml</td>
<td>Hemophilia A. von Willebrand’s disease(type 1)</td>
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<tr>
<td>Profact Nasal Spray</td>
<td>Buserelin</td>
<td>150mcg</td>
<td>Buserelin</td>
<td>Aventis Pharma</td>
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<tr>
<td>Synarel Nasal Spray</td>
<td>Nafarelin</td>
<td>200mcg</td>
<td>Endometriosis</td>
<td>Pharmacia</td>
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<td>Syntocinon Nasal Spray</td>
<td>Oxytocin</td>
<td>30ml</td>
<td>Lactation induction</td>
<td>Novartis Pharma</td>
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<td>Antepan Nasal Spray,Relefact TRH Nasal Spray</td>
<td>Protirolene</td>
<td>1mg</td>
<td>Thyroid diagnostics</td>
<td>Aventis Pharma</td>
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<tr>
<td>Beconase AQ Nasal Spray</td>
<td>Beclometasone diopriquate monohydrate</td>
<td>50 mcg</td>
<td>Seasonal and perennial allergic rhinitis</td>
<td>Allen and Hanbury’s/Glaxo Wellcome Inc</td>
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<tr>
<td>Vancenase AQ Nasal Spray</td>
<td>Beclometasone diopriquate monohydrate</td>
<td>84 mcg</td>
<td>Seasonal and perennial allergic rhinitis</td>
<td>Schering Plough Inc</td>
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<tr>
<td>Rhinocort Nasal Spray</td>
<td>Budesonide</td>
<td>32 mcg</td>
<td>Seasonal and perennial allergic rhinitis and non-allergic perennial rhinitis</td>
<td>Astra USA Inc</td>
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<tr>
<td>Stadol NSO Nasal Spray</td>
<td>Butorphanol tartarate</td>
<td></td>
<td>Migraine headache pain</td>
<td>Bristol Myers Squibb</td>
</tr>
<tr>
<td>Nasalcrom Nasal Solution</td>
<td>Cromolyn sodium</td>
<td></td>
<td>Seasonal or perennial rhinitis</td>
<td>Fison’s Corp</td>
</tr>
<tr>
<td>Decadron phosphate Turinaire</td>
<td>Dexamethasone</td>
<td></td>
<td>Inflammatory nasal conditions or nasal polyps</td>
<td>Merck and Co.Inc</td>
</tr>
<tr>
<td>Nasalide Nasal Solution</td>
<td>Flunisonide</td>
<td></td>
<td>Seasonal or perennial rhinitis</td>
<td>Roche laboratories</td>
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<td>Flunase Nasal Spray</td>
<td>Fluticasone propionate</td>
<td>50 mcg</td>
<td>Seasonal or perennial rhinitis</td>
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<td>Nasacort Nasal Inhaler</td>
<td>Triamcinolone acetone</td>
<td>220 mcg</td>
<td>Seasonal or perennial allergic rhinitis</td>
<td>Rhone Poulenc Rorer</td>
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<td>Asco*Top Nasal Spray</td>
<td>Zolmitriptan</td>
<td>5 mg</td>
<td>Migraine</td>
<td>Astra Zeneca</td>
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<td>Imigran* Nasal Spray</td>
<td>Sumatriptan</td>
<td>20 mg</td>
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<td>Glaxo SmithKline</td>
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<td>Migranal* Nasal Spray</td>
<td>Dihydroergotamine</td>
<td>2 mg</td>
<td>Migraine</td>
<td>Novartis Pharma</td>
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<td>Aerodiol* Nasal Spray</td>
<td>Estradiol</td>
<td>300 mcg</td>
<td>Hormone replacement</td>
<td>Servier</td>
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Source of Support: Nil, Conflict of Interest: None.