AN INNOVATIVE APPROACH FOR IN SITU GELLING SYSTEM FOR NASAL DRUG DELIVERY: AN OVERVIEW

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ABSTRACT

Intranasal delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. The conventional nasal drug delivery systems including solutions, suspensions, and ointments show drawbacks such as short residence in the nasal cavity, highly variable efficiency, low permeability, and inconvenient administration. In situ gel-forming systems are an interesting polymeric system that exists as flowing aqueous solution before administration and undergoes phase transition to form a viscoelastic gel in a physiologic environment. Benefiting from the merits of both a solution and a gel, an impressive number of in situ gel-forming systems induced by temperature, pH and ions have been prepared for use in nasal drug delivery in the past few years. In situ gel-forming systems increase the retention of drugs in the nasal cavity, and some of them also show permeation-enhancing capabilities. This article reviews the in situ gel-forming systems used for nasal drug delivery and introduces their gelling mechanisms and other favorable features for intranasal delivery. It also describes the release patterns and drug stability of in situ gels as well as their in vivo performances and local safety following nasal administration.

KEYWORDS: Intranasal drug delivery, Bioavailability, Permeation enhancers.
INTRODUCTION

a) Gel
Gel is the state which exists between solid band liquid phase. The solid component comprises a three dimensional network of inter-linked molecules which immobilizes the liquid phase.

b) In-Situ Gel Delivery System
In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. In situ gel phenomenon based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot. It permits the drug must be delivered in a liquid form to solution form.

Nasal Drug Delivery
Intranasal route is considered for the drugs that are ineffective orally and are used chronically where rapid entry into the circulation is desired and they require small doses. The absorption of drugs from the nasal mucosa most probably takes place via the aqueous channels of the membrane. Therefore, as long as the drug is in the form of solution and the molecular size is small, the drug will be absorbed rapidly via the aqueous path of the membrane. The absorption from the nasal cavity decrease.  

Advantages of In Situ Gel
a) Increased residence time of drug in nasal cavity.
b) Decreased frequency of drug administration.
c) Results in rapid absorption and onset of effect.
d) Avoids degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
e) Low dose required.
f) Minimized local and systemic side effects.
g) Improved bioavailability of drug.
h) Direct transport into systemic circulation and CNS is possible.
i) Offers lower risk of overdose of CNS acting drug.
j) Improved patient compliance.

Limitations of In Situ Gel
a) All drugs cannot be given by nasal route.
b) Frequent use of this routes leads to nasal mucosal damage.
c) Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailability.

d) Drug cannot be withdrawal if once administered.

e) Volume that can be delivered into nasal cavity is restricted to 25-200 μl.

f) Adversely affected by pathological conditions.

g) Drug permeability may alter due to ciliary movement.

h) Nasal irritants drugs cannot be administered through this route.

i) Exact mechanism is not yet clearly.

Profile of an ‘ideal’ drug candidate for nasal delivery [1,2]

Properties of Nasal In Situ Gel

a) It should be low viscous.

b) It should be free flowing to allow for reproducible administration to the nasal cavity, as droplet mist or as a spray.

c) Nasal in-situ gel should have long residence time.

d) The nasal in-situ gel follows phase transition mechanism and to stand with the shear forces in the nasal cavity wall.

Anatomy and Physiology of Nasal Cavity

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 it also functioned as filtration and humidifies 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 a function of nose. [9,10] The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm², and is divided into two nasal cavities via the septum. The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm. [1]
In studying drug absorption from the nasal mucous membrane, it is essential to have a clear understanding of anatomy and physiology of the nose and how it relates to the characteristics of the delivery system used. The nasal passage which runs from the nasal vestibule to the nasopharynx has a depth of approximately 12-14 cm. In this passage the nasal cellular apparatus is in close contact with mucus which protects the mucosa from the inspired air. There are 3 distinct functional zones in the nasal cavities, viz. vestibular, respiratory and olfactory regions. The zones are arranged anteroposteriorly in the sequence of order. The vestibular area serves as a baffle system and its surface is covered by a common pseudostratified epithelium where the long hairs may provide the function of filtering air borne particles. Respiratory area has a surface lined by a pseudostratified columnar epithelium and is normally covered by a dense layer of mucus that is constantly moving towards the posterior apertures of the nasal cavity by a powerful system of motile cilia. The olfactory segment is lined with a specialized type of pseudostratified columnar epithelium known as olfactory epithelium, which contains receptors for the sense of the smell. This segment is located along the dorsal roof of the nasal cavity. Olfactory mucosal cell types include: bipolar neurons, supporting (sustentacular) cells, basal cells and Bowman's glands. The axons of the bipolar neurons form the olfactory nerve (cranial nerve-I). Bowman's glands are serous glands in the lamina propria, whose secretions trap and dissolve odoriferous substances.

The total surface area of both nasal cavities is about 150 cm² and the total volume is about 15 ml. Approximately 1.5 cm from the nares (nostrils) is the narrowest portion of the entire

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Figure 1: Anatomy of the nose (To the right is a cross-section of the nose).
airway, the internal ostium (or nasal valve) with a cross-sectional area of about 30 mm$^2$ on each side. The nasal valve accounts for approximately 50% of the total resistance to respiratory airflow from the nostril to the alveoli. [3]

Each of the two nasal cavities is limited by the septal wall and the lateral wall dominated by inferior, middle and superior turbinates (Figure 1). They are important for maintaining the slit-like cavity thus facilitating humidification and temperature regulation of inspired air. Under and lateral to each of the turbinates are passages called the inferior, middle and superior meatus. The inferior and middle meatus receive the openings of the nasolacrimal duct and the paranasal sinuses. The mucous membrane in a meatus will not be hit by an ordinary intranasal spray. The individually variable caliber and shape of the lumen of the nasal cavities make it difficult to give uniform recommendations for intranasal drug administration and limits permeation of substances. The atrium is a transitional epithelial region with stratified, squamous cells anteriorly and pseudostratified columnar cells with microvilli posteriorly. [3,28]

**Blood Supply to Nasal Cavity** [4,5]

Nasal vasculature is richly supplied with blood to fulfill the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. Blood supply comes from branches of both the internal and external carotid artery including branches of the facial artery and maxillary artery.

Three regions can be distinguished in each part :-

1. **The Respiratory region:-** The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption. The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia (where applicable). They may also serve to prevent drying of the mucosa by trapping moisture.

2. **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 often yellow in color, in contrast to the surrounding pink tissue. Humans have relatively simple noses, since the primary function is breathing, while other mammals have more complex noses.
better adapted for the function of olfaction. The olfactory epithelial layer predominantly contains three cell types:

The olfactory neural cells, The subtentacular (also known as supporting) cells and The basal cells.

3. The Vestibular region: It is anterior part of nasal cavity. Surface area is 0.6 cm². 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 borne particles. Drug absorption is very difficult in this region but it afforded high resistance against to environment. It is considered to be the least important of the three regions with regards to drug absorption.[4,5]

Mechanism of Drug Absorption Through Nose

The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers. [5,6]

A. The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. Poor bio-availability was observed for drugs with a molecular weight greater than 1000 Daltons. [5,6]

B. The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junction. [5,6]

Nasal Drug Delivery System

Intranasal (IN) delivery is suitable for the local and systemic delivery of diverse therapeutic compounds. Among the non-invasive routes, nasal administration offers promising potential as a viable alternative for the delivery of some drugs. Hence there has been a surge of interest that has led to many investigations involving the nasal cavity as a feasible site for the administration of much therapeutic agents. [7]

1. The nasal epithelium is thin, porous (especially when compared to other epithelial surfaces) and highly vascularised. This ensures high degree of absorption and rapid
transport of absorbed substances into the systemic circulation for initiation of therapeutic action.

2. A porous endothelial basement membrane that poses no restriction to transporting the drug into general circulation.

3. Absorbed substances are transported directly into the systemic circulation thereby avoiding the first pass metabolic effect generally experienced following oral drug administration.

4. In some cases, drugs can be absorbed directly into the CNS after nasal administration by passing the tight blood brain barrier.

5. Generally, the enzymatic activity of the nasal epithelium is lower than that of the GIT or liver and higher bioavailability of drugs especially proteins and peptides can be achieved. In addition, enzyme inhibitors are more effective following nasal than oral application because of a higher degree of dilution in the latter than in the former.\[7\]

a) Realization of pulsatile delivery of some drugs like human growth hormone, insulin, etc. is higher with NDD.

b) The nose is amenable to self-medication that not only lowers the cost of therapy but improves patient compliance as well. The risk of overdosage is low and nasal lavage can be used to remove unabsorbed excess drug.

c) Reformulation of existing drugs as NDD products offers companies the possibility to extend the life cycle of their products.

6. Limitations: Only a limited amount of the formulation can be administered intranasally. Application of large quantities will disturb the normal functioning of the nose (olfaction and humidification of inspired air).

The dosing regimen as a result of drainage of the solution or expulsion of the dose due to sneezing.

The high porosity of the nasal epithelium is still not sufficient for absorption of all compounds especially hydrophilic ones and large molecules like proteins.

In addition, the nasal mucosa is enzymatically active albeit to a lesser extent compared with the GIT.\[7,8\]
Various Approaches of In-Situ Gelation \[8\]

To cause sol to gel phase transition on the nasal surface the following type of systems are recognized:

a) pH Triggered system  
b) Temperature dependent system  
c) Ion activated system  
d) Induced photo polymerization gelation (UV Induced gelation)  
e) Solvent exchange induced gelation.

i. pH Triggered System

All the pH sensitive polymer contain acidic or basic groups that either accept or release proton in response to in environmental pH. In the case of anionic groups swelling of gel increases as the external pH increases, but decrease if polymer contains cationic groups.

ii. Temperature Dependent System

Temperature sensitive gels are classified into two type first negatively thermo sensitive and second positively thermo sensitive. CST is critical solution temperature at which temperature gelation occurs.

a) Negatively thermo sensitive

Negative temperature sensitive gel had a lower critical solution temperature (LCST) and contract upon heating above the LCST.

b) Positively thermo sensitive

Positive temperature sensitive gel had an upper critical solution temperature (UCST).

iii. Ion Activated System

In situ formation is based on chemical reactions, following chemical reactions cause gelation, undergoes in situ gelling in the presence of mono- and divalent cations, including Ca\(^{2+}\), Mg\(^{2+}\), K\(^+\) and Na\(^+\). Alginic acid undergoes gelation in presence of divalent/polyvalent cations.

iv. Induced Photo Polymerization Gelation

Photo polymerization is commonly used for insitu formation of biomaterials. A solution of monomers or reactive micromere and initiator can be injected into a tissue site and application of electromagnetic radiation used to form gel. The photo reaction provides rapid polymerization rate at physiological temperature. The photo polymerization systems when
introduced to the desired site via injection get photo cured in situ with the help of fiber optic cables and then release the drug for prolonged period of time.

1. Polymer Used in In situ Gel Drug Delivery System
For achieving better drug product effectiveness, reliability we select appropriate polymer for the formulation. Material that show sol to gel transition in aqueous solution used in insitu gelation. Some example of polymers are capable of insitu gelation such as poloxamer, pluronics, various co-polymers such as PEO-PLLA and PEG-PLGA-PEG. Pectin, gelrite, cellulose acetophalate latex, gellan gum, alginate, matrigel, carbopol, chitin. The gel formation is induced by temperature change poloxamer, cellulose acetophalate latex, carbopol gelation induced by pH change.

2. Stimuli Responsive in Situ Gelling System
Physical or chemical changes in response to small external changes in the environmental condition. Temperature induced in situ gel system is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both in vitro and in vivo. In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20–25 °C) and undergo gelation when in contact with body fluids (35–37 °C), due to an increase in temperature. The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC) and xyloglucan etc.

3. Osmotically Induced in Situ Gelling System
In this method, gelling of the solution instilled is triggered by change in the ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations. The polymer which shows osmotically induced gelation are gellan gum, hyaluronic acid and alginites etc.

4. Chemically Induced in Situ Gel System
The chemical reaction which forms in situ gel systems are Ionic crosslinking, enzymatic crosslinking and Photo-polymerization.
a) Ionic cross linking
Certain ion sensitive polysaccharides such as Carragenan, Gellan gum (Gelrite), Pectin, Sodium alginate undergo phase transition in presence of various ions such as K\(^+\), Ca\(^{2+}\), Mg\(^{2+}\), Na\(^+\). These polysaccharides fall into the class of ion-sensitive ones. For example, Alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca\(^{2+}\) due to the interaction with gulcuronic acid block in alginate chains.

b) Enzymatic cross linking
In situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiological conditions without need for potentially harmful chemicals such as monomers and initiators.

c) Photo-polymerization
In situ photo-polymerization has been used in biomedical applications for over more than decade. A solution of monomers or reactive macromere and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromere because they rapidly undergo photo-polymerization in the presence of suitable photo initiator. Photopolymerizable systems when introduced to the desired site via injection get photocured in situ with the help of fiber optic cables and then release the drug for prolonged period of time. \(^{[8,9]}\)

Different Factors Affecting in Situ Gel \(^{[9,24]}\)

a) Factors Related to Drug
1. Molecular Weight: Based on the reports by Fisher et al it can be concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug.
2. Chemical Form: Chemical form is the important parameter in drug absorption because conversions of the drug into a salt or ester form and may alter its absorption.
3. Polymorphism: Polymorphism is known to affect the dissolution rate and solubility of drugs thus their absorption through biological membranes. So it is of prime importance that polymorphic stability and purity of drugs for nasal powders and/or suspensions should study.
4. **Solubility & Dissolution Rate**: For better absorption drug should get dissolve. If particles are present, it is somewhat difficult for absorption.

5. **Lipophilicity**: From literature study it has been revealed that as lipophilicity goes on increasing it increases permeation through the nasal mucosa. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Drug like testosterone has been absorbed nasally already prove in animal models.

6. **Partition Coefficient and pKa**: As pH partition theory states that unionised species are absorbed well as compared with ionized hence it is same in the case of nasal absorption also. [9]

**b) Factors related to Formulation**

1. **pH**: The pH of the formulation, as well as that of nasal surface can affect a drug’s permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5.

2. **Osmolarity**: Optimum osmolarity should maintain as it causes shrinkage of the nasal epithelial mucosa and alters the permeation of drugs.

3. **Viscosity**: A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

4. **Buffer Capacity**: Nasal formulations are generally administered in small volumes ranging from 25 to 200μL. Hence, nasal secretions may alter the pH of the administrated dose. This can affects the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

5. **Drug Concentration, Dose & Dose Volume**: Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. [10]
c) Physiological factors

1. **Effect of Deposition on Absorption**: Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability while posterior portion of the nose where the drug permeability is generally higher, provides shorter residence time.

2. **Nasal blood flow**: Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

3. **Effect of Enzymatic Activity**: Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino-peptidase at the mucosal membrane.

4. **Effect of Mucociliary Clearance**: The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered.

5. **Effect of Pathological Condition**: Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption. \[^{10,22}\]

**Methods to Improve Nasal Absorption**

Followings are some approaches which have been used successfully for the improvement of nasal drug absorption. \[^{11}\]

1. **Permeation enhancers**: Various types of permeation enhancers have been investigated to improve the nasal absorption like fatty acids, bile salts, phospholipids, surfactants, cyclodextrins etc.

2. **Prodrug approach**: Prodrugs are the inactive chemical moiety which becomes active at the target site. This approach is mainly used to improve the physicochemical properties such as taste, solubility, stability etc. of formulation.

3. **In situ gel**: These formulations generally controlled the problems of administration along with conversion into gel by the influence of stimuli includes temperature, pH and ionic concentration etc.

4. **Nasal enzymes inhibitors**: Enzymes inhibitor like protease and peptidase are used as inhibitors for the formulation of peptide and protein molecules.
5. **Structural modification:** Drug structure can be modified without changing the pharmacological activity to improve the nasal absorption. Chemical modifications are mainly used to modify the drug structure.

6. **Mucoadhesion:** Mucoadhesion can be defining as the state in which two materials held together for long period. Mucoadhesive polymers make intimate contact with biological membrane, after the establishment of contact and penetrate into the tissue surface.

a. **Natural mucoadhesive polymers:** Availability of natural polymers can be easily ensured by natural sources which is an environmental friendly processing with low cost. Some examples which include Potato starch, Rice starch, Maize starch, Wheat starch, Gaur gum, Tragacanth, Xanthan gum etc.

b. **Synthetic mucoadhesive polymers:** Synthetic polymers produce environmental pollution during synthesis and have a high cost of production. These polymers include methyl cellulose, Poly ethylene oxide, Poly vinyl alcohol, Ethyl cellulose, Hydroxyl propyl methyl cellulose etc.

**Formulation and Active Agent that have been Utilized in Nasal Drug Delivery**

**Table 1: Formulation And Active Agent That Have Been Utilized In Nasal Drug Delivery.**

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Formulation</th>
<th>Active agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>In-situ nasal gel</td>
<td>Midazolam, Insulin, Triptans, Diltiazem</td>
</tr>
<tr>
<td>2.</td>
<td>Nasal inserts</td>
<td>Chlorpromazine, Albuterol</td>
</tr>
<tr>
<td>3.</td>
<td>Microspheres</td>
<td>Beta-amyloid fibril, Starch microspheres, Dextran Gentamicin, Insulin, Desmopressin</td>
</tr>
<tr>
<td>4.</td>
<td>Microparticles</td>
<td>Serum, Albumin, Thiolated Chitosan microparticles</td>
</tr>
<tr>
<td>5.</td>
<td>Dry powder</td>
<td>Zolmitriptan.</td>
</tr>
</tbody>
</table>
Challenges for Nasal Delivery Systems

Table 2: Challenges for nasal delivery systems. \cite{13}

<table>
<thead>
<tr>
<th>Problem</th>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic degradation</td>
<td>Inhibit nasal enzymes</td>
<td>Enzyme inhibitor, prodrugs</td>
</tr>
<tr>
<td>Mucociliary clearance</td>
<td>Overcome it</td>
<td>Deposit formulation in anterior cavity</td>
</tr>
<tr>
<td>Less permeation</td>
<td>Enhance drug permeation, modify the membrane</td>
<td>Permeation enhancer, Prodrugs</td>
</tr>
<tr>
<td>Poor physico-chemical properties of drug</td>
<td>Improve it</td>
<td>Prodrugs, cosolvents.</td>
</tr>
</tbody>
</table>

Advancement in Nasal Dosage form \cite{13}

1. Nasal Drops: Nasal drops are one of the most simple and convenient systems developed for nasal delivery. Due to ease of self-administration it is becoming more popular. The main disadvantage of this system is the lack of dose precision.

2. Nasal Sprays: Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose. These are preferred over powder sprays because powder results in mucosal irritation.

3. Nasal Powders: These formulations are developed when there is problem with stability. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug.

4. Nasal Gels: The nasal gel showed growing interest due to reduction of post-nasal drip, high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption.

5. Nasal Inserts: Nasal inserts are novel, bioadhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to imbibe nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.

Novel Nasal Drug Formulations \cite{13,14}

This includes the following formulations enlisted as;

- Nanoparticle - e.g. Vaccine
- Liposomes - e.g. Demopressin
- Microsphere - e.g. Insulin
Microemulsion - e.g. Zolmitriptan

Available Nasal Products

Table 3: List Of Available Nasal Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Supplier</th>
<th>Main indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>Beconase</td>
<td>GlaxoSmithKline</td>
<td>Rhinosinusitis</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Rhinocort</td>
<td>AstraZeneca</td>
<td>Rhinosinusitis</td>
</tr>
<tr>
<td>Buserelin</td>
<td>Suprefact</td>
<td>Sanofi-Aventis</td>
<td>Treatment of prostate cancer</td>
</tr>
<tr>
<td>Cynocobalamin</td>
<td>Nascobal</td>
<td>Strativa pharma</td>
<td>Vit B12 deficiency</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Desmospray</td>
<td>Ferring pharma.</td>
<td>Control of dehydration in diabetes insipidus</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Aerodiol</td>
<td>Servier lab.</td>
<td>HRT</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Instany</td>
<td>Nycomed Pharma</td>
<td>Pain management</td>
</tr>
<tr>
<td>Levocabastin</td>
<td>Livostin</td>
<td>Jansen-Cilag</td>
<td>Rhinosinusitis</td>
</tr>
<tr>
<td>Mometazone</td>
<td>Nasonex</td>
<td>Scharing-plough</td>
<td>Scharing-plough</td>
</tr>
<tr>
<td>Mupirocine</td>
<td>Bactroban</td>
<td>GlaxoSmithKline</td>
<td>Eradication of nasal Staphylococci</td>
</tr>
</tbody>
</table>

Microsphere Based Drug Delivery System

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 μm. They are made of polymeric, waxy or other protective materials i.e. biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatine; the synthetic polymers include polylactic acid and polyglycolic acid. Microspheres are small and have large surface to volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important often dictating their activity. \[^{15,16,26}\]

Microparticles are of two types

1. **Microcapsules** :- The entrapped substance is completely surrounded by a distinct capsule wall.

2. **Microspheres** :- The entrapped substance is dispersed throughout the microsphere.
Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. However, the success of these microspheres is limited due to the short residence time at the site of absorption. It would therefore advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres.\textsuperscript{[15,26]}

### General Method of Preparation of Microspheres\textsuperscript{[17]}

The microspheres can be prepared by using any of the several techniques enlisted following. But the choice of the technique mainly depends on the nature of the polymer used for the intended use and the duration of therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below,

A. The particle size requirements.
B. The drug or the protein should not be adversely affected by the process.
C. Reproducibility of the release profile and the method.
D. No stability problem.
E. There should be no toxic products associated with final product.
F. General Methods are:
   1. Single emulsion technique
   2. Polymerization techniques
   3. Normal polymerization
   4. Interfacial polymerization
5. Phase separation / coacervation techniques
6. Spray drying and spray congealing
7. Solvent evaporation
8. Chemical and thermal cross-linking

Freeze drying Loading of Drug \cite{17}

The active components are loaded over the microspheres principally using two methods i.e. during the preparation of the microsphere or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and Nasal in Situ Gel: A Novel Drug Delivery System surface adsorption. Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross-linking agent, surfactant, stabilizers, etc.), heat of polymerization, agitation intensity, etc. Percent incorporation in preformed microspheres is relatively less but the major advantage of loading method being there is no effect of process variables. The loading is carried out in pre-formed microspheres by incubating them with high concentration of the drug in a suitable solvent.\cite{17} The drug in these microspheres is loaded via penetration or diffusion of the drug through the pores in the microspheres as well as adsorption on their surface. The solvent is then removed, leaving drug loaded microspheres. Drug Release Kinetics 25 Release of the active constituents is an important consideration in case of microspheres. Many theoretically possible mechanisms may be considered for the release of drug from the microparticles. \cite{18}

1. Liberation due to polymer erosion or degradation.
2. Self-diffusion through the pores.
3. Release from the surface of the polymer.
4. Pulsed delivery initiated by the application of an oscillating or sonic field.

In most of the cases, a combination of more than one mechanism for drug release may operate. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The drug could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second pore diffusion mechanism and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuses into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the
membrane. The burst effect is mainly controlled by three factors, viz. the macromolecule: polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. The pore diffusion method is named so because the dispersed protein/drug creates a water filled pore network through which the active principle diffuses out in a controlled manner. In case of the biodegradable polymers, the release is controlled by both the erosion as well as diffusion process. The polymer erosion i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix. This plasticization of the matrix finally leads to the cleavage of the hydrolytic bonds. The cleavage of the bond is also facilitated by the presence of the enzyme (lysozymes) in the surroundings. The erosion of the polymer may be either surface or bulk leading to the rapid release of the drug/active compound. The rate and extent of water uptake thereof determines release profile of the system and depends on type of the polymer, porosity of the polymer matrix, protein/drug loading, etc. [18]

**Evaluation of Formulation** [19,20]

1) **Clarity:** The clarity of in situ gel was examined by visually under dark background.[24]

2) **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. For determining the pH of the formulation of nasal in situ gel, taken 1 ml quantity of each formulation transferred into a different beaker and diluted it with distilled water up to 25 ml and then pH of each formulation was determined by using pH meter (model no CL 54).

3) **Drug content:** 1 ml of formulation was taken in 10 ml volumetric flask and then it was diluted with 10 ml of distilled water then volume adjusted to 10 ml, 1 ml from this solution again diluted with distilled water up to 10 ml. After this absorbance of prepared solution was measured at particular wavelength of the drug by using U.V. visible spectrophotometer.

4) **Viscosity measurement:** Viscosity of nasal in situ gel was measured by using (cone and plate viscometer) programmable Brookfield DV-II model viscometer. The viscometer was equipped with the temperature control unit and the sample were equilibrated for 10 min before the measurement. The viscosity of nasal in situ gel were recorded at various temperature from 4°C to 40 °C respectively against increasing the shear rate.

5) **Measurement of gelation temperature:** 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 in situ 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.

6) Determination Of Mucoadhesive Strength: Mucoadhesive strength is known as the
force to detach the in situ gel formulation from nasal mucosal tissue, for determining the
mucoadhesive strength we use modified special chemical balance. A small section of
nasal mucosa of goat was cut & tied or fixed on 2 glass vial with the help of rubber band
or thread and stored it at 37°C ±2°C for 10 minute and then 50 mg of gel was placed on
first vial and it placed below the height adjustable balance, while on another hand second
vial was fixed in inverted position to the underside of the same balance after this height
both vial were adjusted and come in intimate contact for 5 minute to ensure the contact
between nasal mucosal tissue and the in situ gel formulation. Then weight was put off on
the other side of balance, until vials got detached, it expressed as the strength or stress in
dyne/cm². [21,22,27]

A. Stress is calculated by the formula

Detachment Stress (dyne/cm²) = M × G ÷ A

Where,

M = weight 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

Franz having capacity 2.4 diameter and 15 ml diffusion cell was used for in vitro diffusion study of in situ gel. Dialysis (22 μm pore size) or cellophane membrane (12000-18000 mol wt) with diffusion area 8 cm² used. 60 ml of phosphate buffer (6.4 - 6.6pH) was prepared and membrane was soaked with phosphate buffer (6.4- 6.6 pH), after this temperature was maintained at 37°C±0.5°C, after this phosphate buffer placed into the acceptor chamber and gel containing drug equivalent to 10 mg was placed in donor chamber, at predetermined time point, 1ml sample was withdrawn from acceptor chamber and then replaced the sample volume with equal amount of phosphate buffer after each sampling process, for a period of 300 minute, after each sampling, the samples were suitably diluted and measured spectrophotometrically at specific wavelength of drug. The concentration of drug was determined with the help of previous calibration curve. [23,27]

In Vitro Permeation Study of in Situ Gel

To check permeation of drug and capacity of permeation enhancer which was added in formulation. Fresh nasal tissue section of goat obtains from slaughter house. Tissue was inserted in the diffusion cell. Gel containing drug equivalent to 10 mg was placed in donor chamber, at predetermined time point, 1ml sample was withdrawn from acceptor chamber and replacing the sampled volume with same amount of phosphate buffer, for a period of 300

Figure 3: A Modified Balance, B Weights, C Glass Vial, E, F Membrane, G Height Adjustable Pan. [27]
minute, after each sampling, the sample were suitably diluted and measured spectrophotometrically at specific wavelength of drug. [24,25,27]

B. Permeability Coefficient Calculated from the Slope of the Graph

\[ P = \text{Slope} \times \frac{V_d}{S} \]

Vd = volume of the donor solution
S = surface area of tissue
P = permeability coefficient.

D.S.C (Differential Scanning Calorimetry), X Ray Diffraction and FTIR (Fourier Transform Infra –Red Spectroscopy) Studies: used for drug and polymer interaction, compatibility and to check matrix formation [25].

REFERENCES


