ABSTRACT

Recently, controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. Various biodegradable polymers that are used for the formulation of in situ gels include gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly(DLlactic acid), poly(DL-lactide-co-glycolide) and poly-caprolactone. Mainly in situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. The in situ gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. From a manufacturing point of view, the production of such devices is less complex and thus lowers the investment and manufacturing cost.

KEYWORDS: Biodegradable polymers, controlled release, in situ gels, sustained release.
INTRODUCTION

The bioavailability of the drug and hence its therapeutic effectiveness are often influenced by the route selected for administration. For a medication to achieve its maximum efficacy a drug should be administered easily and it should be capable of being absorbed efficiently so that enhanced bioavailability can be accomplished. Patient compliance with the drug regimen depends on route selected, frequency of administration, the type and size of medication and condition being treated. For many systemically acting drugs oral route has been preferred route for the administration. However when administered by oral route, many therapeutic agents have been reportedly subjected to extensive presystemic elimination by gastrointestinal elimination and/or hepatic metabolism. Results of low systemic bioavailability, short duration of therapeutic activity, or formation of inactive metabolites have been reported.\textsuperscript{[1,4]}

Delivery of drug via the absorptive mucosa in various easily accessible body cavities, like the ocular, nasal, buccal, rectal and vaginal mucosa, have the advantage of bypassing hepatogastrointestinal first-pass elimination associated with the oral administration. Due to dual biophysical and biochemical nature of these membranes drugs of hydrophilic and lipophilic nature can be readily absorbed. In addition of this mucosal membranes may also be useful sites with good accessibility for easy application of drug delivery systems, especially for those with bioadhesive properties. With an attempt to give a controlled of drug, to overcome the problems of the oral drug delivery, and to increase the half life of the drugs new and novel mucosal drug delivery system were investigated. Each of these routes has its own unique pharmaceutical utility characteristics.

There are situations in which a systemic medication is required but the parenteral administration may be either undesirable or impractical, e.g. chronic disease state. The oral administration may not be possible due to some potential systemic bioavailability problems. Research in formulation development of mucosal drug delivery system is directed to investigate the permeability characteristics of weakly lipophilic drugs through the water channels of jejunum, rectum and nose. These studies have revealed that all the three routes show better permeability of drugs due to sufficiently large pore size.
Table 1: Mucosal pathway to by-pass the Hepatic-Gastrointestinal elimination

<table>
<thead>
<tr>
<th>Mucosal Delivery</th>
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| Ocular delivery | ➔ Nasolacrimal drainage system ➔ Nose  
| Nasal delivery  | ➔ Nasal Epithelium  
| Pulmonary delivery | ➔ Respiratory Membrane  
| Buccal, Sublingual, | ➔ Gingual Oral mucosa  
| Rectal Delivery | ➔ Rectal Mucosa  
| Vaginal Delivery | ➔ Vaginal Mucosa  

These systems have potential to revolutionize the method of systemic medication. Mucosal membranes, particularly the nasal mucosa also offer the potential for a rapid absorption of the drugs useful in emergency situation. Historically, the use of nasal route for the administration of drugs has received the attention of mankind since ancient time. Intranasal route of drug administration termed ‘NASAYA KARMA’ has been as accepted form of treatment in the Ayurvedic system of Indian medicine.

Nasya (nasal medication) is especially designed for the treatment of disease of pars above the shoulders. Nose is the gateway of the head. Nasal medication cures the disease spreading through the nasal epithelium. Nasya medication is namely virechana is required in headache, loss of movement of head, epilepsy and skin diseases. Indians have used psychotropic drugs and hallucinogens in the form of snuff. For many years drugs have been administered intranasally for their local effect over the nasal mucosa e.g. antihistamines, decongestant, vasoconstrictors, antibiotics etc.

In recent years, many drugs have been shown to achieve better systemic availability by self-medication through nasal route than by oral administration. Thus, there has been growing recognition that, the benefits of intravenous infusion can be closely duplicated without its hazards by using the nasal route as a port of drug administration for vaccines, hormones, peptides and certain other drugs. This route provides a continuous drug delivery into the systemic circulation with similar rapidity. It offers several advantages over other modes of drug administration. Two categories of therapeutics delivered by nasal route are available in international pharmaceutical market. The first comprises of low molecular weight and hydrophobic for local disorder such as antibiotics, topical steroids and decongestants, while second category comprises of few drugs which have sufficient nasal absorption to exhibit etc.
Features of Nasal Route

Systemic nasal absorption of drug is a new attractive alternative to parenteral drug therapy, as it offers numerous advantages such as:

- The nasal cavity provides a large surface area for drug deposition and absorption.
- The nasal epithelium is thin, porous and highly vascularised. This is responsible for the high degree of absorption and rapid transport of substances into the systemic circulation for initiation of therapeutic action.
- Unlike the skin nasal mucosa, is not constructed from the keratinized stratum corneum. The sub-epithelial layer of the nasal mucosa with numerous microvilli is highly vascularized with large and fenestrated capillaries facilitating rapid absorption with low metabolism of drugs.
- Rate and extent of absorption and plasma concentration versus time profiles are relatively comparable to that obtained by intravenous medication.
- Nasal route avoiding the first pass metabolic effect because absorbed substances are transported directly into the systemic circulation.
- With the help of nasal route drug can be targeted into the CNS bypassing the tight blood brain barrier.
- The enzymatic activity in the nasal cavity is very low as compare to the liver and GIT, which make this route safe for the delivery of some proteins and peptidal drugs.
- Better drug levels can be achieved compared to intravenous administration. The nose is amenable to self medication which lowers the cost of therapy as well as improves patient compliance. The risk of over dosage is low.
- Suitable for drug treatment in long term therapy.
- Painful condition which is associated with injection form can be avoided by using a nasal administration.

Disadvantage of Nasal Drug Delivery

There are risks of local side effects and irreversible damage of cilia on nasal mucosa, both from the drug and from the constituents those are added to the formulation for nasal drug administration.

- Only a small amount of the formulation can be administered intranasaly because large quantity will create problem during the normal functioning of the nose.
• It could also lead to irreproducibility of the dosing regimen which may be arised due to drainage of the solution in the nasopharynx or expulsion of the dose due to sneezing.
• Nasal route is not appropriate for the administration of hydrophilic compounds and large molecules.
• In some pathological condition like common cold and rhinitis drug administration is a quite difficult.
• Drug absorption and permeability of the different part of the nasal cavity is different so the prediction of the affect of formulation is difficult.
• There could be a mechanical loss of dosage form into the other parts of the respiratory tract like lungs, because of improper technique of administration.
• After the administration of the formulation toxicity and irritability can produce which make this route unacceptable.
• Low bioavailability results from mucocilliary clearance, enzymatic degradation and metabolism at mucosal site.[7]

Many factors affect the systemic bioavailability of nasally administered drugs. These factors can be attributed to the physicochemical properties of the drug, the anatomical and physiological properties of the nasal passage and the type and characteristics of selected nasal drug delivery system. These play significant role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are as follows

A) Physicochemical properties of drugs.
• Molecular size
• Lipophilicity.
• Enzymatic degradation in nasal cavity.
• Solubility and dissolution rate.

B) Nasal physiological factors
• Membrane permeability
• Environmental pH
• Mucociliary clearance
• Cold and Rhinitis
C) Effect of drug formulation

- Viscosity
- pH
- Pharmaceutical form
- Pharmaceutical excipients

1) Physicochemical properties of drug

Molecular size
The molecular size of the drug influence absorption of the drug through the nasal route. The lipophilic drugs have direct relationship between the MW and drug permeation whereas watersoluble compounds depict an inverse relationship. The rate of permeation is highly sensitive to molecular size for compounds with MW ≥ 300 Daltons (Corbo et al., 1990).

Lipophilicity
On increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that these mucosa are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes.

Enzymatic degradation in nasal cavity
In case of peptides and proteins are having low bioavailability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier.

2) Nasal physiological factors

Membrane permeability
Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts.

Environmental pH
The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show
that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form.

**Mucociliary clearance**
Mucociliary clearance is one of the functions of the upper respiratory tract is to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. When such materials adhere to, or dissolve in, the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract.

**Cold, Rhinitis**
Rhinitis is a most frequently associated common disease, it influence the bioavailability of the drug. It is mainly classified into allergic rhinitis and common cold, the symptoms are hyper-secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants.

3) **Effect of drug formulation**
Factors that affect the delivery of drug across nasal mucosa such as surfactants, dose pH, osmolarity, viscosity, particle size and nasal clearance, drug structure can be used to advantage to improve absorption.

**Viscosity**
The increased viscosity of a formulation increases the drug absorption as it increases the contact time of the drug with the nasal mucosa. The increased viscosity reduces the mucociliary beatings and hence the drug permeability is also increased. However, sometimes, enhancing formulation viscosity does not increase the drug absorption. In a study performed to evaluate the influence of formulation viscosity on the retention time of metoclopramide hydrochloride in nasal cavity and on its absorption, it was found that the residence time enhanced as viscosity increased and the drug absorption reduced. This observation has been attributed to a decrease in the drug diffusion from the formulation pH.

The extent of nasal absorption depends on the pKa of drug and pH at the absorption site, which depends on the pH of formulation. The pH of formulation must be selected to provide maximal drug stability and if possible should be assured the greatest quantity of non-ionized drug species. However, the pH of formulation can induce nasal mucosa irritation and, hence, it should be similar to that found on human nasal mucosa i.e. 5.0-6.5.
Excipients
Solubilizers, buffer components, antioxidants, preservatives, humectants, gelling/viscosifying agents, and flavoring or taste masking agents are some of the most usual excipients used in the nasal formulations.

TYPES OF INTRANASAL DRUG DELIVERY
The drug delivery through the nasal route can be divided into the following:
- Local delivery
- Systemic delivery
- Delivery via vaccines
- Nose to brain drug delivery

Local delivery
It is generally used for the treatment of conditions like the allergy, sinusitis, nasal congestion, infections. The drugs most commonly used are the antihistaminics and the corticosteroids and nasal decongestants. It allows a rapid symptom relief, it is effective in low drug doses, minimizing the potential of systemic toxic effects. Recently, a topical antibiotherapy has been utilized for the treatment of chronic rhinosinusitis.

Systemic delivery
The intranasal administration is a very effective way to systemically delivery of drugs as an alternative to oral and intravascular routes. The nasal route has been seen to be advantageous over both the oral and the parenteral routes. Some recent examples include analgesics, cardiovascular drugs like propranolol and carvedilol, hormones such as progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac. Zolmitriptan and sumatriptan for the treatment of migraine are already available in the market.\(^{[5]}\)

Delivery via vaccines
Nasal vaccination is a promising alternative to the parenteral route, because it is able to enhance the systemic levels of specific immunoglobulin G and nasal secretory immunoglobulin. The systemic and local immunological responses are mainly mediated by the nasal associated lymphoid tissue (NALT) composed of agglomerates of dendritic cells, T-cells and B-cells involved in immune responses. Examples of the intranasal vaccines include vaccines for influenza A and B virus, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus.
Nose to brain drug delivery
The brain is a delicate organ with many vital functions and it is isolated and protected from the outside environment by the blood brain barrier. Over the last few years, intranasal route has emerged as a promising approach for brain delivery of drugs. The delivery from the nose to the CNS may occur via olfactory neuroepithelium and may involve paracellular, transcellular or neuronal transport. Drug delivery into CNS through intranasal route has been reported in the case of Alzheimer’s disease, brain tumours, epilepsy.

Formulation development research in nasal drug administration
Most of the over the counter nasal preparation are formulated as solution, to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area. The nasal residence time of such formulation is short (3-20 min) and exhibit high inter individual variability. This route provides fast peak levels in circulation.

Large number of drugs has been evaluated for systemic bioavailability after transnasal administration in experimental animal models. Transnasal administration of drugs in diverse dosage forms such as sprays, powders, and microspheres has been attempted for improved residence and bioavailability.

The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Some of these delivery systems and their important features are summarized below:

Nasal Drops
Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

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 from 25 to 200 μm. The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.
Nasal Powder
This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system.

Nasal Gels
Some of challenges associated with the nasal delivery of the drug can be solved by the utilization of combination of mucoadhesive and thermoreversible polymers in the formulation. Clearance of the drug can be controlled by the use of mucoadhesivepolymer. These polymers adhere on the nasal epithelia and increase the resident time and possibly enhances drug absorption. This mechanism may not work for some compounds especially protein molecules. On the other hand drainage of the solution can be controlled by the thermoreversible polymers in the formulation. The special feature of thermoreversible polymers is that they are in solution form before the administration but after convert into gel by the nasal cavity temperature.$^9$

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post-nasal drip due to 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 to mucosa for better absorption.

Mucoadhesive polymeric nasal gel contains the mucoadhesive agent which is responsible for the bioadhesion with the nasal mucosa. There are several polymers are available now which serve as a mucoadhesive agents such ashydroxypropylcellulose, chitosan , carbopol, arboxymethylcellulose, sodium alginate, hyaluronic acid and polyacrylic acid.

Gels
A gel is a soft, solid or solid like material which consist of atleas two component, one of which is a liquid present in abundance.
Polymer gels are produced through the cross-linking of polymer chains by the formation of either covalent bonds (chemical cross-linking) or non-covalent bonds (physical cross-linking). Non-covalent bonds, can for example be hydrogen bonds and ion-bridge, the latter being common in the gelation of polyelectrolytes.

The term hydrogel has been extended. Since its introduction by Thomas Graham, and it now includes three-dimensional cross-linked polymeric network that are capable of swelling in aqueous media.

Gels or jellies are semisolid systems consisting of suspensions of small inorganic particles or large organic molecules interpenetrated by a liquid. Reversible gels refer to those that have the capacity to make, break, and modify the bonds responsible for holding the network together. Gels that do not have this capability because they are held together by covalent bonds are termed permanent gels.\textsuperscript{10,11}

**Principle involved in in-situ gelling**

The principle involving the in situ gelling of solid nasal formulations is that the nasal formulations imbibe the nasal fluid after administration and forms gel in the nasal cavity. The avoidance of foreign body sensation is an advantage in the case of nasal gels. The bioadhesive properties of the gels help in keeping the gel and mucosa intact which also acts as a release controlling matrix system. This helps in the sustained delivery of drugs. In the nose the mucus layer comes and goes around the cilia, forward in the propulsion phase, backward in the preparatory phase. At the propulsion phase, cilia extremity scrapes the upper layer of mucus penetrating it almost 0.5mm. Ciliary activity zones then occur at various intervals. Cilia situated backward helps to remove any obstacle if there is any interference in the propulsion phase. After the formation of gel, dissolution occurs and or the mucociliary removal towards the nasopharynx occurs. Therefore there is no need to remove the dosage form after it has been depleted of drug.\textsuperscript{13,14}
Polymers used in thermoreversible in situ formulations

1. Pluronics or Poloxamers

These are a class of thermoreversible gels that have the capacity to make, break and modify the bonds responsible for holding the network together. There are different classes of Pluronics (pluronic F-127, F-188 etc). Their thermoreversible property make them useful as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes. The potential use of PF-127 as an artificial skin has also been reported. Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene polyoxypropylene copolymers in a concentration ranging from 20-30%. These polymers are produced by condensation of ethylene oxide and propylene oxide. These are white, waxy, free flowing granules that are practically odorless and tasteless. Reverse thermal gelation and low toxicity have been the basis of research into the use of PF-127 as a possible drug delivery system in man.[16-19] It has been considered for topical delivery of lidocaine, anti cancer agents and for the covering of burnt wounds. Its use in ophthalmic purpose was also studied using pilocarpine as model drug and PF-127 as vehicle. Finally it is also studied as a potential vehicle for injectables by both the intramuscular and subcutaneous routes. The aqueous solutions of Poloxamer are stable in the presence of acids, alkalis and metal ions. Commonly used Poloxamers include the 188(F-68 grade), 237(F-87 grade), 338(F-108 grade) and 407(F-127 grade) which are freely soluble in water. The flake form is designated as “F”. Of all these PF-127 has a good solubilizing capacity, low toxicity and is considered as a good carrier for drug delivery systems.[21-24] PF-127 is more soluble in cold water than in hot water as a result of increased salvation and hydrogen bonding at low temperatures. These Poloxamers have the reversible property of being gel upon warming to room temperature and convert back to liquid when refrigerated (4-50C).[20]
Figure 6: Chemical structure of Pluronic F-127 (a) ethylene oxide portion (b) propylene oxide portion.

Hydroxy propyl methyl cellulose (HPMC)\textsuperscript{41}, Methyl cellulose\textsuperscript{42}, Poly-(N-isopropylacrylamide)\textsuperscript{25-27} are the other thermoreversible polymers which can be used as a carrier in the delivery of various drugs.

Following considerations must be kept in mind while selecting a thermoreversible polymer for nasal administration:\textsuperscript{28}

- Quick transition from liquid to solid upon temperature change: this keeps the gel to stay at the site.
- Prevent the wastage of dosage form from the applied site.
- Solid- to- gel state reversible property of polymer may be adjusted from temporary to permanent by changing its chemical composition.
- Increase drug concentration at the site of deposition.

2. Carbopol

They are very high molecular weight polymers of acrylic acid and are used mainly in liquid or semisolid pharmaceutical formulations such as gels, suspensions and emulsions, as a thickening and viscosity agent in order to modify the flow characteristics.\textsuperscript{28} They are also used for mucoadhesive properties and a relevant amount of work has been done on the bioadhesive potential of carbopol polymers. Carbopol are used in formulations for ophthalmic, rectal, buccal, nasal, intestinal, vaginal and topical preparations. Carbopol gels are prepared by the dispersion of polymers in water. In which it swells upto1000 times the original volume (BF Goodrich handbook) and neutralizes the system. It permits the ionization of the carboxylic groups and as a result strong gel forms.\textsuperscript{29}

3. Chitosan

Chitosan is a biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible Ph dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to
the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.[9-32]

4. Gellan gum[29-32]
Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. The formulation consisted of gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in Int. J. Pharm. Sci. Rev. Res., 24(1), Jan – Feb 2014; nº 01, 1-7 ISSN 0976 – 044X

International Journal of Pharmaceutical Sciences Review and Research
Available online at www.globalresearchonline.net 5 situ. In situ gelling gellan formulation as vehicle for oral delivery of theophylline is reported.[32]

5. Xanthan gum
Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β- D-glucose residues) and a trisaccharide side chain of β-D-mannose- β-D-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain. [32]

6. Alginic acid
It is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages. The proportion of each block and
the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of di and trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the \(\alpha\)-L-glucuronic acid blocks of the alginate chain. Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favorable biological properties such as biodegradability and nontoxicity. A prolonged precorneal residence of formulations containing alginic acid was looked for, not only based on its ability to gel in the eye, but also because of its mucoadhesive properties.\[33-34\]

**Table 3: Some nasal mucoadhesive delivery systems**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mucoadhesive polymer</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metochlopramide Hydrochloride</td>
<td>Poloxamer407/Polyethylene</td>
<td>Gel</td>
</tr>
<tr>
<td>Metochlopramide Hydrochloride</td>
<td>Carbopol 981 Solution, glycol Gel</td>
<td>Powder</td>
</tr>
</tbody>
</table>

**Evaluation of in situ gels**

**In vitro nasal permeation studies**

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.\[35\]

**In Vivo Nasal Absorption studies**

A number of animal models are used for the in-vivo studies; these include the rat model, rabbit model, dog model, sheep model, monkey model.

**Gelation temperature**

It is defined as the temperature at which the liquid phase makes a transition to gel, and is determined by placing a specific quantity of the formulation into a transparent vial containing a magnetic bar. The vial was heated at a constant rate. The gelation temperature was measured when the magnetic bar stops.\[36\]

**Gel strength**

It is evaluated using a rheometer. Depending on the mechanism of gelling of the gelling agent used a specific amount of the gel is placed in a beaker and is raised at a certain rate so pushing a probe slowly through the gel. The changes in the load of the probe can be measured as a function of depth of immersion of the probe below the gel surface.\[37\]
Drugs those are suitable to be administered by nasal route

The intra nasal administration is a promising route for the administration of systemically acting drugs with poor bioavailability. Antimigraine drugs, peptide drugs (hormone treatments), anesthetics, anti emetics, vasopressin, corticosteroids, sedatives, narcotics and a number of drugs can be administered by this route.

Classification of gels.

Gels are generally classified as a two-phase system, if the particle size of the dispersed phase is large; or as single phase gels, when the organic macromolecules are uniformly distributed throughout a liquid such that no apparent boundaries exist between the dispersed macromolecules and the liquid. PF-127 is included in the group of hydrogels. One of the main characteristics of hydrogels is that they contain ingredients that are dispersible as colloids or are water-soluble.

CONCLUSION

In a nut shell, the advantages of intranasal delivery are numerous and very importantly it is rapid and non-invasive. It reduces systemic exposure and thus reduces the side effects. It also bypasses the BBB and delivers the drug directly into the CNS. It acts as an alternative to parenteral and oral route for delivery of some drugs. Taking into consideration the current research interest in nasal delivery and positive outcomes from the clinical trials throughout the world it wont be wrong to expect a wide range of nasal products reaching the market in the near future. However, still some research needs to be conducted in delivery of peptide and protein and vaccines through nasal delivery and delivery of drug from nose to brain.

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