ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 02, pp.18763-18769, February, 2018

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

IN-SITU GEL FOR NASAL DRUG DELIVERY

***Mayuri M. Ban, Vijay R. Chakote, Gunesh N. Dhembre, Jeevan R. Rajguru and Deepak A. Joshi**

Dept. of Pharmaceutics, S.V.P College of Pharmacy Hatta, Hingoli – 431705
Maharashtra, India

ARTICLE INFO

Article History:
Received 25th November, 2017
Received in revised form
11th December, 2017
Accepted 19th January, 2018
Published online 28th February, 2018

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

ABSTRACT

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

Citation: Mayuri M. Ban, Vijay R. Chakote, Gunesh N. Dhembre, Jeevan R. Rajguru and Deepak A. Joshi, 2018. "In-situ Gel For Nasal Drug Delivery", *International Journal of Development Research*, 8, (02), 18763-18769.

INTRODUCTION

(Pires *et al*., 2009; Dressman *et al*., 2008; Shojaei, 1998; Ugwoke *et al*., 2005) Oral drug delivery is the most desirable, preferred and convenient route for the administration of a drug, whenever systemic effects are intended, due to ease of manufacture and administration. However, low oral bioavailability of some actives due to extensive hepatic metabolism and gastrointestinal degradation has prompted the search for more effective routes for their systemic delivery. Transmucosal routes of drug delivery (the mucosal linings of the nasal, rectal, vaginal and buccal cavity), parenteral route and transdermal route offer distinct advantages over per-oral administration.

Corresponding author:* **Mayuri M. Ban,
Dept. of Pharmaceutics, S.V.P College of Pharmacy Hatta, Hingoli – 431705, Maharashtra, India.

These include possible bypass of first-pass effect, avoidance of hence small dose of a particular drug is required. Reduction in dose will diminish the side effects and ultimately reduce the treatment cost. While parenteral route is associated with pain at the site of injection, less patient compliance and is inconvenient for long term therapy, the transdermal route on the other hand, though successfully exploited for delivery of certain drugs is limited in its use due to poor permeability of the skin to many drugs. The transmucosal routes, vaginal and rectal routes are less preferred as these routes cause irritation and are less patient compliant. In buccal route, the drugs with unpleasant taste may present problem of acceptability. Thus, intranasal drug delivery can be visualized as the promising route for administration of drugs as it has the potential to overcome some major limitations associated with the above listed routes. It is an attractive approach for the systemic delivery of drugs because concentration time profile of drugs

achieved after nasal administration is often similar to that obtained after intravenous administration, with resultant rapid onset of pharmacological activity. In addition, intranasal delivery provides a convenient route for the delivery of drugs to central nervous system (CNS) as well as for the products with local activity. Intranasal administration offers several practical advantages from the patient's point of view (rapid onset of action, non invasiveness, essentially painless, ease of delivery, favorable tolerability profile, improved patient compliance, ease of convenience, self-medication) and pharmaceutical industry viewpoint (no need of sterilization of nasal preparations). Hence, if the intrinsic value of intranasal route to overcome patient compliance is augmented with its pharmacokinetic advantages, it appears to be an appropriate route for the treatment of not only acute or chronic nasal diseases, but also for systemic effects.

The richly supplied vascular nature of the nasal mucosa and high drug permeation rate makes the nasal route of administration attractive for many drugs, including small molecular weight polar drugs, proteins and peptides. Nasal route is also utilized in the delivery of macromolecules like vaccines and DNA. In addition, absorption of drug at the olfactory region of the nose provides a potential for a pharmaceutical compound to be available to the CNS. Intranasal delivery has also become an alternative to invasive delivery methods like intra-cerebroventricular or intra-parenchymal injections to bypass the blood--brain barrier (BBB) and rapidly target therapeutics directly to the CNS by utilizing pathways along olfactory and trigeminal nerves innervating the nasal passage. Intranasal administration rapidly delivers the drug directly from the nasal mucosa to the brain and spinal cord with the aim of treating CNS disorders by minimizing systemic exposure.

Mechanism of drug absorption by nasal route (Behl *et al*., 1998; Verma *et al*., 2010; Hussain, 1998)

The nasal absorption of drugs for systemic or CNS effect occurs when it passes through the mucus layer and epithelial membrane before reaching the blood circulation or passes directly to the CNS. For the systemic effect, absorption of drug is considered to take place in the respiratory region consisting of turbinates and part of the nasal septum. The olfactory region, next to respiratory region, is the foremost site from where drug can be absorbed directly into the brain for the CNS effects. When drug is given intranasally, it can directly reach the brain either by direct transport from olfactory region to the brain or from blood (systemic circulation) to the brain or through trigeminal neural pathway by which drug partly travels from the nasal cavity to the cerebrospinal fluid (CSF).

Consequently, the olfactory region of nasal mucosa that provides a direct connection between nose and brain can be exploited for targeting of drug molecules acting on CNS in conditions like Alzheimer's disease, Parkinson's disease, depression, migraine, schizophrenia, epilepsy, brain tumors, psychosis and pain. The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small and uncharged particles easily pass through the mucus layer. However, large or charged particle may find it difficult to cross the mucus layer. Mucin, which is the principal protein in the mucus, has the potential to bind to solutes and thus hinders the diffusion of drugs. After a drug's passage through the mucus, there are several mechanisms for absorption through the mucosa. These are discussed below.

Paracellular route

Paracellular route is also known as aqueous route of transport. This route is slow and passive which involves the transport of drug through the epithelium via gaps or pores between the tight junctions. Tight junctions are dynamic structures localized between the cells, which open and close to a certain extent, the size of these channels is less than 10 A^0. Hence, avoid the passage of large molecules and is dependent on the molecular weight of the drug with a molecular size cut off of 1000 D. But with the help of permeation enhancers' good bioavailability can be enhanced for drugs having molecular weight at least up to 6000 D. Polar drugs such as alniditan, morphine, sumatriptan, insulin, mannitol, calcitonin and leuprolide are transported through paracellular route and have poor bioavailability when given nasally.

Tran cellular route:

Transcellular route is lipoidal route that is responsible for the transport of lipophilic drugs and shows a rate dependency transport on the lipophilicity of the drugs. It includes efficient concentration-dependent passive diffusion through the interior of the cell, by receptor or carrier mediation and by vesicular transport mechanism. The carriers that mediate transcellular transport in the nasal mucosa includes: organic cation transporters and amino acid transporters. It seems that compounds with a molecular weight higher than 1000 D such as proteins and peptides are transcellularly transported by endocytic processes. Lipophilic drugs such as propanolol, progesterone, pentazocine and fentanyl are also transported transcellularly that demonstrate rapid and efficient absorption when given nasally.

Intranasal formulations and their limitations (Chugh *et al*., 2009; Arora *et al*., 2002)

A myriad of intranasal formulations are available that include nasal drops, solution sprays, suspension sprays, emulsions, powders, ointments, gels, liposomes, microspheres and nanoparticles. These non-mucoadhesive formulations administered in limited volume of 25 -- 200 µl exhibit short residence time due to mucociliary clearance. Consequently, the half-life of clearance for both liquid and powder formulations is of the order of 15 -- 30 min. This is mainly due to the mucus which moves through the nose at a rate of 5 -- 6 mm/min resulting in particle clearance within the nose, about every 12 -- 15 min. This limits the time available for drug absorption from the applied dosage form and results in poor nasal bioavailability. . In order to prevent rapid mucociliary clearance and improve the bioavailability of drugs, there is a persistent need for the development of controlled release delivery system. Mucoadhesive nasal drug delivery systems can be looked on as a viable option that have the capability to adhere to the nasal mucosa, will increase the residence time within the nasal cavity, intensify the contact between the nasal mucosa and the drug, increase the drug concentration at the site of deposition and facilitate drug absorption to enhance bioavailability.

The advantages of in situ nasal gels over other nasal formulations include:

- Reduction in post-nasal drip into the back of the throat and therefore minimization of bad taste problem and loss of drug from the nasal cavity.

- Reduction in anterior leakage of the drug out of the nasal cavity.
- Localization of formulation on the mucosa thereby providing a better chance for the drug to be absorbed.
- Gels can afford the use of soothing agents or emollients which may not be sutaible for solutions, suspensions or powder dosage form so can reduce irritation potential.
- Can be developed for both systemic and local delivery, and vi) precise dose can be administered by the use of metered dose nasal actuator system.

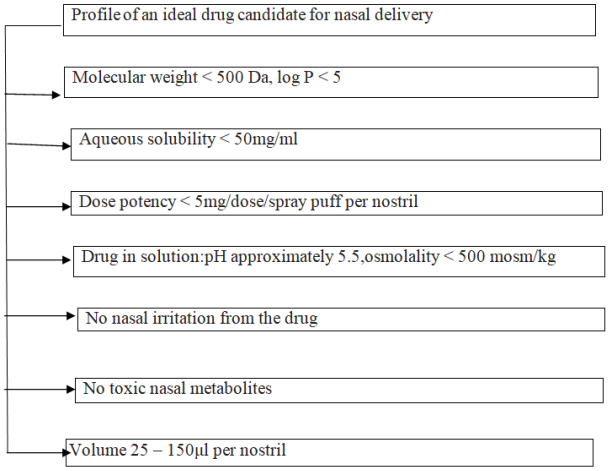

Figure1. Profile of an ideal drug candidate suitable for nasal drug delivery System

Methods of formulation (Shojaei , 1998; Nandgude *et al*., 2008; Behl *et al*., 1998; Verma *et al*., 2010)

In general, two methods are used for the preparation of in situ nasal gel namely:

Cold Method and 2. Hot Method

In cold method, the drug is stirred with sufficient quantity of double distilled water and kept overnight at 4 ^{0}C in a refrigerator. The in situ gelling polymer is added slowly with continuous stirring. The dispersion is then stored in a refrigerator until clear solution is formed and finally volume is adjusted. This method is selected when poloxamer, chitosan or carbopol is used as a gelling polymer. Considering the fact that polymeric dispersion of poloxamer remains as solution at lower temperature and gets converted into gel at higher nasal temperature because the solubility of polypropylene oxide chain of poloxamer decreases at high temperature which results in precipitation or salting out of polymer. Similarly, chitosan also requires low temperature to remain as solution at room temperature, its hydrophobicity increases with increase in temperature.

Hot Method: This method is utilized when gellan gum or pectin is used as a gelling polymer. At higher temperature, gellan chains dissolve in water and assume a random-coil conformation with a high segmental mobility at high temperature and remain as a solution at higher temperature. Sol—gel transition occurs on cooling gellan gum solution in the presence of ions like K+ or Ca2+. Similarly, pectin also requires higher temperature for its demethoxylation, which helps in the formation of solution or dissolving of pectin.

Polymers used for designing triggered systems

Though a range of mucoadhesive polymers with varying capacity are available, the literature predominantly reports the use of six gelling polymers for nasal purpose. These include pectin, carbopol, gellan gum, chitosan, poloxamer and ethyl (hydroxyethyl) cellulose (EHEC). A brief description of mechanism of gel formation of each of them follows in the preceding text.

Pectin

The functionality of pectin is determined by the degree of methoxylation which in turn is the percentage of galacturonic acid (major component of pectin) that is methoxylated. The mechanism of gelation of aqueous solution of pectin with low degree of methoxylation is as follows: the carboxyl groups of pectin backbone interact with Ca2+ and induce the formation of 'egg box' structure.

As explained by Fraeye *et al*., in this 'egg box' model, there is an initial dimerization steps of two homogalacturonic chains by cooperative bridging of parallel facing chains through Ca2+. This is possible due to rigid nature of homogalacturonic chains and binding of first calcium cation by two pectin chains facilitates their alignment with respect to each other, which in turn allows the easier binding of a next calcium ion, and so on along the sequence. The most favorable arrangement is the antiparallel orientation of the two chains, and this initial dimer association is strongly stabilized by hydrogen bonding, in addition to electrostatic interaction. The minimum number of successive non-methoxylated galacturonic acid residues necessary to form a cooperative egg box has been estimated to be 6 -20.

Carbopol

Carbopol shows sol--gel transition in aqueous solutions as the pH is raised above its pKa. The acidic carboxyl groups of the polymer partially dissociate in water and begin to uncoil to produce a flexible coil structure. In acidic conditions, a small proportion of the carboxyl groups present on the polymer dissociate, producing a flexible coil structure. In an alkaline environment, the carboxyl groups ionize, generating negative charges along the polymer backbone. Electrostatic repulsion of the anionic group causes uncoiling and expansion of the molecule which results in polymer swelling and gel formation. Further addition of carbopol thins the gel because the cations screen the carboxyl groups and so the electrostatic repulsion decreases.

Gellan gum

Gellan gum is an anionic exocellular polysaccharide which is completely de-esterified by alkali treatment for commercial use and this deacylated gellan gum has following tetrasaccharide repeat units: (1,3)b-D-glucose, (1,4)b-D-glucuronic acid, (1,4) b-D-glucose, (1,4)a-L-rhamnose, has lower sol—gel transition temperature and stronger gel strength than the native one. The gelation of gellan gum in aqueous solutions involves two steps. The first step is the formation of double helical junction zones by conformation change from random coil and the second step is the aggregation of the double helices to form junction points, which results in gelation by complexation with cations and hydrogen bonding with water.

Divalent cations such as Ca2+, produces strongest gel with low acyl gellan when compared with monovalent cations. In the presence of divalent cations, gelation occurs with the subsequent aggregation of double helices mediated by cations and the sol--gel transition appears at temperatures lower than coil--helix transition. By contrast, divalent cations immediately interact with gellan chains segments as cooling takes place, forming ordered structures at temperatures higher than the coil--helix transition.

Chitosan

Chitosan is a linear polysaccharide which becomes water-soluble after the formation of carboxylate salts, such as formate, acetate, lactate, malate, citrate, glyoxylate, pyruvate, glycolate and ascorbate due to its cationic nature. Due to the presence of nitrogen in the molecular structure, cationicity and capacity to form polyelectrolyte complexes is the unique property of chitosan which is responsible for the in situ gel formation. Many divalent anions such as polyol-phosphate, sulfate, oxalate, molybdate or phosphate are responsible for the gelation of chitosan aqueous solutions. Mostly, b-glycerophosphate is used because itmaintains the chitosan solubility at physiological pH and the temperature-sensitive character of these chitosan. The b-glycerophosphate solution allows rapid hydrogel formation on heating. The b-glycerophosphate addition to chitosan aqueous solution modulates electrostatic and hydrophobic interactions, and hydrogen bonding between chitosan chains, which are the main molecular forces involved in gel formation.

Poloxamer

Poloxamer is commercially available as pluronic and the gelation mechanism (s) of its aqueous solution have been investigated by various techniques. Ultrasonic velocity and dynamic light scattering measurements on the poloxamer 407 solutions indicated that the intrinsic changes in micellar properties, such as aggregation number and micellar symmetry cause aqueous poloxamer solutions to form a gel. It was also concluded that decrease in the critical micelle concentration occur with increasing temperature. In recent studies on aqueous solution of poloxamer done by light-scattering, small-angle X-ray scattering, rheology, small-angle neutron scattering and dielectric behavior measurement, clearly indicated the unimers to micelles transition, and the occurrence of gelation when the micellar volume fraction increased to critical value (0.5) for hard-sphere crystal formation. As the temperature further increased, the aggregation conformation of poloxamer hydrogels changed from spherical micelles closely packed in a cubic lattice into the rod-like micelles packed in a hexagonal system, which resulted in decrease of the intermicellar interactions. When the temperature was further increased, the sol to gel transition occurred due to reduction of inter-micellar interactions caused by partial dehydration of the polyethylene oxide blocks.

Ethyl (hydroxyethyl) cellulose

EHEC is a non-ionic amphiphilic polysaccharide which consists of unevenly distribution of both hydrophilic and hydrophobic units in the polymer backbone. It has been reported that the EHEC solutions completely changed their thermal behavior with the addition of an ionic surfactant, like cetyl triammonium bromide and sodium dodecyl sulfate.

In the presence of ionic surfactants, the surfactant is bound to the polymer and this endows an apparent polyelectrolyte character to the originally non-ionic character. Small-angle neutron scattering demonstrated that there is a temperature induced association and gelation of semi-dilute solutions of EHEC in the presence of an ionic surfactant. In the presence of ionic surfactants, it is further expected that the formation of mixed micelles between the hydrophobic groups in EHEC and the amphiphilic surfactants creates the conditions necessary to induce a sol--gel transition as the temperature is increased.

Approaches of in situ gelation

Ideally, an in situ gelling system should be a low viscosity solution that allows easy syringeability and no difficulties are envisaged during its administration by the patient. When instilled into the nose as a liquid drop it should readily undergo phase transition to form gel that is strong enough, prevents nasal mucociliary clearance and resides in the nasal cavity for prolonged period of time. Thus, in situ gel may be able to release the drug in a sustained manner, will assist in enhancing the bioavailability and reduce the need for frequent administration to improve patient compliance.

Phase transformation may be accomplished by varieties of trigger mechanisms that are discussed below (Chugh et al., 2009; Arora, 2002; Ugwoke, 2005)

Temperature-triggered in situ gel (Behl et al., 1998).

The most important polymer of this category is poloxamer 407 (pluronic F 127) and is widely used in formulation of in situ nasal gel. Chitosan is another thermally triggered polymer used in the formation of in situ nasal gel. Both undergo phase transition at physiological temperature. The choice of a particular hydrogel depends on the therapeutic use and on its intrinsic properties. A mixture of N-[(2-hydroxy-3-trimethylammonium) propyl] 27 chitosan chloride (HTCC) and a,b-glycerophosphate (a,b-GP) was used as a promising mucosal vaccine delivery vehicle which was solution at room temperature and could gelate rapidly at body temperature that prolonged the residence time of H5N1 split antigen in nasal cavity. This system disorganizes ZO-1 protein in nasal epithelial tissue and thus enhances the transepithelial transport via the paracellular routes. The hydrogel also displayed low toxicity to nasal tissue and epithelial cells, though frequently administered in the nose of mice.

Thus, hydrogel can be used as a safe and effective delivery system for nasal immunization. Chaudhari *et al*. developed thermoreversible nasal gel of rizatriptan benzoate containing poloxamer 407 and poloxamer 188 as a gelling polymer and xanthan gum and locust bean gum as a mucoadhesive polymer. Increase in mucoadhesive polymer caused increase in gelling temperature and retarded the release of rizatriptan from the nasal gel formulation. Xanthan gum showed higher retardation than the locust bean gum. In another report on rizatriptan benzoate, Chand *et al*. have also described in situ nasal gel of rizatriptan benzoate containing chitosan and aqueous b-glycerophosphate mixture formulation which served as thermoreversible system. The weakly basic glycerophosphate prevented precipitation of chitosan on increase in pH and facilitated hydrophobic interactions on slight elevation of temperature resulting in thermoreversible systems. Temperature-triggered nasal delivery has also been explored for delivery of macromolecule insulin.

Wu *et al*. prepared thermo-sensitive in situ nasal gel of insulin using quaternized chitosan HTCC, PEG and a,b-GP. Confocal laser scanning microscopic study revealed enhancement in the absorption of fluoresce in isothiocyanate-labeled insulin in the nasal cavity of rat from the in situ gel. The results showed that all the three polymers can be used for nasal drug delivery to improve the absorption of hydrophilic macromolecular drugs. Agrawal *et al*. also developed a thermo-sensitive in situ gel for nasal delivery of insulin by utilizing chitosan and polyvinyl alcohol. The formulation was able to effectively reduce bloodglucose levels when evaluated for in vivo hypoglycaemic effect. In another report, Vamshi and Madhusudan formulated an insulin gel for intranasal administration using chitosan as gelling agent and evaluated for in vitro release and hypoglycemic activity in rabbits. The in vivo efficacy of in situ nasal gel was assessed by measuring the blood glucose levels at specified time intervals. By use of penetration enhancer, insulin traversed the nasal mucosa and rapidly passed into the systemic circulation. Thus, insulin gel delivered via nasal mucosa can be a pleasant and painless alternative to injectable insulin. Zaki *et al*. enhanced bioavailability of metoclopramide HCl by formulating it as a mucoadhesive in situ nasal gel with modulated rheological and mucociliary transport properties. Different formulations were developed using thermo gelling polymer poloxamer 407, different mucoadhesive polymers (chitosan, hydroxypropyl cellulose, carbopol and polyvinyl alcohol) and PEG polymers. PEG counteracted the effect of the mucoadhesive polymer by decreasing the gel consistency and increasing the sol--gel transition temperature as well as in vitro drug release. Preformulation studies showed that the gelation temperature of pluronic F 127 increased with the drug and PEG 6000, but decreased with mucoadhesive polymer. From the results, it can be concluded that PEG 6000 increased the drug diffusion and permeability while the mucoadhesive strength got decreased. Majithiya *et al*. developed in situ nasal gel of sumatriptan using thermoreversible polymer pluronic F 127 and mucoadhesive polymer carbopol 934P. To ensure gelation at physiological temperature after intranasal administration, formulations were modulated so as to have gelation temperature below 34 ^{0}C.

As the concentration of carbopol increased, the gelation temperature of the formulation decreased with increased permeation rate. Badgujar *et al*. also reported sumatriptan succinate in situ mucoadhesive gel by utilizing pluronic F 127 and carbopol 974P. Nasal bioavailability of sumatriptan succinate was improved by increasing its nasal retention time and by using novel permeation enhancer fulvic acid extracted from shilajit. The gels prepared with and without permeation enhancer (fulvic acid) were evaluated for in vitro drug diffusion and the results showed that in situ gel containing fulvic acid had significantly higher permeability as compared with the in situ gel without fulvic acid. Mahajan *et al*. formulated and evaluated in situ nasal gel of artemether using temperature-sensitive polymer pluronic F 127 and mucoadhesive agent hydroxypropyl methyl cellulose (HPMC) K4M in different ratios. As the drug was poorly water soluble, its solubility was increased by preparing inclusion complex of the drug with hydroxypropyl-b-cyclodextrin. The prepared gels were stable, did not cause any remarkable damage to the nasal mucosa and were found to be effective delivery system for the treatment of cerebral malaria. Chao *et al*. prepared thermo-sensitive in situ nasal gel of fexofenadine hydrochloride to enhance permeation and solubility of it by using poloxamer 407, hydroxypropyl-b-cyclodextrin and chitosan. Human nasal epithelial cell monolayers cultured by air--liquid interface method, were used for permeation study. Chitosan caused increase in gelation temperature and viscosity and thus decreased the drug release from gels. Mucoadhesive in situ nasal gels of midazolam hydrochloride were prepared using poloxamer, with and without permeation enhancer (0.5% w/v sodium taurocholate) taking variable different concentrations (0.5, 1, 1.5% w/v) of three mucoadhesive agents, Ficus carica mucilage (FCM), HPMC and carbopol 934P. In vivo experiments in rabbits revealed that in situ nasal gels prepared from FCM provided better bioavailability of midazolam hydrochloride than the gels prepared from the HPMC and carbopol 934P. Patel *et al*. prepared and evaluated a thermoreversible gel of flunarizine hydrochloride for improved drug residence time in the nasal cavity using poloxamer 407 as thermally triggered polymer. Inclusion complex using b-cyclodextrin was prepared for increasing the solubility of flunarizine in nasal secretions. However, when the drug release of the various formulations was compared, it was found that the b-cyclodextrin formulations improved both the drug residence time as well as rate of absorption and hence are expected to improve the bioavailability of the drug. Using a combination of mucoadhesive polymers. Pluronic F 127 and hydroxypropyl cellulose, Bhalerao *et al*. developed an intranasal delivery system of ondansetron hydrochloride to overcome the poor bioavailability of drug due to first-pass effect.

They observed an increase in bioadhesion strength on increasing the concentration of bioadhesive polymers, but at the same time a decrease in spreadability was documented. Mehta *et al*. developed thermally triggered in situ nasal gel of pheniramine and phenylephrine HCl using poloxamer as gelling polymer and HPMC and xanthan gum as mucoadhesive agents. The results revealed that the formulation containing HPMC E-15 was able to form a consistent mucoadhesive gel. Temperature-mediated in situ nasal gel of ropinirole was reported by Khan *et al*. In vivo bioavailability and its efficiency in brain targeting were assessed in rats following intranasal administration of 99mTc-ropinorole in situ gel. The bioavailability measured as (AUCbrain) after nasal administration of ropinirole in situ nasal gel was 8.5 times more than that obtained following intravenous administration of ropinirole solution. Park *et al*. designed an intranasal delivery system for plasmid DNA composed of in situ gelling polymer (poloxamer 407) and mucoadhesive polymer vehicle (polycarbophil or polyethylene oxide) which could effectively and safely improve the nasal retention and absorption of plasmid DNA. Three hours post dose, the nasal tissue levels of plasmid DNA given in poloxamer/polycarbophil and poloxamer/ polyethylene oxide (0.8%) were 10- and 40-fold higher than saline. From the results it was been observed that the gelation temperature of the formulations decreased slightly by the mucoadhesive polymers, but not by plasmid DNA. When poloxamer/polycarbophil (0.2%) was used, highest absorption was observed with an area under the curve value 11-fold higher than saline (conventional vehicle). The absorption of plasmid DNA varied with the contents and type of mucoadhesive polymers. The in vitro release of plasmid DNA from the gels followed Fickian diffusion.

pH-triggered in situ gelation (Nandgude *et al*., 2008)

Carbopol 934 and carbopol 940 are used as a key ingredient to affect pH-induced sol--gel conversion of the formulations for

nasal delivery. Shah *et al*. designed and optimized pH-triggered mucoadhesive in situ nasal gel of sodium cromoglycate using pH-sensitive polymer carbopol 940 and different grades of mucoadhesive polymer HPMC (HPMC K100, HPMC K4M and HPMC K 15M). The optimized formulation containing carbopol 940 (0.75%) and HPMC K4M (0.5%) provided sustained in vitro release of the drug over an extended period of 8 h. The formulation had higher permeation than the pure drug solution due to permeation-enhancing property of carbopol due to its high Ca2+ binding ability. Rathnam *et al*. formulated in situ gel for nasal administration of progesterone using carbopol as a gelling polymer, b-cyclodextrin and hydroxypropyl-b cyclodextrin as solubilizer and absorption enhancer, respectively. In vivo studies performed in rabbits revealed rapid increase in plasma levels and bioavailability with nasal gel in comparison with nasal suspension. Aikawa *et al*. reported pH-triggered in situ nasal gel of chlorpheniramine maleate using polyvinylacetal diethylaminoacetate and its effect in the in vitro and in vivo experiments was evaluated.

The formulation underwent hydrogel formation with change in pH. Higher the polyvinylacetal diethylaminoacetate concentration, lower was the drug release and the apparent disappearance rate constant of drug also decreased. The authors visually confirmed hydrogel formation on mucous membranes in rat nasal cavity. Nakamura *et al*. prepared microparticles of budesonide using polymethacrylic acid and PEG and investigated the uptake and release kinetics of budesonide as well as pharmacokinetics following nasal administration. These microparticles were loaded into pH-sensitive polymers using ethanol to solubilise the drug. Maximum loading of drug was seen in 25% ethanolic solution. The release of budesonide obeyed Fickian release behavior after an initial rapid burst. The peak plasma concentration was achieved after 45 min of nasal administration of formulation. Nandgude *et al*. in 2008 developed in situ nasal gel of salbutamol sulfate using pH-triggered system containing carbopol 934P (0.1 - 0.5% w/v) along with viscosity builder and mucoadhesive agent such as HPMC K4M (0.5 - 1.5% w/v) which improves and strengthen the gel integrity. The optimized formulation B7 (0.4% w/v carbopol, 1% w/v HPMC K4M) provided sustained in vitro release of drug over an extended period of 48 h which can be a competent alternative to conventional nasal drops.

Ion-activated in situ gelation

The ion-activated gelation can be accomplished by the polymers that undergo phase transition in presence of ions. Gellan gum is an anionic polysaccharide that undergoes phase transition (sol--gel transition) in the presence of monovalent and divalent cations like Ca2+, Mg2+, K+ and Na+ present in the nasal secretions. Cao *et al*. in 2009 developed an ionactivated in situ nasal gel of mometasone furoate using gellan gum as carrier and studied its efficacy on allergic rhinitis model in rats. The results revealed that mometasone furoate in situ gel could be more effective than the nasal suspension in the treatment of allergic rhinitis. It also possessed thermogelling properties and the in situ gel formed by this polymer was able to preserve its integrity without dissolving or eroding in order to localize the drug for extended period of time at absorption site. In situ gel was found to be safe and promising therapeutic alternative to existing medications for motion sickness.

Thiolated gellan gum is yet another ion-activated polymer that was used to formulate an in situ gel of dimenhydrinate for the nasal delivery where carbopol 934P was used as a mucoadhesive agent. The phase transition (sol--gel transition) occurred in the presence of monovalent and divalent cations like Ca2+, Mg2+, K+ and Na+ present in the nasal secretions. In vitro permeation revealed that permeation was increased with increase in thiolated gellan gum polymer content. In another report on dimenhydrinate, Mahajan *et al*. Developed in situ gelling system based on gellan gum and thiolated gellan gum, where gelation occurred at physiological ion content after intranasal administration.

They showed similar property with respect to viscosity and in vitro drug diffusion. However, formulations based on thiolated gellan gum were characterized by better mucoadhesiveness in terms of detachment stress, which increased with increasing concentration of thiolated polymer and improved permeation profile than gellan gum formulation. Chelladurai *et al*. formulated and evaluated bioadhesive in situ nasal gel of Ketorolac tromethamine, a potent non-narcotic analgesic with moderate anti-inflammatory activity. Pectin- and chitosan-based gelling systems were prepared by varying their concentration. HPMC was added in both chitosan- and pectin-based gelling systems which increases the viscosity and gel strength. For selected gels, the anti-inflammatory activity and mucosal irritancy were also evaluated in rats and the results obtained were compared with per oral, intraperitoneal and nasal solution administration of ketorolac tromethamine. The in situ gel exhibited prolonged drug release characteristics with controlled anti-inflammatory effect. Thus, bioadhesive gelling systems can be considered as a viable alternative for systemic medication of drugs through nasal route.

Miscellaneous trigger mechanisms

Interestingly, water has also been utilized as triggering agent for microemulsion of zolmitriptan using water, oil, surfactant and co-surfactant by Shelke and Devarajan. For this the authors constructed pseudo-ternary phase diagrams using water titration method at ambient temperature (25^0C) to determine microemulsion regions and gelling regions. It has been reported that as the surfactant concentration increased the gel region increased. Thus, the conversion of the formulation into gel in presence of water presented the advantages of enhanced bioavailability as well as rapid onset of action. Another novel gel triggering approach of hypo-osmotic thermogelling system has been reported by Morath and Edman.

According to the study, insulin (3 IU/kg bodyweight) was given to rats intranasally in a formulation composed of EHEC, sodium dodecyl sulfate, m-cresol and glycerol which contained osmotic active agents like glycerol/ creatinine for the preparation of hypo-, iso- and hyperosmotic thermogelling system, respectively. Plain insulin solution containing sodium dodecyl sulfate, m-cresol and glycerol consisting osmotic active agents like glycerol/creatinine was used as reference. According to the researchers, the hypo-osmotic thermogelling system containing EHEC was able to lower plasma glucose more efficiently than insulin delivered in iso- and hyper-osmotic gels. The plain hypoosmotic insulin solution did not have any effect on plasma glucose. It suggests a synergistic effect of the hypo-osmotic environment and the EHEC gel.

Conclusion

Nasal drug delivery is fast emerging field as an alternative route for the administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation, undergo first-pass hepatic metabolism, are incompletely absorbed in the GIT or produce undesirably slow effects when administered orally. Nasal route circumvents bioavailability issues associated with listed factors and also offers the advantage of controlled drug delivery for extended periods of time. The success of a controlled release product is directly linked to patient compliance which in situ gels can offer. Exploitation of polymeric in situ nasal gels for controlled release of drug provides numerous advantages over conventional dosage forms and can be considered as reliable and non-invasive drug delivery system. Exploration of novel gel triggering mechanisms and use of water-soluble, biodegradable polymers for product development of the in situ nasal gel formulations makes them more acceptable.

REFERENCES

Arora, P., Sharma, S. and Garg, S. 2002. Permeability issues in nasal drug delivery. *Drug Discov Today* ;*7:967-75*

Behl, C.R., Pimplaskar, H.K., Sileno, A.P, *et al*. 1998. Effects of physicochemical properties and other factors on systemic nasal drug delivery. *Adv Drug Deliv Rev* ;*299:89-116*

Chugh, Y., Kapoor, P. and Kapoor, A.K. 2009. Intranasal drug delivery: a novel approach. *Indian J Otolaryngol Head Neck Surg* ;*61:90-4*

Dressman, J.B., Thelen, K. and Jantratid, E. 2008. Towards quantitative prediction of oral drug absorption. Clin Pharmacokinet ;*47:655-67*

Hussain, A. 1998. Intranasal drug delivery. *Adv Drug Deliv Rev* ;*29:39-49*

Nandgude, T., Thube, R., Jaiswal, N., *et al*. 2008. Formulation and evaluation of Ph induced in-situ nasal gel of salbutamol sulphate. *Int J Pharm Sci Nanotechnol*;*1:177-83*

Pires, A., Fortuna, A., Alves, G. and Falcao, A. 2009. Intranasal drug delivery: how, why and what for. *J Pharm Pharm Sci* ; *12(3):288-311*.. Publication briefly describes the intranasal delivery.

Shojaei, H. 1998. Buccal mucosa as a route for systemic drug delivery: a review. *J Pharm Pharm Sci* ;*1:15-30*

Ugwoke MI, Agu RU, Verbeke N, *et al*. 2005. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. *Adv Drug Deliv Rev57*:*1640-65*

Verma, P., Thakur, A.S, Deshmukh, K., *et al*. 2010. Routes of drug administration. *Int J Pharm Stud Res* ;*1(1):54-9*

****