Review Article

In Situ Gel: An Innovative Approach for Safe and Sustained Nasal Drug Delivery

Sreeja C Nair, Mable Sheeba John, Anoop K R*
Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, AIMS Health Sciences Campus, Kochi, India.
***Corresponding author's E-mail:** anoopkrpharma@gmail.com

Accepted on: 02-04-2013; **Finalized on:** 31-12-2013.

ABSTRACT

The human nose has the potential to be an alternative route for the systemic delivery of a wide range of therapeutic agents. The richly supplied vascular nature of the nasal mucosa and its high drug permeation makes it a potential route for the administration of many drugs including proteins, peptides and vaccines. Nasal route is most suitable for those drugs which cannot be administered orally due to gastric degradation or hepatic first pass metabolism. In situ forming polymeric systems are formulations that are in sol form before administration into the body but once administered, undergo gelation in situ, to form a gel. The formation of in situ gel depends on factors like temperature, modulation, pH change, presence of ions etc. Temperature modulated gel is the widely accepted in situ formulation. The article provides a detailed review on the mechanism of in situ gel formation and the type of polymers used along with their evaluation. The uses of the strategies which enhance the nasal bioavailability are being used to formulate a number of drugs for delivery via the nasal route. A combination of mucoadhesive polymer along with thermoreversible polymer can be utilized for easy and safe delivery of therapeutic agents including biopharmaceuticals.

Keywords: Thermoreversible, Mucoadhesive, Nasal Drug Delivery (NDDS), Pluronic.

INTRODUCTION

The generation of a new drug molecule is an expensive and time consuming process. Hence the safety and efficacy ratio of "old" drugs can be improved by delivering these drugs at controlled and slow delivery or targeted delivery.[1] This leads to the development of in situ gelling nasal drug delivery systems. In situ gel is drug delivery systems that are in sol form before administration in the body, but once administered, undergo gelation in situ, to form a gel. [2]

Intra nasal administration has been accepted since ancient era, in the Ayurvedic system of Indian medicine [3]. Many drugs have shown better systemic bioavailability through nasal route as they are significantly degraded in the GIT or under goes first pass effect in the liver. Due to the non invasive nature and increased patient comfort and compliance they are preferred for long term therapy as the parenteral route is considered inconvenient. Nasal drug delivery is suitable for restricting and obstacles blood brain barrier so that drugs can be delivered in the biophase of the CNS via the olfactory neurons which is viewed as a potential route for the administration of vaccines .[4, 5]

Table 1: Advantages of NDDS over oral and iv.[6]

Features	Nasal delivery	Oral delivery	I.V
High serum drug levels	Yes	No	Yes
Rapid onset	Yes	No	Yes
Titrable	Yes	No	Yes
Painless	Yes	Yes	No
Easy to use	Yes	Yes	No

Nose

The nose performs three different processes like deposition, clearance or translocation & absorption of drugs which takes place inside the nose makes it a complex organ from kinetic point of view. [7, 8] The nasal septum divides the nasal cavity into two symmetrical halves. The nasal mucosa of the nose is the only location in the body that provides a direct connection between the central nervous system and the atmosphere. [9,10] Drugs administered through the nasal mucosa rapidly traverse through the cribriform plate into the central nervous system by three routes.[11]

- Directly by the olfactory neurons.
- Through supporting cells and surrounding capillary bed.
- Directly into the cerebrospinal fluid.

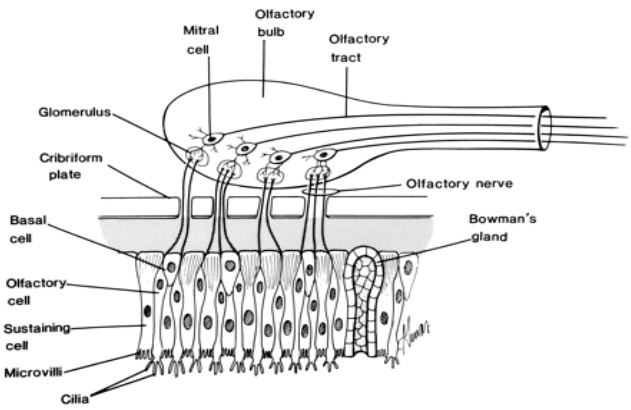

Figure 1: Anatomy of the nasal mucosa-cribriform plate interface.

Nasal cavity

The nasal cavity offers a number of unique advantages such as easy accessibility and good permeability especially for lipophilic, low molecular weight drugs. The nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150 cm^2. These thermoreversible Drug delivery systems promotes the ease and convenience of administration, deliverance of accurate dose and also prolongs the residence time of drug in contact with mucosa, which are the problems that are encountered in semisolid dosage forms. [12]

Respiration and olfaction is the major function of nasal cavity. The nasal cavity extends back from the outer nose into the head and connects with the sinuses which are the hollow areas. The nasal cavity is suffused with nasal hairs, which can filtrate and block larger particles from the inhaled air. The nasal cavity is covered with a thin and smooth layer of mucosa-nasal mucosa. The nasal mucosa is supplied with blood and glands that secrete fluids which can enhance the humidity and prevent the mucosa from being too dry.[13,14] The nasal cavity is divided by nasal septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. There are four areas in each symmetrical halves. [15-17]

Nasal vestibule- region are very resistant to dehydration and limits permeation of substance due to the presence of stratified epithelial cells. [18]

Atrium-it is a transitional epithelial region with stratified squamous cells anteriorly and pseudo stratified columnar cells and is less permeable to drug molecules due to small surface area and stratified cells.

Respiratory region-this region receives maximum secretions due to large number of pseudo-stratified columnar epithelia cells, seromucus glands, goblet cells and nasolacrimal duct. It is also richly supplied with blood vessels for heating and humidification of inspired air which make this region the most permeable in the nasal cavity.

Olfactory region-this area contains the peripheral organ of smell and act as a channel for the direct supply of drug to the brain. [19]

Table 2: Advantages and limitations of drug delivery through nasal cavity[20-22]

.	Limitations
✓ High degree of absorption and rapid transport of substance due to thin porous and highly vascularised epithelium	× Administration of only a small amount of the formulation is possible as large quantities creates problem for the normal functioning of the nose.
✓ Avoids the hepatic first pass metabolism.	× Surface area for absorption is smaller when compared to the GIT.
✓ Drugs can be targeted to the CNS bypassing the tight blood brain barrier.	× Drainage of the solution in the nasopharynx or expulsion of drug due to sneezing leads to irreproducibility of dosing regimen.
✓ Proteins and peptides can be safely delivered via this route due to the low enzymatic activity in the nasal cavity compared to the liver and GIT.	× Not appropriate for hydrophilic compounds and large molecules.
✓ Patient compliance and cost of therapy is low as nose is amenable to self medication.	× Possibility of irritation in the nasal mucosa.
✓ The risk of over dosage is low.	× Use of excipients like absorption enhancers in large amount may lead to toxicity problems.
✓ Bioavailability of small molecules is very good and that of larger molecules can be increased by the use of permeation enhancers.	× Drug administration is difficult in the case of pathological conditions like common cold and rhinitis.
	× Absorption and permeability depends on the physiology of nasal mucosa.

Nasal mucosa

It lines the entire nasal cavities and is continuous with the adjoining cavities to which the nasal cavity communicates (e.g. the nasopharynx and paranasal sinuses) except for the vestibule of nose and is firmly bound to the periosteum and perichondrium of the supporting structures of the nose. The anterior nasal cavity is lined with stratified squamous and transitional epithelium, and the highly vascular respiratory epithelium is mostly ciliated, columnar and stratified (Mygrind et al., 1982).

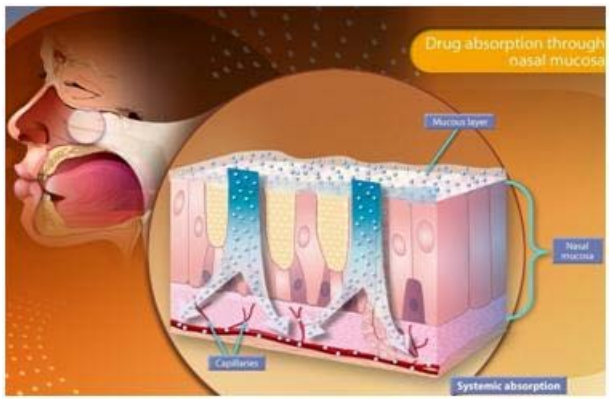

Figure 2: Absorption of drug through nasal mucosa.

Mechanism of nasal absorption

The first step in the absorption of drugs from the nasal cavity is the passage through the mucus. Small unchanged particles easily pass through this layer while large charged particles find it more difficult to cross. The primary protein present in mucus is mucin which has a tendency to bind to solutes which in turn hinder diffusion. Also structural changes due to environmental changes like pH, temperature, etc are also possible. The passage of drug through the mucus has been explained by several mechanisms such as transcellular or simple diffusion across the membrane, paracellular transport which occurs between cells and transcytosis which involves vesicle carriers cellular transport out of which two are considered important. Potential metabolisms before reaching the systemic circulation and limited residence time in the nasal cavity are the major obstacles for drug absorption. [23-25]

a) First mechanism- also known as paracellular transport this utilizes the aqueous route of transport and is slow and passive. This route is not suitable for the drugs having molecular weight greater than 1000 Daltons due to poor bioavailability.[26]

b) Second mechanism– also known as transcellular route which utilizes the lipoidal route for transport of lipophilic drugs.

c) Drugs also cross cell membranes by an active transport route via carrier mediated or transport through the opening of tight junctions.

E.g. chitosan a natural biopolymer from shell fish opens tight junctions between epithelial cells to facilitate transport. [27]

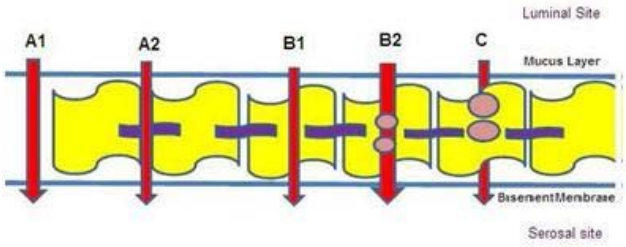

Figure 3: Intercellular spaces, (A2) Tight junctions, (B1) Passive diffusion, (B2) Active transport, (C) Transcytosis.

In situ forming polymeric delivery systems

These are the novel drug delivery systems that favours the ease and convenience of administration and delivery of accurate dosage forms which are the major problems encountered by the normal semi solid dosage forms. Ordinary gels are difficult to administer and an accurate dose cannot be measured while mucoadhesive powders are not highly favored products as they can cause irritation on the nasal mucosa and give a gritty feeling to the tissues. An in situ mucoadhesive gel appears to be very attractive since they are fluid like prior to administration which makes them easy to administer as a drop allowing accurate dosing.[28-29]

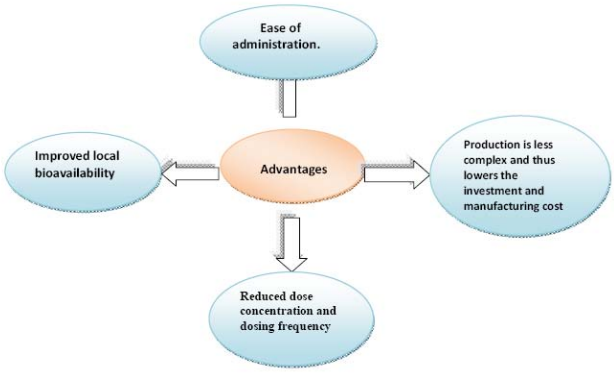

Figure 4: Advantages of in situ polymeric system

Formulation of in situ gels depends on various physical and chemical stimuli like temperature modulation, pH change, solvent exchange, electric field, light, magnetic field, presence of ions and ultraviolet radiation from which the drug gets released in a sustained and controlled manner. Among them temperature responsive systems are the most important as they are predominantly studied. Smart polymeric systems provide promising means of delivering these drugs. Various natural and synthetic polymers are used for the preparation of in situ gels which undergoes a sol-gel transition when administered.

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 helps 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. [30, 31]

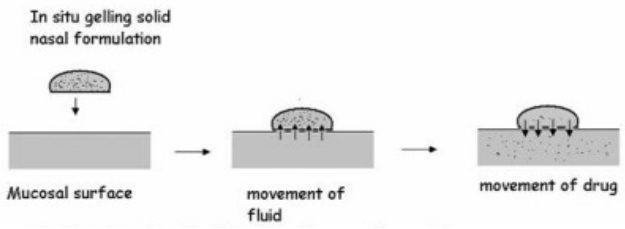

Figure 5: principle of solid in situ gelling nasal formulation.

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.[32-35] 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-127grade) 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. [36-39]

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 (4-5^{0}C). [40]

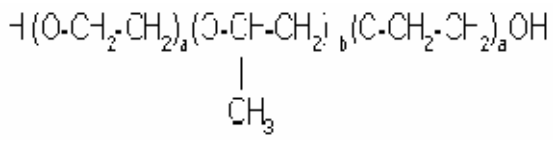

Figure 6: Chemical structure of Pluronic F-127 (a) ethylene oxide portion (b) propylene oxide portion.

Hydroxy propyl methyl cellulose (HPMC)[41], Methyl cellulose[42], Poly-(N-isopropylacrylamide)[43-45] 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: [46]

- ✓ 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. [46] 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. [47]

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.[48-51]

4. Gellan gum [52,53]

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

situ. In situ gelling gellan formulation as vehicle for oral delivery of theophylline is reported. [54]

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. [55]

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 α-Lglucuronic 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. [56,57]

Table 3: Some nasal mucoadhesive delivery systems

Drug	Mucoadhesive polymer	Dosage form
Metochlopramide hydrochloride	Poloxamer407/Polyethylene glycol	Gel
Metochlopramide hydrochloride	Carbopol 981	Solution, Gel, Powder

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. [58]

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. [59]

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. [60]

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[61], corticosteroids [62-65], sedatives[66], narcotics[67] and a number of drugs can be administered by this route.

CONCLUSION

Developments in the field of polymer science have lead to the emergence of various stimuli sensitive hydrogels like pH, temperature formulations which are used for targeted drug delivery.

Sustained and prolonged release of the drug, stability and biocompatibility makes the in situ systems very reliable. Due to the extensive research in the nasal delivery, nasal formulations have acquired the fourth position in the market. Soon it is expected that this will grow further within next few years. In the in situ gelling nasal formulations, there is no need to remove the dosage form from the nasal cavity; therefore these formulations will become the efficient way of drug delivery. In the future, the in situ gelling nasal drug delivery will continue to advance and will represent a viable alternative to the oral and injectable routes of administration. Drugs for acute and long term diseases and novel nasal vaccines with better local or systemic protection against infections will be available. The development of drugs that directly target the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects is also in the pipeline.

REFERENCES

1. Kshirsagar N.A, Drug delivery systems, Indian Journal of Pharmacology, 32, 2000, S54-S61.
2. Peppas NA, Langer R, New challenges in biomedicals, Science, 263, 1994, 1715-20.
3. Mygind N, Dahl R, Anatomy, physiology and function of the nasal cavities in health and disease, Adv Drug Deliv Rev, 29, 1998, 3-12.
4. Illum L, Nasal drug delivery: possibilities, problems and solutions,J Control Release, 87, 2003, 187-198.
5. Yamaya M, Finkbeiner WE, Chun SY, Widdicombe JH, Differentiated structure and function of cultures from

human tracheal epithelium, Am J Physiol, 262, 1992, 713-724.

6. Pranshu Tangri, Nasal Drug Delivery Systems: Scope And Potential, Drug Invention Today, 3, 2011, 18-21.
7. Ridley D, Washington N, Wilson C.G, Drug delivery to the buccal and nasal cavities, anatomical and physiological considerations, in: D. Duchene (Ed.), Buccal and nasal administration as an alternative parenteral administration,Editions de Sante, Paris, 3, 1992, 29-39.
8. Arora P, Sharma S, Garg S, Permeability issue in nasal drug delivery, Drug Discov Today, 7, 2002, 967-975.
9. Ugwoke M.I, Verbeke N, Kinget R, The biopharmaceutical aspects of nasal mucoadhesive drug delivery, J. Pharm. Pharmacol, 53, 2001, 3-21.
10. Chien Y.W., Su K.S.E., Chang S.F. (1989) Nasal systemic drug delivery. Drugs and the pharmaceutical sciences, New York, Marcel Dekker.
11. Proctor F, Clearance of inhaled particles from the human nose, Archives of Internal Medicine, 131, 1973, 132-139.
12. Behl CR, Pimplaslar HK, Sileno A.P, DeMeireles J, Romeo, Effects of physicochemical properties and other factors on systemic nasal drug delivery, Adv Drug Del Rev, 29, 1988, 89-116.
13. Ugwoke M.I, Verbeke N, Kinget R, The biopharmaceutical aspects of nasal mucoadhesive drug delivery, J. Pharm. Pharmacol, 53, 2001, 3-21.
14. Arora P, Sharma S, Garg S, Permeability issue in nasal drug delivery, Drug Discov. Today, 7, 2002, 967-975.
15. Lansley A.B, Mucociliary clearance and drug delivery via the respiratory tract, Adv. Drug. Deliv. Rev, 11, 1993, 299-327.
16. Tos M, Distribution of mucus producing elements in the respiratory tract. Differences between upper and lower airways, Eur. J. Respir. Dis, 128, 1983, 269-279.
17. Kaliner M, Marom Z, Patow C, Shelhamer, Human respiratory mucus, J. Allergy Clin. Immunol, 73, 1984, 318-323.
18. Nitin Sharma, Mucoadhesive Thermoreversible nasal delivery system, Journal of Pharmacy Research, 3, 2010, 991-997
19. Richard, E.G., Lowerence S.O, Physiological determinants of nasal absorption, J.Cont. Rel, 6, 1987, 361-366.
20. Illum L., Fisher A.N, Jabbal-Gill.I, Davis S.S, Bioadhesive starch microspheres and absorption enhancing agents act synergistically to enhance the nasal absorption of polypeptides, Int. J.Pharm, 222, 2001, 109-119.
21. Behl C.R, Pimplaskar H.K, Sileno A.P, deMeireles J, Romeo V.D, Effect of physicochemical properties and other factors on systemic nasal drug delivery, Adv. Drug. Deliv. Re, 29, 1998, 89-116.
22. Dyer A.M, Hinchcliffe M, Watts P, Castile J, Jabbal Gill I, Nankervis R, Smith A, Illum L, Nasal delivery of insulin using novel chitosan based formulation: A comparative study in two animal models between simple chitosan formulation and chitosan nanoparticles, Pharm. Res, 19, 2002, 998-1008.
23. Illum L, Fisher A.N, Jabbal-Gill I, Davis S.S.,Bioadhesive starch microspheres and absorption enhancing agents act synergistically to enhance the nasal absorption of the polypeptides, Int. J.Phar, 222, 2001, 109-119.
24. Pontiroli A, Albertto M, Calderara A, Pajetta E, Pozza G, Absolute bioavailability of nicotine applied to different Nasal administration of glucagon and human calcitonin to nasal regions, Eur J Clin Pharmacol, 41, 1991, 585-588.
25. Talegaonkar S, Mishra PR, Intranasal delivery: An approach to bypass the blood brain barrier, Indian J Pharmacol, 36(3), 2004, 140-147.
26. Aurora J, Development of Nasal Delivery Systems: A Review**,** Drug Deliv Technol, 2(7), 2002, 1-8.
27. Dodane V, Khan MA, Merwin JR, Effect of chitosan on epithelial permeability and structure, Int J Pharm, 182, 1999, 21-32.
28. Zhidong L, Jaiwel L, Shufang N, Hui L, Pingtain D, Weisan P, Study of an alginate/HPMC based insitu gelling ophthalmic delivery system for gatifloxacin, Int JPharm, 315,2006, 12-17.
29. Al-Tahami K, Singh J, Smart polymer based delivery systems for peptides and proteins. Recent Pat Drug Delivery Formula, 1, 2007, 66-71.
30. Dondeti, Zia, H., Needham, T.E, Bioadhesive and formulation parameters affecting nasal absorption. Int. J. Pharm, 127, 1996, 115-133.
31. Schipper, The nasal mucociliary clearance: relevance to nasal drug delivery, Pharma. Res, 7, 1991, 807-814.
32. Park J.S, Oh Y.K, Yoon H, Kim J.M, and Kim C.K, In situ gelling and mucoadhesive polymer vehicles for controlled intranasal delivery of plasmid DNA, J. Biomed Mater, Res, 59, 2002, 144-51.
33. Bromberg, L.E, Enhanced nasal retention of hydrophobically modified polyelectrolytes, J. Pharm. Pharmacol, 53, 2001, 109-14.
34. Paulsson M, Hagerstrom H, and Edsman K, Rheological studies of the gelation of deacetylated gellan gum (Gelrite) in physiological conditions, Eur. J. Pharm. Sci, 3, 1999, 99-105.
35. DiBiase, and Rhodes, Formulation and evaluation of Epidermal Growth Factor in Pluronic-127 Gel.Drug Develop. Ind. Pharm, 22(8), 1996, 823-831.
36. Gilbert, Hadgraft J, Bye, and Brookes L, Drug Release from Pluronic F-127 Gels, Int. J. Pharm, 32, 1986, 223-228.
37. Miyazaki S, Takeuch, S, Yokouchi C, Takada, M, Pluronic F-127 gels as vehicles for Topical administration of Anticancer Agents, Chem. Pharm. Bull, 32(10), 1984, 4205-4208.
38. Yeon S, Chul J, Moo Y, Poly(ethylene oxide)-poly(ethylene oxide)/ ply(∈ caprolactone) (PCL) amphiphilic block copolymeric nanospheres: Thermo-responsive drug release behaviors, J. Control. Rel, 2000, 65, 345-358.
39. Loyd, Allen V, Compounding gels, Current and Practical Compounding Information for the Pharmacist, Secundum Artem, 4(5), *1994,* 1-13.
40. Harrington W.F, Vonhippel P.H, The structure of collagen and gelatin, Adv. Protein Chem, 16, 1961, 1-138.

41. Anderson N.S, Campbell J.W, Harding M.M, Rees D.A, Samuel J.W.B, X-ray diffraction studies of polysaccharide sulphates: double helix model for carragenans, J. Mol. Bio, 45, 1969, 85-99.
42. Heymann E, Studies on sol-gel transformations;The inverse sol-gel transformation of methylcellulose in water, Trens. Faraday Soc, 31, 1935, 846-864.
43. Sarkar N, Thermal gelation properties of methyl and hydroxypropyl methylcellulose, J. Appl. Polym. Sci, 24, 1979, 1073-1087.
44. Shirakawa M, Yamatoya K, Nishinari K, Tailoring xyloglucan properties using an enzyme, Food Hydrocolloids, 12, 1998, 25-28.
45. Feil H, Bae Y.H, Feijen J, Kim S.W, Effect of comonomer hydrophilicity and ionization on the lower critical solution temperature of N-isopropylacrylamide copolymers, Macromolecules, 26, 1993, 2496-2500.
46. Lin H.H, Cheng Y.L, In-situ thermoreversible gelation of block and star copolymer of poly (ethylene glycol) and poly (N-isopropylacrylamide) of varying architecture, Macromolecules, 34, 2001, 3710-3715.
47. Blanco-Fuente H, Anguiamo-Igea S, Otero-Espinar F.J, Blanco-M´ende, In vitro bioadhesion of carbopol hydrogels, Int. J. Pharm, 142, 1996, 169–174.
48. G. Molinaro, J.C. Leroux, J. Damas, A. Adam, Biocompatibility of thermosensitive chitosan-based hydrogels: an in vivo experimental approach to injectable biomaterials, Biomaterials, 23, 2002, 2717–2722.
49. Jarry.C, Chaput.C, Chenite.A, Renaud M.A, Buschmann.M, Leroux J.C, Effects of steam sterilization on thermogelling chitosanbased gels, J. Biomed. Mater. Res, 58, 2001, 127–135.
50. C. Jarry, J.C. Leroux, J. Haeck, C. Chaput, Irradiating or autoclaving chitosan/polyol solutions: Effect on thermogelling chitosan-bglycerophosphate systems, Chem. Pharm. Bull, 50, 2002, 1335–1340.
51. Carlfors J, Edsman K, Petersson R, J ornving. K, Rheological evaluation of Gelrite® in situ gels for ophthalmic use, Eur.J. Pharm. Sci, 6, 1998, 113–119.
52. Chu J.S, Yu D.M, Amidon G.L, Weiner N.D, Goldberg, A.H, Viscoelastic properties of polyacrilic acid gels in mixed solvents, Pharm. Res, 9, 1992, 1659–1663.
53. Al-Shamklani A, Bhakoo M, Tuboku MA, Duncan R, Evaluation of the biological properties of alginates and gellan and xanthan gum, Proc Int Symp Control Release Bioact Mater, 18, 1991, 213-4.
54. Sechoy O, Tissie G, Sebastian C, Maurin F, Driot JY, Trinquand C, A new long acting ophthalmic formulation of carteolol containing Alginic acid, Int J Pharm, 207, 2000, 109-16.
55. Smart JD, Kellaway IW, Worthington HE, An in vivo investigation of mucosa adhesive materials for use in controlled drug delivery, J Pharm Pharmacol , 36, 1984, 259-99.
56. SuishaF, Kawasaki N , Miyazaki S, Shirakawa M, Yamotoya K, Sasaki M , Xyloglucan gels as sustained relese vehicles for intraperitoneal administration of mitomycin C, Int J Pharm, 172, 1998, 27-32.
57. Miller SC, Donovan MD, Effect of poloxamer407 gels on the miotic activity of pilocarpine nitrate in rabbits, Int J Pharm, 5, 1982, 142-52.
58. Kashyap N , Viswanad B, Sharma G.Bhardwaj V, Ramarao P, Kumar M.N.V, Design and Evaluation of biodegradable, biosensitive insitu gelling systems for pulsatile delivery of insulin, Biomaterials, 32, 2007, 2051-60.
59. Harris AS, Hedner P, Vilhardt H, Nasal administration of desmopressin by spray and drops, J Pharm Pharmacol, 39, 1987, 932-934.
60. Frankland AW, Walker SR, A comparison of intranasal betamethasone valerate and sodium cromoglycate in seasonal allergic rhinitis, Clin Allergy, 5, 1975, 295-300.
61. Small P, Barrett D, Effects of high doses of topical steroids on both ragweed and histamine-induced nasal provocation, Ann Allergy, 67, 1991, 520-524.
62. Mabry RL, Corticosteroids in the management of upper respiratory allergy: the emerging role of steroid nasal sprays, Otolaryngol Head Neck Surg, 107, 1992, 855-860.
63. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM, Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids, N Engl J Med, 316, 1987, 1506-1510.
64. Walbergh EJ, Wills RJ, Eckert J, Plasma concentrations of midazolam in children following intranasal administration, Anesthesiology, 74, 1991, 233-235.
65. Tsai SK, Mok MS, Lippmann M, Rectal ketamine vs intranasal ketamine as premedicants in children. Anesthesiology, 73, 1990, A1094
66. Wilton NC, Leigh J, Rosen DR, Pandit UA, Preanesthetic sedation of preschool children using intranasal midazolam, Anesthesiology, 69,1988, 972-975.
67. Karl HW, Keifer AT, Rosenberger JL, Larach MG, Ruffle JM, Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients, Anesthesiology, 76, 1992, 209-215.

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