Review Article

Smart Polymers in Nasal Drug Delivery

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Nasal drug delivery has now been recognized as a promising route for drug delivery due to its capability of transporting a drug to systemic circulation and central nervous system. Though nasal mucosa offers improved bioavailability and quick onset of action of the drug, main disadvantage associated with nasal drug delivery is mucocilliary clearance due to which drug particles get cleared from the nose before complete absorption through nasal mucosa. Therefore, mucoadhesive polymeric approach can be successfully used to enhance the retention of the drug on nasal mucosal surface. Here, some of the aspects of the stimuli responsive polymers have been discussed which possess liquid state at the room temperature and in response to nasal temperature, pH and ions present in mucous, can undergo *in situ* gelation in nasal cavity. In this review, several temperature responsive, pH responsive and ion responsive polymers used in nasal delivery, their gelling mechanisms have been discussed. Smart polymers not only able to enhance the retention of the drug in nasal cavity but also provide controlled release, ease of administration, enhanced permeation of the drug and protection of the drug from mucosal enzymes. Thus smart polymeric approach can be effectively used for nasal delivery of peptide drugs, central nervous system dugs and hormones.

Key words: Nasal drug delivery, smart polymers, temperature responsive, pH responsive, ion responsive

Now days, there has been significant interest and developments in transdermal and transmucosal routes of drug administration because these routes of drug administration are noninvasive, self-administrable and can decipher the problems associated with oral route of drug administration such as first pass metabolism, drug degradation in variable pH condition in gastrointestinal tract, inadequate absorption and slow onset of action[1,2]. Transdermal delivery is the most widely considered route for topical drug delivery. But keratinized outermost layer of the skin i.e. stratum corneum can act as a permeability barrier for the transportation of the drug to the systemic circulation. Several mucosal surfaces such as nasal, rectal, vaginal, ocular and oral have been investigated as delivery routes and proved efficient due to low level of keratinization compared to skin. But rectal, vaginal and ocular route for systemic drug delivery possess lack of patient compliance and are more suitable for local drug delivery. Nasal and oral transmucosal routes have proved to be attractive for systemic drug delivery[1]. Several nasal and oral transmucosal products have been successfully marketed and various products are in developmental stage[1,3]. For some drugs, with intranasal administration it is possible to obtain pharmacokinetic profiles similar to those obtained after an intravenous injection[4]. Some of physiological features of the nasal and oral mucosa affecting permeability of drug molecules are discussed in Table 1[1,3,5-8].

Nasal cavity has been used from ancient time as a drug delivery route to alleviate diseases and disorders. One of the '*panchakarmas*' stated in Ayurveda is '*nasyakarma*', a practice in which a drug is administered through the nostrils[9]. Nasal cavity is an excellent doorway for the entry of the drug moiety to systemic circulation and central nervous system. As mentioned above nasal cavity is lined with mucous membrane with large absorptive surface area, low thickness, high vascularity, porous and thin endothelial basement membrane below the epithelium leads to high permeability of nasal mucosa. Therefore,

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after absorption through nasal mucous membrane, drug can be directly reach to the systemic circulation with enhanced bioavailability and improved onset of action[3,5,6]. Also it has the potential to target the drug directly across the blood brain barrier via olfactory and trigeminal nerve cells[10].

NASAL ANATOMY AND PHYSIOLOGY

The human nasal cavity is separated into 2 halves by nasal septum and has the total volume of 15-20 ml. Nasal cavity is divided into 5 regions, nasal vestibule, atrium, respiratory region, olfactory region and extends posteriorly to nasopharynx. Vestibule is the most anterior part of the nasal cavity (fig. 1). Respiratory region occupies most of the volume of the nasal cavity and lined by respiratory epithelium. If we rank the permeability, vestibule is least, atrium is less and respiratory region is most permeable area of the nasal cavity. Beneath the respiratory epithelium, there is a thin and porous basement membrane. Respiratory mucosa comprises of several types of cells, ciliated pseudostratified columnar epithelial cells, goblet cells, basal cells and nonciliated cells (fig. 2). Basal cells are thought to be precursors of columnar and goblet cells. Goblet cells are mucosecretory cells. Ciliated pseudostratified columnar cells are the tall columnar cells which bear 4-6 µm long and 0.3 µm wide hairs like projections called cilia. There are approximately 100 cilia per cell also nonciliated and ciliated cells possess about 300 microvilli each. Cilia are responsible for mucocilliary clearance (MCC), the protective mechanism of respiratory system[6,11].

Mucosa of the nasal cavity is covered with mucus; Mucus is a complex submucosal secretion comprises of about 95% water, 2% mucin, 1% salts, 1% of other proteins for example albumin, immunoglobulins, lysozyme and lactoferrin, and 1% lipids. Nasal mucosa covered with the blanket of mucus which

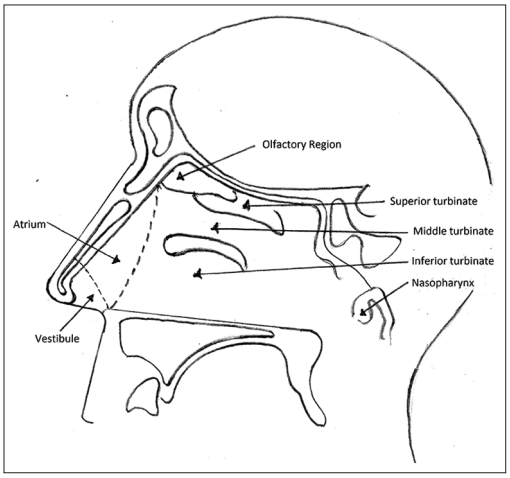

Fig. 1: Schematic diagram of the sagittal section of human nasal cavity.

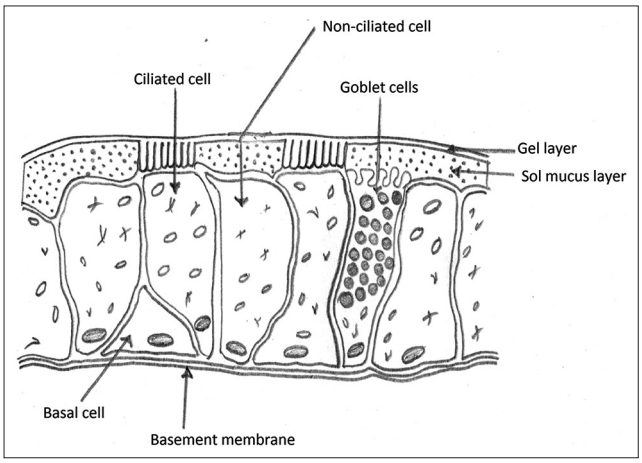

Fig. 2: Cell types of the nasal epithelium.

TABLE 1: PHYSIOLOGICAL FEATURES OF THE NASAL AND ORAL MUCOSA AFFECTING PERMEABILITY OF DRUG

Parameters	Nasal mucosa	Oral mucosa
Thickness	1-2 mm	500-600 µm in buccal; 100-200 µm in sublingual
Surface area	150-180 cm^2 Presence of microvilli enhances effective surface area	100 cm^2
Permeability:		
Epithelium	The nasal mucosa possesses porous epithelium	Membrane coating granules release lipophilic material into the intercellular spaces to maintain epithelial cohesion, this lipophilic material slow down the passage of hydrophilic materials across the epithelium
Endothelial basement membrane	Porous and thin structure of endothelial basement membrane possesses no restriction to the entry of the drug molecule to the systemic circulation	The charge on the constituents of the basal lamina and high level of hydration of connective tissues may limit the rate of penetration of lipophilic compounds
Vascularity	Arterial supply: External and internal carotid artery, maxillary artery via sphenopalatine artery, ophthalmic artery via ethemoid branches, facial artery, palatine artery Venous supply: Pterygoid plexus, Ophthalmic vein, facial vein	Arterial supply: External carotid artery, buccal artery, facial artery, infra orbital artery, posterior alveolar artery, sublingual artery

is 5 µm thick comprises of 2 layers, lower sol layer and upper gel layer. The cilia provide sweeping motion into the sol layer by moving back and forth. The entrapped foreign particles along with the gel layer get transported to the nasopharyngeal area for ingestion. The beating action exhibited by cilia at a frequency of 10 to 13 Hz results in the movement of mucus. As mucus moves at a rate of 5 to 6 mm per min, the particles get cleared within 20 min from nose. New mucus layer occupy the epithelium about every 10 min. The MCC can be influenced by environmental and pathological conditions. It specifies that the area of the high permeability characteristics in the nasal cavity where drug should be retained for its higher absorption, from that region only it is clearing rapidly due presence of ciliated cells[6,12]. However problems associated with the nasal drug administration are anterior leakage if dose volume is not maintained in between 25-200 µl and post nasal drip due to MCC[12]. Therefore it is necessary to enhance the contact time of the drug with nasal mucosal surface or prolong the retention of the drug on mucosal surface.

Now a days, various products are available in market to treat local and systemic conditions include nasal sprays and nasal drops[3]. Nasal drops have the problem of anterior leakage from nasal cavity. Liquid nasal sprays get spread on the nasal mucosa finely to provide prompt drug absorption but it may get cleared from plasma shortly. Extended or prolonged drug release hardly expected from such systems and formulations with the viscosity more than 0.5 Pa.s are difficult to be sprayed in nasal cavity[13]. Therefore *in situ* nasal gelling systems with smart polymers (Stimuli responsive polymers) came into the picture, which are liquid at a room temperature, and can be instilled easily or sprayed in nasal cavity and where they attain semisolid or gel form to get retained in nasal cavity. Nasal cavity has the temperature of about 32±2° and pH 5.5-6.5 also mucous secreted by nasal submucosal glands comprises of sodium, calcium and potassium ions. In response to these conditions certain temperature, pH and ion responsive polymers can undergo reversible gelation upon exposure to nasal cavity and can be used in delivering drug in controlled manner[12,14-16].

Advantages of smart polymers in nasal drug delivery[17]:

Along with ease of administration, prolonged retention in nasal cavity and sustainable drug delivery, these systems possess some additional advantages such as, polymers used in stimulus responsive *in situ* nasal gel may have absorption enhancement effect on drug e.g. chitosan derivatives like trimethyl chitosan enable the paracellular transport of large molecules across the mucosal surface by opening tight junctions. Isoforms of the P450 enzyme, rhodanase, glutathione S-transferases, and carboxylesterases have been detected in the human nasal mucosa. Entrapment of the drug in viscous gel matrix can protect the drug from enzymatic degradation.

Temperature responsive polymers in nasal drug delivery:

This type of polymers exhibit sol to gel transition upon exposure to the nasal temperature, for example poloxamer 407, which is a thermosensitive polymer frequently used for *in situ* gelation. It is a nonionic surfactant consists of polyoxyethylene-polyoxypropylene copolymers. At a given temperature when poloxamer is dispersed in aqueous phase above the critical micellar concentration, there is formation of micelles with hydrophilic shell and hydrophobic core. Micellization is mainly the function of hydrophobic block. At higher concentrations these micelles start arranging themselves in various structures (liquid crystalline phases) like lamellar, cubic and hexagonal. At higher temperature the hydrophilic chains of the copolymer (polyoxyethylene) become desolvated due to the rupture of the hydrogen bonds present between the chains and solvent. This leads to enhanced hydrophobic interactions among the polyoxypropylene chains, and leads to gel formation. At low temperatures a liquid micellar phase is stable however at high temperature it transforms into the cubic structure. Thermoreversible gelling properties of various poloxamer grades depends upon the molecular weight and ratio of molecular weight of hydrophilic core to molecular weight of hydrophobic core[18,19]. Poloxamer 407 aqueous solution 16-18% exhibited thermoresponsive gelling at 32±2°, which is closer to nasal temperature[20-22].

Though poloxamer is responsible for *in situ* gelling comparatively low molecular weight and nonionic nature makes the poloxamer weak mucoadhesive agent. Therefore to enhance the retention, mucoadhesive polymers like carbopol 934P, chitosan, sodium carboxymethyl cellulose (NaCMC), hydroxypropyl methylcellulose (HPMC),

hydroxypropyl cellulose and methylcellulose can be added to the poloxamer gel in the concentration range 0.2-0.5%. As mentioned above mucous comprises of mucin which is anionic polyelectrolyte rich in sulphate groups therefore polymers having ability to interact electronically or to form hydrogen bonds can act as good candidates for mucoadhesion. In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 1 00 000 D. Therefore anionic polymers like Carbopol 934P, NaCMC, HPMC K-15 due to their hydrogen bond forming ability with mucin and cationic polymers like chitosan and its derivatives, aminated gelatin due to their ability to form ionic interaction have proved efficient bioadhesives in nasal drug delivery[23]. Addition of mucoadhesive agents reduces the gelling temperature of the poloxamer[22]. Also other formulation additives can influence gelling time and temperature of poloxamer. Jadhav *et al*. formulated thermoresponsive nasal gel of *Nardostachys jatamansi* with poloxamer 407-polyethylene glycol (PEG) 400-PEG 4000[24]. It is reported that as the concentration of the PEG 4000 increases there is increase in the gelling temperature. This can be predicted as; PEG is nonionic, hydrophilic compound, which may establish intermolecular hydrogen bonding with poloxamer chains and water. At the elevated temperature, this hydrophilic interaction has to be weakened and hydrophobic interaction between poloxamer chains should become dominant for gelling. Therefore with increasing concentration of PEG, there is delayed gelation time and temperature[24].

Hydrophobically modified polyelectrolytes:

These are the alternatives for above discussed systems. Mucoadhesion of the poloxamers can be enhanced by using copolymers containing both hydrophobic segment (assist the copolymer to aggregate and gel) and a polyelectrolyte segment (provide mucoadhesiveness). Hydrophobically modified polyelectrolytes are the class of polymers where polymers having ionizable groups are attached to hydrophobic backbone. One of the example of this is copolymer of pluronic and poly(acrylic acid), which at low concentrations has shown thermogelling property and enhanced mucoadhesion. poly(acrylic acid) is the standard polymer used regularly as a benchmark for providing mucoadhesiveness. Bromberg worked with different polymers such as Pluronic-poly(acrylic acid) copolymers, Carbomer and Pluronic F127. The study reported enhancement of the residence time of fluorescent labels by the Pluronic-poly(acrylic acid) copolymers compared to other polymers in rat nasal cavity[25,26].

Actually poloxamer F127 is thermosensitive polymer and poly(acrylic acid) is pH-sensitive polymer. Due to presence of carboxylic acid in poly(acrylic acid), which get deprotonated at the basic pH and acquire negative charge. Thus polymers possessing similar charged group causes repulsion and the material expand in dimensions leading to gelation. In hydrophobically modified system, in order to achieve adequate mucoadhesion to the polymer, high concentration of the pH sensitive polymer i.e. poly(acrylic acid) has to be used. This makes physical mixture and/or random copolymer of thermosensitive and pH-sensitive polymer only pH-sensitive. It loses its thermosensitivity. But 1–5% w/v Pluronic-poly(acrylic acid) graft-copolymer (1:1) solution shows $10–10^3$ fold increase in viscosity at the nasal temperature. Graft-copolymerization retains the thermosensitivity of Pluronic-poly(acrylic acid) copolymer at physiological pH[27].

Chitosan-based temperature responsive systems in nasal drug delivery:

Aqueous chitosan solutions are pH-dependent gelling systems. Amino groups present on chitosan get protonated towards acidic pH (below the pKa value of chitosan 6.2) and repulsion between them causes expansion/swelling of the system thus pH-dependent gelling phenomenon is observed with chitosan[28]. But Nazar *et al.* synthesized thermosensitive *in situ* nasal gel from *N*-trimethyl chitosan chloride with PEG and glycerophosphate for drug delivery[29]. Basics of this thermosensitive gelling of chitosan found in U.S. patent 6,344,488 by Chenite *et al.*[30]

Chenite *et al*. mixed chitosan acidic solution with glycerophosphate aqueous solution, which can undergo gelling at 37° and pH above 6.5[30]. Mechanism of this gelling was predicted as, at lower temperature strong interaction between chitosan and water prevents the aggregation of hydrated chitosan molecules. But at elevated temperature, (a) chitosan/chitosan inter chain hydrogen bonding; (b) chitosan/organophosphate electrostatic attractions (between ammonium group of chitosan and phosphate group of glycerophosphate; (c) structuring action of the polyol parts on water molecules facilitates hydrophobic interactions

between chitosan chains. Thus chitosan-chitosan and chitosan-phosphate interaction at elevated temperature responsible for gelling[29].

Any solution of chitosan-glycerophosphate cannot undergo gelation as long as pH of the solution maintained below 6.45. Thermoreversible gelation property exhibited by chitosan-glycerophosphate solution in the pH range 6.5-6.9 and above pH 6.9 irreversible gelation occurs[29]. But drawback with this system is chitosan-based thermosensitive gel undergo a slow transition from sol to gel at body temperature because chitosan is soluble in low pH in its protonated form especially in the acidic environments. Therefore, Nazar *et al.* substituted chitosan with N-trimethyl chitosan chloride, a positively charged, water soluble chitosan derivative and added PEG 4000 which provides additional sites for hydrogen bonding and allows the formation of more extensive gel network[29]. N-trimethyl chitosan of medium average molecular weight and low degree of quaternisation (3.6% w/v) with 5.8% w/v PEG 4000 and 2.5% w/v glycerophosphate undergo thermal gelation at 32.5° within 7 min and exhibit good mucoadhesive properties[30]. Wu *et al.* formulated temperature sensitive hydrogel using *N*-[(2-hydroxy-3-trimethylammonium)propyl] chitosan chloride (HTCC) and PEG with a small amount of α,β-glycerophosphate[31]. HTCC is water soluble, mucoadhesive derivative of chitosan which has absorption enhancement effect on nasal mucosa. Role performed by α,β-glycerophosphate and PEG are same as discussed earlier. Insulin loaded this thermogel delivered through nasal route showed enhanced retention, absorption and decreased blood glucose concentration drastically almost 40–50% of initial blood glucose concentration for at least 4 to 5 h after administration in rats[31]. Incorporation of glycerophosphate responsible for turbid nature of the gel and negatively charged moieties of glycerophosphate may interact with various bioactive components[32].

Chitosan-polyvinyl alcohol:

Polyvinyl alcohol (PVA) is water-soluble polyhydroxy polymer. At the lower temperature PVA-chitosan is a liquid solution. At the room temperature there is existence of intermolecular H-bonds between –OH and $–NH_2$ groups of chitosan and –OH groups of PVA, also H bonding between water and PVA due to hydrophilic nature of PVA. These hydrophilic interactions lead to dissolution of chitosan chains. At lower temperature low mobility of the chitosan chains prevent association of junction chains. At the higher temperature intermolecular H bonding gets ruptured, mobility of chitosan chains enhances which removes surrounding water molecules and increases association of hydrophobic chitosan chains with each-other. Thus, hydrophobic interaction between chitosan chains is dominant at higher temperature responsible for thermo responsible gelling while at lower temperature hydrophilic interactions of PVA with water and chitosan are dominant. If ratio of PVA to chitosan is exceeded than 10:1, temperature sensitive *in situ* gelling property vanishes[33].

Agrawal *et al.*[32] incorporated insulin in chitosan-PVA thermosensitive gel and evaluated *in vitro* and *in vivo*. Formulation containing 3% chitosan and 2% PVA showed thermo responsive gelling, high swelling index and the potential of controlling the blood sugar level for 6 h[32].

Poly(N-isopropylacrylamide) (PNiPAAm):

Some copolymers can be considered by their critical solution temperature around which their solubility behavior gets changed. In other words, hydrophobic and hydrophilic interactions between the polymeric chains and the aqueous media sharply get altered. Polymer is soluble in water when the temperature is lower than the lower critical solution temperature (LCST) and hydrophilic interactions between polymer chains and water are dominant, but as the temperature increases above the LCST hydrophobic interactions between polymer chains become stronger[34]. LCST of (PNiPAAm) is 32° therefore it can be effectively used for localization of drug in nasal cavity. Ryden and Edman[35] observed influence of intranasal administration of insulin on plasma glucose levels in rats by incorporating insulin in particulate systems based on solid epichlorohydrine cross-linked dextran spheres and 2 thermogels namely ethyl (hydroxyethyl) cellulose and (PNiPAAm)-co-polyacrylamide. Ethyl (hydroxyethyl) cellulose also possessed thermogelling characteristics like (PNiPAAm) and having LCST at 30-32°. Addition of small amount of ionic surfactant to ethyl(hydroxyethyl) cellulose leads to the formation of micelle aggregates, which interact with polymer chains at elevated temperature to form stiff gel[35]. Examples of thermresponsible nasal gels are shown in Table 2.

TABLE 2: EXAMPLES OF THERMORESPONSIBLE NASAL GELS

Drug	Category	Composition of thermo-responsive gel	References
Venlafaxine hydrochloride	Dual acting antidepressant	17% poloxamer 407, 1% methocel A4M (mucoadhesive)	[21]
Fexofenadine hydrochloride	Antihistaminic	Poloxamer 407, chitosan (mucoadhesive)	[36]
Hydroxypropyl ß-cyclodextrin inclusion complex of artemether	Antimalarial	Poloxamer 407 (18%), HPMC K4M (0.5–1.5%)	[37]
Midazolam hydrochloride	Antiepileptic	16% poloxamer 407, carbopol 934P, HPMC, mucilage extracted from *Ficus carica* (mucoadhesive agent)	[20]
Ondansetron hydrochloride	Management of nausea and vomiting associated with cancer chemotherapy	18% poloxamer 407, hydroxypropyl cellulose	[22]
Metoclopramide	Antiemetic	Poloxamer 407, carbopol, polyethelene glycol 6000, hydroxypropyl cellulose, PVA, chitosan	[38]
Sumatriptan	Antimigraine	Poloxamer 407, carbopol 934P	[39]
Plasmid DNA	-	Poloxamer 407 (12% w/w), poloxamer 188 (20% w/w), polycarbophil, polyethelene oxide	[40]
Ropinirole	Dopamine agonist	Chitosan/ß-glycerophosphate, HPMC for mucoadhesion	[41]
Ellagic acid	Treatment of brain cancer	Chitosan/ß-glycerophosphate	[42]
Insulin	Peptide hormone	3.6% HTCC, 5.4% PEG 4000, 3% α,ß-glycerophosphate	[31]
Insulin	Peptide hormone	3% chitosan and 2% PVA	[32]
Insulin	Peptide hormone	Poly(N-isopropylacrylamide)	[35]

HPMC: Hydroxypropyl methylcellulose, HTCC: hydroxypropyl trimethylammonium chitosan chloride, PVA: polyvinyl alcohol

pH-responsive polymers in nasal drug delivery:

Generally pH sensitive polymers are the ionisable moieties (weakly basic/weakly acidic) on the hydrophobic backbone. Polymers having acidic groups e.g. carboxylic acid group get deprotonated at the (basic) pH and acquire negative charge. Thus polymers possessing similar charged group causes repulsion and the material expand in dimensions. When pH becomes normal the functional groups lose their charge hence the repulsion disappears and the material regains its original shape. Same mechanism expected with the polymers having basic groups which get protonated in acidic pH and causes electrostatic repulsion[28]. Carbopol 934, an acrylic acid derivative showed *in situ* gelling by deprotonation at nasal pH. Nandgude *et al.* formulated pH induced *in situ* nasal gel of salbutamol sulphate using 0.4-0.5% w/v carbopol 934 for sustained release and enhanced bioavailability whereas chitosan exhibit acidic pH-responsive gelation[43]. Amino groups present on chitosan get protonated towards acidic pH and repulsion between them causes expansion/swelling of the system thus pH dependent gelling[28].

Hornof *et al.* evaluated viscoelastic properties of chitosan-thioglycolic acid conjugates *in vitro*[44]. Chitosan-thioglycolic acid also called as thiolated chitosan. This polymer is formed by amide linkage between amino group of chitosan and carboxylic group of thioglycolic acid. *In situ* pH dependent gelation due to formation of intermolecular and intramolecular disulphide bonds at physiological pH was reported with this polymer. At the physiological pH, concentration of the H^+ ions decreases due to which thiol groups (-SH) present on the chitosan get converted to thiolated ions (S^-) which represents active form for oxidation to form intermolecular and intramolecular disulphide bonds. Also thiolated chitosan has superior mucoadhesive properties over unmodified chitosan. This new excipient found promising for gelation at physiological pH because the elastic properties of this gel were found to increase significantly with the degree of thiolation at pH 5.5[44].

Polymethacrylic acid and polyethylene glycol (P(MAA-g-EG)):

Nakamura *et al.* formulated mucoadhesive pH sensitive budesonide micro particles of polymethacrylic acid and PEG for nasal delivery[45]. Mechanism behind its swelling at nasal pH is same as that of carbopol i.e. deprotonation at nasal pH and deswelling in acidic pH due to its strong intermolecular interaction with PEG. Following intravenous administration of budesonide, the plasma concentration peaked immediately and decreased rapidly over the next 4 h but with nasal administration of the polymeric formulations, the peak plasma concentration was reached in about 45 min, and the concentration in plasma remained constant for a minimum of 8 h. Thus intranasally administered budesonide-polymer possess enhanced durability of the drug concentration in plasma[45].

Polyvinylacetal diethylamino acetate:
Aikawa *et al.*[46] incorporated chlorpheniramine maleate and tetrahydrozoline hydrochloride in polyvinylacetal diethylamino acetate pH sensitive gel. Polyvinylacetal diethylamino acetate forms transparent solution at pH 4, which shows abrupt changes at pH 7 by turbidometry studies. This change appeared to be due to precipitation or hydrogel formation. The hydrogel formation on the mucous membranes in the rat nasal cavity was visually confirmed. Dynamic light scattering and scanning electron microscopy indicate there is pore shrinkage of the hydrogel with increase in the temperature from 25-37° at pH 7.4, which potentially responsible for controlling the drug release[46,47]. Examples of pH responsive nasal gels are listed in Table 3.

Ion responsive polymers in nasal drug delivery:
Ion responsive polymers generally have ionisable groups. These polymeric systems exhibit uncommon rheological behavior upon coulombic interaction with appositely charged species. Gellan gum is anionic polysaccharide composed of 1,3-β-D-glucose, 1,4-β-D-glucoronic acid, 1,4-β-D-glucose and 1,4-α-L-rhamnose repeat units. It has the characteristic property of temperature-dependent and cation-induced gelation. Upon complexation with cations and hydrogen bonding with water, there is formation of double helical junction zones and a three-dimensional network responsible for *in situ* gelling[48].

Cao *et al.* developed ion-activated *in situ* gel of mometasone furoate with 0.2-0.5% w/v gellan gum and 0.15% xylan gum[49]. Sodium, potassium and calcium ions present in nasal mucous interact with anionic groups of the gellan gum which results into sol to gel transition to produce prolonged release of mometasone furoate[15]. Also *in situ* nasal gel formulation of scopolamine hydrobromide with gellan gum was compared with subcutaneous and oral administration in rats, the study exhibited decreased symptoms of motion sickness with nasal gel formulation. Prolonged radioactivity of ^{99m}Tc in the rabbit nasal cavity indicated prolonged retention of gel in nasal cavity[49].

TABLE 3: EXAMPLES OF pH-RESPONSIVE NASAL GEL

Drug	Category	Composition of pH-sensitive gel	References
Salbutamol sulphate	β_2-adrenergic agonists used in treatment of bronchospasm	0.4-0.5% carbopol 934P, HPMC	[43]
Budesonide	Glucocorticoid steroid used for the treatment of asthma, rhinitis	Polymethacrylic acid and polyethylene glycol	[45]
Chlorpheniramine maleate, tetrahydrozoline hydrochloride	Antihistaminic	Polyvinylacetal diethylamino acetate 3-7%	[46]

Krauland *et al.* modified gellan gum by linking covalently l-cysteine to deacetylated gellan gum[50]. The deacetylated gellan gum-cysteine conjugate displayed superior *in situ* gelling properties *in vitro* compared to unmodified polymer[50].

Another famous example of ion responsive *in situ* gelling nasal drug delivery is PecFent® (fentanyl citrate) nasal spray which uses Archimedes Pharma's patented drug delivery system, PecSys™. PecSys™ is a proprietary pectin-based drug delivery system which delivers fentanyl in controlled manner with fast onset of action and is designed as fine mist spray which forms a gel when it comes in contact with the nasal mucosa. In PecFent® gelling agent is a mixture of sucrose and low methoxyl (LM) pectin. Pectins are heterogeneous polysaccharides comprising a backbone of galacturonic acids units linked by α-1,4 bonds, with a component of neutral sugars such as galactose, xylose, rhamnose and arabinose either in the backbone or as side chains. LM pectin has the degree of esterification ≤50%. High methoxyl (HM) pectins have a degree of esterification (DE) of >50%. Gelling properties of pectin are highly affected by degree of esterification. LM pectins can form gel in the presence of divalent cations, such as calcium following similar mechanism of gellan gum due to the formation of intermolecular junction zones by side by side association of homogalacturonic smooth regions of different chains. Unlike LM pectin HM-pectin forms gel with sugar and acid but in PecFent® sucrose may be added to stabilize the structure of junction zones[51-54].

When nasal fentanyl-pectin spray compared with fentanyl chitosan and fentanyl in chitosan-poloxamer 188 in phase I studies, it exhibited the most favorable tolerability profile and lowest nasal reactogenicity symptom incidence compared to fentanyl chitosan and fentanyl in chitosan-poloxamer 188. In pharmacokinetic studies, PecFent showed superior pharmacokinetic profile compared to transmucosal oral fentanyl citrate[55]. Ion sensitive nasal *in situ* gels are listed in Table 4.

TABLE 4: ION SENSITIVE NASAL *IN-SITU* GELS

Drug	Category	Gelling agents	References
Fentanyl citrate	Management of breakthrough pain in cancer	1% w/v pectin LM	[56]
Gastrodin	CNS diseases such as vertigo, headache, insomnia, neuralgia, neurasthenia and epilepsy	0.5% w/v deacetylated gellan gum	[57]
Mometasone furoate	Antiinflammatory in the treatment of allergic rhinitis	Gellan gum (0.2-0.5%), xylan gum (0.15%)	[15]
Dimenhydrinate	Antiemetic	Gellan gum and carbopol 934P	[58]
Radix bupleuri	Antipyretic, antiinflammatory	0.5% w/v gellan gum	[59]
Scopolamine hydrobromide	Antiemetic	0.2-1% w/v gellan gum	[49]

LM: Low methoxyl, CNS: central nervous system

CONCLUSION

Era of the nasal drug delivery has already been started and we can expect more nasal products in upcoming years in market. Nasal drug delivery has the great future with peptides/protein drugs, CNS drugs, drugs in crisis treatment as well as in long term treatment. Problems associated with retention of the drug, permeability and physicochemical properties of the drug can be deciphered with development of stimuli responsive polymeric approaches. Still *in situ* gel forming nasal drug delivery limited to very few stimuli responsive polymers. Stimuli responsive polymers like poly(N,N-diethyl acrylamide), poly(N-vinyl caprolactum) having LCST which can be modulated nearer to the nasal temperature, grafted copolymers can also be used in *in situ* gelling nasal drug delivery. Stimuli responsive vesicular, nanoparticulate systems can be expected of great potential towards efficient nasal drug delivery systems.

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Conflicts of interest:
There are no conflicts of interest.

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