ABSTRACT

In-situ gel, or in vivo gel, environment sensitive gel, is a new dosage form which has been applied as nasal drug delivery. Nasal route has been explored widely for delivery of a large number of drug molecules, owing to its rich vasculature and thin epithelial lining. When a drug is administered via nasal route it directly reaches systemic circulation and provides rapid onset of action. Compared with liquid nasal formulations, nasal in situ gels are instilled as low viscosity solutions into the nasal cavity and upon contact with the nasal mucosa, the polymer changes conformation producing a gel, so it cannot only prolong the contact time between the drug and the absorptive sites in the nasal cavity, but also release drug slowly and continuously. The phase transition can be induced by a shift in pH, a shift in temperature or by the presence of cations. The prepared gels were characterized for physical appearance, pH, solution viscosity, drug content, In vitro drug release studies were conducted in Simulated nasal fluid pH and drug was analyzed by UV spectrophotometry. Diffusion data were fitted to various models to ascertain kinetics and mechanism of drug release from gels. Fourier Transform Infra Red (FTIR) spectra of the optimized formulations revealed no drug excipient interaction.

KEYWORDS: Insitu gel, Nasal drug delivery, Phase transition, Nasal Cavity.

1. INTRODUCTION

Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a three dimensional network of inter connected molecule or aggregates which immobilizes the liquid continuous phase.[1]
Gels may also be classified based on the nature of the bonds involved in the three-dimensional solid network. Chemical gels arise when strong covalent bonds hold the network together and physical gels when hydrogen bonds and electrostatic and van der waals interaction maintain the gel network.

1.1 In-Situ Gel Delivery Systems[2]

In-situ gelation is a process of gel formation at the site of application after the composition or formulation has been applied to the site. In the field of human and animal medicine, the sites of application refers to various injection sites, topical application sites, surgical sites, and others where the agents are brought into contact with tissues or body fluids. As a drug delivery agent, the in-situ gel has an advantage related to the gel or polymer network being formed in-situ providing sustained release of the drug agent. At the same time, it permits the drug to be delivered in a liquid form. In situ is a Latin phrase meaning in the place.

Importance Of In Situ Gelling System[3]

- The major importance is the possibilities of administrating accurate & reproducible quantities compared to already formed gel.
- In-situ forming polymeric delivery system such as ease of administration
- Reduced frequency of administration.
- Improved patient compliance & comfort.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.
- Extended nasal retention time.

Ideal Characteristics Of Polymers

A polymer used to in situ gels should have following characteristics-

- It should be biocompatible.
- It should be capable of adherence to mucus.
- It should have pseudo plastic behaviour.
- It should be good tolerance & optical activity.
- It should influence the tear behaviour.
- The polymer should be capable of decrease the viscosity with increasing shear rate thereby offering lowered viscosity during blinking & stability of the tear
- Film during fixation.
1.2 Polymers Used In In-Situ Gelling Systems

Materials that exhibit sol to gel transition in aqueous solution at temperatures between ambient and body temperature is of interest in the development of sustained release vehicles with in situ gelation properties. Polymers capable of in-situ gelation include Poloxamer, Pluronics, various copolymers such as PEO-PLLA and PEG-PLGA-PEG, cellulose acetophalate latex, Pectin, Gelrite, Gellan gum, Alginate, Carbopol, chitin and Matrigel. The gel formation is induced by temperature change (Poloxamer, Pluronics, PEO-PLLA diblock copolymer, PEG-PLGA-PEG triblock copolymer, and Matrigel), pH change (cellulose acetophalate latex and Carbopol), or reaction with mono- or di-valent cations (Gelrite).

1.3 Characteristics of gels

Gels may appear transparent or turbid based on the type of gelling agent used. They exhibit different physical properties, namely, imbibition, swelling, syneresis, and thixotropy.

**Imbibition** refers to the uptake of water or other liquids by gels without any considerable increase in its volume.

**Swelling** refers to the increase in the volume of gel by uptake of water or other liquids. This property of most gels is influenced by temperature, pH, presence of electrolytes, and other formulation ingredients.\[^{14}\]

**Syneresis** refers to the contraction or shrinkage of gels as a result of squeezing out of dispersion medium from the gel matrix. It is due to the excessive stretching of macromolecules and expansion of elastic forces during swelling. At equilibrium, the system still maintains its physical stability because the osmotic forces of swelling balance the expanded elastic forces of macromolecules. On cooling, the osmotic pressure of the system decreases and therefore the expanded elastic forces return to normal. This results in shrinkage of the stretched molecules and squeezing of dispersion medium from the gel matrix.

1.4 Classification of Gels

Gels are classified as hydrogels and organogels based on the physical state of the gelling agent in the dispersion. Hydrogels are prepared with water soluble materials or water dispersible colloids. Organogels are prepared using water - insoluble oleaginous materials.
Hydrogels[^15] Natural and synthetic gums such as tragacanth, sodium alginate, and pectin, inorganic materials such as alumina, bentonite, silica, and veegum, and organic materials such as cellulose polymers form hydrogels in water. They may either be dispersed as fine colloidal particles in aqueous phase or completely dissolve in water to gain gel structure. Gums and inorganic gelling agents form gel structure due to their viscosity increasing nature. Organic gelling agents which are generally high molecular weight cellulose polymer derivatives produce gel structure because of their swelling and chain entanglement properties. The swollen molecular chains are held together by secondary valence forces, which help in retaining their gel structure. The physical strength of the gel structure is based on the quantity of gelling agent, nature and molecular weight of gelling agent, product pH, and gelling temperature. Generally high molecular weight polymers at higher concentrations produce thick gels. The gel forming temperature (gel point) varies with different polymers. Generally natural gums form gel at lower temperatures. Gelatin, a natural protein polymer, forms gel at about 30°C. If the temperature is increased, gel consistency is not obtained even at higher concentrations of gelatin. On the other hand, polymers such as methylcellulose gain gel structure only when the temperature is above 50°C due to its decreased solubility and precipitation. Knowledge of the gel point for each gelling agent is therefore essential for preparing physically stable hydrogels.

Organogels

Organogels are also known as oleaginous gels. They are prepared using water - insoluble lipids such as glycerol esters of fatty acids, which swell in water and form different types of lyotropic liquid crystals. Widely used glycerol esters of fatty acids include glycerol monooleate, glycerol mono palmito stearete, and glycerol mono linoleate. They generally exist as waxes at room temperature and form cubic liquid crystals in water and increase the viscosity of dispersion.

Waxes such as carnauba wax, esparto wax, wool wax, and spermaceti are used in cosmetic organo gels preparations. A large quantity of water is entrapped between the three dimensional lipid bilayers. The equilibrium water content in organogels is about 35%. The structural properties of the lipid, quantity of water in the system, solubility of drug incorporated, and external temperature influence the nature of the liquid crystalline phase.

The bipolar nature of organogels allows incorporation of both hydrophilic and lipophilic drugs. Release rates can be controlled by altering the hydrophilic and hydrophobic
components. Biodegradability of these waxes by the lipase enzyme in the body makes organogels suitable for parenteral administration. The water present in the gel framework can be completely removed with some gelling agents. Gelatin sheets, acacia tears, and tragacanth ribbons are generally prepared by removal of water from their respective gel matrix. These dehydrated gel frameworks are called as xerogels.

1.5 Sol-Gel Transition

The sol phase is defined as a flowing fluid, whereas the gel phase is non-flowing on an experimental time scale, while maintaining its integrity. Above the critical concentration (critical gel concentration, (CGC) of a polymer, the gel phase appears. The CGC is most often inversely related to the molecular weight of the polymer employed. The development of physical junctions in the system is regarded as one of the prerequisites in determining pharmacy, which must be sufficiently strong with respect to the entropically driven dissolving forces of the solvent.

The determination of the boundary between the sol and gel phases depends on the experimental method. A simple test-tube inverting method was employed roughly determine the phase boundary. When a test tube containing a solution is tilted, it is defined as a sol phase if the solution deforms by flow, or gel phase if there is no flow. The flow is a function of time, tilting rate, amount of solution, and diameter of the test tube. Considering the time temperature superposition principle in polymer deformation, the test parameters should be fixed before determining the sol–gel boundary.

The falling ball method is another simple way to determine the sol-gel transition condition. When a small heavy ball resting on top of a solution (gel phase) begins to penetrate in to the gel under the specific conditions it can be regarded as a gel-sol transition. When the gelation is induced by temperature the endothermic peak during heating obtained from differential scanning calorimetry (DSC) determines the transition temperature as well as gelation temperature.

1.6 Various Stimuli Responsive Gels

pH-Responsive gels.[16]

Some polymers show pH - dependent swelling and gelling characteristics in aqueous media. A polymer that exhibits such phase transition properties is very useful from the point of drug delivery. Methacrylic acids (e.g., carbomers) that contain many carboxylic acid groups exist
as solution at lower pH conditions. When the pH is increased, they undergo a sol - to - gel transition.\textsuperscript{[17]} This is because of the increase in the degree of ionization of acidic carboxylic groups at higher pH conditions, which in turn results in electrostatic repulsions between chains and, increased hydrophilicity and swelling. Conversely, polymers that contain amine - pendant groups swell at lower pH environment due to ionization and repulsion between polymer chains. The ionic strength of surrounding fluids significantly influences the equilibrium swelling of these pH - responsive polymers. Higher ionic strength favors gel – counter ionic interactions and reduces the osmotic swelling forces.

**Thermo Responsive gels\textsuperscript{[18]}**

A dispersion which exists as solution at room temperature and transforms into gel on instillation into a body cavity can improve the administration mode and help in modulating the drug release. Many polymers with thermo responsive gelling properties are currently being synthesized and evaluated. A triblock copolymer that consists of polyethylene glycol – polylactic acid, glycolic acid – polyethylene glycerol (PEG – PLGA – PEG) is solution at room temperature and gels at body temperature. Polaxomers, which are made of triblock poly (ethylene oxide) – poly (propylene oxide) – poly (ethylene oxide), exhibit gelatin properties at body temperatures. Similarly, xyloglucan and xanthan gum aqueous dispersions are solutions at room temperature and become gel at body temperature. These are considered convenient alternatives for rectal suppository formulations which usually cause mucosal irritations due to their physical state. The physicochemical properties of these chemically modified thermo responsive gels are altered by changing the ratio of hydrophilic and hydrophobic segments, block length, and polydispersity. ReGel by MacroMed contains a triblock copolymer PLGA – PEG – PLGA, undergoes sol - to - gel transition on intratumoral injection, and releases paclitaxel for six weeks.

**Ionic-Responsive gels**

Administration of sodium alginate aqueous drops into the eye results in alginate gelation due to its interaction with calcium ions in the tear fluid. Alginate with high gluronic acid and deacetylated gellan gum (Gelrite) show sol - to - gel conversions in the eye due to their interaction with cations in the tear fluid. Timolol maleate sterile ophtshalmic gel - forming solution (Timoptic -XE) that contains Gelrite gellan gum is commercially available.

**Enzyme-responsive gels**
Dextran-tyramine (dex-TA) conjugates were in situ cross linked in the presence of H$_2$O$_2$ and horseradish peroxidase (HRP), yielding chemically cross linked, highly elastic and degradable hydrogels. The HRP-mediated coupling reaction of phenol moieties in dex-TA conjugates occurred via a carbon–carbon bond at the ortho positions and/or via a carbon–oxygen bond between the carbon atom at the ortho position and the phenoxy oxygen. The gelation time could be varied from 5 s to 9 min, depending on the polymer concentrations and enzyme or H$_2$O$_2$/tyramine ratio.

1.7 Various Applications Of In Situ Gelling Systems

1) In Situ Forming Polymeric Systems For Ocular Delivery

For in situ based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, anti-inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics cause rapid elimination of the drug from the eyes. So to overcome bioavailability problems, ophthalmic in situ gels were developed$^{19}$. Aqueous solution of gellan dropped into eye undergoes transition into gel state due to the temperature and ionic condition (Ca$^{++}$) in the tear. Drug release from these in situ gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops.

Various water soluble polymers such as carbopol system hydroxypropylmethylcellulose system, poly (Methacrylic acid)-poly (ethylene glycol) come under the category of pH induced in situ precipitating polymeric systems. Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH.

2) In Situ Forming Polymeric Systems For Rectal And Vaginal Delivery$^{20}$

In situ gels also possess a potential application for drug delivery by rectal and vaginal route. For a better therapeutic efficacy and patient compliance, a mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating clotrimazole-β-cyclodextrin complex was formulated for treatment for vaginitis$^{21,2}$. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymer such as Carbopol 934 and hydroxyl propyl methyl cellulose to ensure long residence time at the application site.
3) In Situ Forming Injectable Drug Delivery Systems

The development of injectable in situ forming drug delivery has received a considerable interest over the last decade. 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 solution to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to 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 slats to chitosan aqueous solution. This system was used successfully to deliver biologically active growth factors in vivo as well as encapsulated matrix for living chondrocytes for tissue engineering applications.

A novel, injectable, thermosensitive in situ gelling hydrogel was developed for tumor treatment. This hydrogel consisted of drug loaded chitosan solution neutralized with β-glycerophosphate. Local delivery of paclitaxel form the formulation injected intratumorally was investigated using EMT-6 tumors implanted s.c. on Balb/c mice. These experiments showed that one intratumoral injection of the thermosensitive hydrogel containing paclitaxel was as effective as four intravenous injections of taxol in inhibiting the growth of EMT-6 cancer cells in mice, but in a less toxic manner.

Synthetic polymers are popular choice mainly for parenteral preparations. Aliphatic polyesters such as poly lactic acid, poly glycolic acid, poly decalactone, etc. are widely used. The feasibility of lactide/glycolide polymers as excipients for the controlled release of bioactives is well proven.

Photopolymerizable systems when introduced to the desired site via injection get photocured in situ with the help of fiber optic cables and then release the drug for prolonged period of time. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes leading to an implant formation. These systems can be used to release water soluble drugs and enzymes at a controlled rate.
Thermosetting systems are in the sol form when initially constituted, but upon heating, they set into their final shape. This sol-gel transition is known as curing. But if this cured polymer is heated further, it may lead to degradation of the polymer. Curing mainly involves the formation of covalent cross links between polymer chains to form a macromolecular network. This system is liquid outside the body and is capable of being injected by a syringe and needle and once inside the body it gels.

In situ precipitating polymeric systems the polymer precipitation form solution may lead to gel formation in situ and this precipitation can be induced by change in temperature, solvent removal, or by change in pH.

4) In Situ Forming Polymeric Systems For Oral Administration

Pectin, xyloglucan and gellan gum are the natural polymers used for in situ forming oral drug delivery systems.

**Pectins** are a family of polysaccharides, in which the polymer backbone mainly comprises α-(1-4)-D-galacturonic acid residues. Low methoxypectins (degree of esterification less than 50 %) readily form gels in aqueous solution in the presence of free calcium ions, which cross link the galacturonic acid chains. Although gelation of pectin will occur in the presence of H⁺ ions, a source of divalent ions, generally calcium ions is needed to produce the gels that are suitable as vehicles for drug delivery. Divalent cations present in the stomach carry out the transition of pectin to gel state when it is administered orally.

The main advantage of using pectin for the formulations is that it is water soluble, so organic solvents are not necessary in the formulation. Sodium citrate may be added to the pectin solution to form a complex with most of calcium ions added in the formulation. By this means, the formulation may be maintained in a fluid state (sol), until the break down of complex in the acidic environment of the stomach, where release of calcium ions causes gelation to occur. The quantities of calcium and citrate may be optimized to maintain the fluidity of the formulation before administration and resulting in gelation, when the formulation is administrated orally.

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like
chains. The sol-gel transition temperature varies with the degree of galactose elimination. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery. It forms thermally reversible gels on warming to body temperature. Its potential application in oral delivery exploits the proposed slow gelation time (several minutes) that would allow in situ gelation in the stomach following the oral administration of chilled xyloglucan solution. The important difference between the gelation properties of the xyloglucan and pluronic F127 from a formulation view point is that xyloglucan forms gels at much lower concentration.

5) In Situ Forming Nasal Drug Delivery Systems\textsuperscript{[25]}

The human nose has the potential to be an alternative route for the systemic delivery of a wide range of therapeutic agents. Recently, the nasal mucosa has been considered as an administration route to achieve faster and higher level of drug absorption. The richly supplied vascular nature of the nasal mucosa coupled with its high drug permeation makes the nasal route of administration attractive for many drugs, including proteins and peptides.

In addition, absorption of drug at the olfactory region of the nose provides a potential for a pharmaceutical compound to be available to the central nervous system.

Because of valuable surface and accessibility, the nasal mucosa represents an interesting administration route, not only for products with local activity, but also for products with systemic activity.

The principle involving the in situ gelling of solid nasal formulations is that the nasal formulations imbibe in the nasal fluid after administration and forms gel into the nasal cavity. The formation of nasal gel avoids the foreign body sensation. Due to bioadhesive property the gel adheres the nasal mucosa. It acts as release controlling matrix and thus act as sustained drug delivery system.
Polymers used in the formulations are polyacrylic acid polymers like carbopol, carrageenan, chitosan and its derivatives, hydroxypropyl methyl cellulose (HPMC), polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, sodium carboxy methyl cellulose (Na CMC), xanthan gum, sodium alginate, polyoxypropylene-polyoxyethylene block copolymers, poloxamer 188 and 407.

An in situ gel system for nasal delivery of mometasone furoate was developed and evaluated for its efficacy for the treatment of allergic rhinitis.

1.8 Nasal Anatomy and physiology
In recent decades, the nasal mucosa has become an established administration site for systemic drug delivery and a desirable alternative to parenteral medication since it is amenable to self-medication, has potential for direct-to-central nervous system delivery, no first-pass metabolism, non-invasiveness and virtually painless. From a pharmacokinetic standpoint, intranasal administration circumvents first-pass elimination and drug absorption is rapid due to the existence of a rich vasculature and a highly permeable structure within the nasal membranes.

The nasal cavity may also be exploited as a route of entry into the systemic circulation mainly for those compounds which can not be given orally because they get destroyed in the gastrointestinal fluids, metabolized in the wall of gastrointestinal tract or undergo extensive first-pass metabolism by the liver during their first passage around the circulation. Currently, many nasal drug products on the market are indicated for the treatment of local disease such as allergic rhinitis, pain and for centrally acting drugs where the direct pathway from the nose to brain might offer a quicker and further specific therapeutic effect. Many low-molecular-weight, non-polar drugs (<300Da) in solution form are able to infiltrate the nasal epithelium.
with effortlessness. The proposed mechanism of absorption is suggested via aqueous channels. Molecules higher than 300 Da, experience difficulty in absorption similar to gastrointestinal tract. The nasal epithelium adds one more hurdle in absorption, which is mucociliary clearance. Absorption enhancers are being used to enhance absorption across the nasal membrane, which may work by solubilize and stabilize the drug or by altering properties of the mucus layer by opening tight junctions between the cells or by increasing membrane fluidity. Currently, there are several various nasal drug delivery systems available in various phases of development to deliver high molecular weight compounds. A system for the nasal drug delivery is highly unlikely given the types of materials being considered, the different physical and chemical characteristics of drugs and the different target areas of the drug within the body. The effectiveness of a particular delivery system is also affected by its formulation as a liquid, powder, gel, microsphere, liposome or nanoparticle. This review focuses on the current state of art in the field of drug delivery through nasal route.

Advantages of Nasal Route

Systemic nasal absorption of drug is a new attractive alternative to parenteral drug delivery system, as it offers the following advantages:

- Rapid absorption
- Higher bioavailability allowing lower doses
- Fast onset of therapeutic action
- Avoidance of liver or gastrointestinal metabolism.
- Avoidance of gastric irritation.
- Ease of selfmedication,
- Improved patient compliance
- Reduced risk of infectious disease transmission.
- Unlike the skin, nasal mucosa is not constructed from the keratinized stratum corneum.

The subepithelial layer of the nasal mucosa with numerous microvilli is highly vascularized, with large and fenestrated capillaries facilitating rapid absorption.

- The rate and extent of absorption as well as plasma concentration vs time profiles are comparable with I.V. administration.
- Various nasal drug delivery systems are available for user-friendly noninvasive painless application.
Limitation of Nasal Drug Delivery System

There is risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the drug substances and from the constituents added to the dosage forms.

- Certain compounds when used as absorption enhancers may disrupt and even dissolve the nasal membrane in high concentration.
- Nasal atrophic rhinitis and severe vasomotor rhinitis can reduce the capacity of nasal absorption, e.g., Caerulein.
- There could be mechanical loss of the dosage form into the other parts of the respiratory tract like lungs.
- Untoward immunogenic effects might arise with the route.

Structure of nasal cavity

The nasal vestibule has the smallest cross-sectional area in the respiratory tract (approximately 0.3 cm$^2$ on each side) that extends from the entrance of nostril, which is guarded by vibrissae (hairs), to the anterior end of the inferior turbinate. The area from the anterior ends of the turbinate to the anterior portion of the nasopharynx constitutes the main nasal passages. Microvilli are found on the columnar cell, which increases the surface area available for absorption. The nasal mucosa is highly vasculature, superficial and deep layers of arterioles supply the lamina propria and between the venules and capillaries. Most of the area of the nasal cavity serves the function of cleaning the air we breathe before it reaches the lungs. It does this with the help of the respiratory mucosa, which lines the walls of the nasal cavity. Within this mucosa, small, hair-like cilia move in a wave-like motion, moving mucus to the back of the throat. The olfactory membrane, or, is a layer of cells on the roof of the nasal cavity.

1.9 Various Dosage Forms Given By Nasal Route

Solution and Sprays

The drug solutions are nasally administered as nasal drops, sprays, and as metered dose nebulizer. The dose of the active ingredient administered depends upon the volume of drug and the concentration of drug in the formulation. The therapeutic levels of nitroglycerine, 3 ng/ml in central venous blood, 1.7 ng/ml in arterial blood, and 0.4 ng/ml in peripheral venous blood were achieved within 2 minutes following intranasal administration of 0.8 mg/ml of nitroglycerine in normal saline. The effect of formulation variables such as dose of active
ingredient, pH of the solution, and its osmolarity on nasal absorption has been reported by various researchers.

**Suspensions**

Suspensions for nasal administration are prepared by suspending the micronized drug in a liquid diluent or carrier suitable for application to the nasal mucosa. The preparation of suspension form gave a better insulin uptake and blood glucose reduction compared with that from the solution.

**Powders**

Powder dosage forms of drugs for nasal administration offer several advantages over liquid formulations. In the powder form, the chemical stability of the drug is increased, a preservative in the formulation is not required, and it is possible to administer larger doses of drugs. Powder form is suitable for number of non-peptide drugs and is well suited for peptide drugs.

Polymer-based powder formulations show no adhesion until their absorption of mucus occurs on the nasal mucosa surface. This allows easy application to the nasal cavity by metered dose in sufflation even if the polymer is highly mucoadhesive. In addition, liquid preparations are more easily cleared to the nasopharynx and oropharynx from where they enter the posterior part of the tongue.

Therefore, administration of nasal powders may increase patient compliance, especially if the smell and taste of the delivered drug is unacceptable. After getting in contact with the nasal mucosa, polymer-based powders are believed to form a viscous gel following absorbing water from the nasal mucus. Then, the free polymer chains penetrating into the tissue crevices can hold back the ciliary movement, which will increase the retention time of the drugs in the nasal cavity.

Dry powder formulations can also avoid the utilization of preservatives and freeze storage, because they do not support microbial growth and are more stable than solution. For these reasons, the dried powder is the most commonly studied formulation for the nasal drug delivery, including small hydrophobic drugs, peptide drugs, and vaccine prepared dry powder nasal influenza vaccine formulation by using spray-freeze-drying method; the results indicated that the powders were amorphous and more stable with respect to liquid
formulations. In vivo experiments demonstrated that the powders significantly increased residence time in rats and elicit enhanced serum and mucosal antibody response.

**Nasal Particulate Drug Delivery System**

Nasal particulate systems using mucoadhesive polymers as carriers include microparticle/sphere and nanoparticle. Particulate drug carrier systems administered through nasal mucosa may protect the drug from enzymatic degradation, increase the drug dissolution rate, intensify the contact of the formulation with the mucosa, enhance the uptake by the epithelium, and act as a controlled release system resulting in prolonged blood concentrations. Among the polymers widely used as nasal drug particulate carrier, the positively charged polymers such as chitosan and aminated gelatin are most attractive because of their hydrogel nature which leads to opening of the tight junctions and their intimate contact with the negatively charged mucosa membrane. In vivo evaluation in rabbits has proved that chitosan nanoparticles were able to improve the nasal absorption to a great extent compared with chitosan solution due to the intensified contact of the nanoparticle with the nasal mucosa as compared with chitosan solutions.

It has been believed that nanoparticles possess superiority over microspheres as nasal drug carrier because their larger surface area results in more intimate contact with the mucosa, which leads to higher local concentration gradient.

Moreover, nanoparticles cross the mucosal epithelium better than microspheres do. Microparticles smaller than 10 μm administered intranasally are believed to be taken up by the M-cells overlaying the nasal-associated lymphoid tissue (NALT) and transported to submucosal layers. However, in case of the nanoparticles, besides the M-cell-associated phagocytosis, the epithelial cells are also involved in the transport of nanoparticles by internalization.

Recent study by showed that FITC-albumin-loaded chitosan nanoparticles, when administered in the nasal cavity, were able to cross the mucosal layer, taken up by rat nasal epithelia and NALT cells. This property of nanoparticles provides a good indication of their potential as gene and vaccine carriers.

Teijeiro-Osorio et al. found that the transfection efficiency of the nanoparticles loaded with pSEAP (100-200 nm) was higher than the naked DNA (control).
Recently, many studies confirmed that association of vaccines to the nanoparticulate systems has shown to enhance the antigen uptake by nasal lymphoid tissues.

**Semisolid dosage forms**

A gel is a soft, solid or solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. A gel should, on a time scale of seconds, not flow under the influence of its own weight. The solid-like characteristics of gels can be defined in terms of two dynamic mechanical properties: An elastic modulus, \( G'(\omega) \), which exhibits a pronounced plateau extending to time at least of the order of second; and a viscous modulus, \( G''(\omega) \), which is considerably smaller than \( G'(\omega) \). The first biological uses of gels (polymerized methyl methacrylate) were presented by the institute for Macromolecular Chemistry in Prague in 1960 and involved the manufacturing of contact lenses, arteries, etc.

Gelation occurs through the cross-linking of polymer chains, something that can be achieved by (i) covalent bond formation (chemical cross-linking) or (ii) non-covalent bond formation (physical crosslinking). Gels have been used for the delivery of drugs for both systemic and local actions (see the review by Peppas et al.). Many different methods using gels have been reported, including subcutaneous delivery for sustained release, buccal delivery, deliveries to the stomach, colon, rectum, vagina, and nasal.

Gel formulations with suitable rheological properties increase the contact time with the mucosa at the site of absorption. The increased contact time is caused by the mucoadhesive properties of the polymer in the gel and by the rheological properties of the formulation reducing the clearance by the nasal and ocular protective mechanisms.

**Nasal dosage form and delivery system**

The final dosage form used for nasal drug delivery is chosen after consideration of a wide range of issues, covering patient convenience, efficiency of drug delivery and formulation reasons. Nasal sprays, nasal gels, squeeze bottles, and liquid droppers are some of the more common delivery methods that can be seen as nasal dosage forms. There are three main ways of depositing inhaled particles or the nasal lining: impaction, sedimentation and diffusion. Impaction occurs when there is a change in direction of the airflow - as happens when inspired air passes through the nasal valve – and the inertia of large or fast-moving particles carries them in their original direction. Sedimentation happens when the moving slowly and the particles settle slowly under the force of gravity. The final method of deposition diffusion
occurs by Brownian motion and is thus limited to very small particles (< 0.5 mm). Nasal dosage forms will usually contain the drug in a liquid or powder formulations delivered by a pressurized or pump system. Liquid formulations used for nasal drug delivery are usually aqueous solutions of the drug and thus have the general benefits and drawbacks of pharmaceutical solutions. They are relatively simple to develop and manufacture compared to solid dosage forms but often have a lower microbiological and chemical stability, requiring the use of various preservatives.

2. CONCLUSION

In situ gel, or in vivo gel, environment sensitive gel, is a new dosage form which has been applied as nasal drug delivery recently. Compared with liquid nasal formulations, nasal in situ gels are instilled as low viscosity solutions into the nasal cavity and upon contact with the nasal mucosa, the polymer changes conformation producing a gel, so it cannot only prolong the contact time between the drug and the absorptive sites in the nasal cavity, but also release drug slowly and continuously. Hence, it is especially useful for those drugs used chronically.

3. REFERENCES


