A REVIEW ON IN SITU NASAL DRUG DELIVERY

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ABSTRACT : In situ forming polymeric formulations are drug delivery systems that are in sol form before administration in the nasal cavity, but once administered, undergo gelation in situ, to form a gel. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. In the recent years, nasal route has been identified as promising drug delivery route for systemic therapy. Mucoadhesive in situ gel formulations have demonstrated increase in the residence time in the nasal cavity as well enhancement of the permeation characteristics of the drug. The in situ gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. Nowadays, it has created much interest, because of its characteristics of high vascularization, high permeability, rapid onset of action, low enzymatic degradation, and avoidance of hepatic first pass metabolism. The main aim of this review is to provide knowledge of different mechanisms of nasal absorption and approaches for nasal drug delivery.

Keywords: Polymer, *In-situ* drug delivery, Formulation, Mucoadhesive, Metabolism, Sustain drug delivery .

INTRODUCTION

The most desirable and convenient method of drug administration is the oral route because of their ease of administration. However, in many instances, oral administration is not desirable since the drug undergoes significant degradation via first pass effect in liver . In the recent years, considerable attention has been focused on the development of new drug delivery systems . The goal of any drug delivery system is to deliver a prescribed therapeutic amount of drug to the proper site in the body. In order to maintain the drug concentration within therapeutically effective range, novel drug delivery system can be employed. NDDS is advanced drug delivery system which improves drug potency, control the drug release to give a sustained therapeutic effect, provide greater safety, finally it target a drug specifically to the desired tissue. The new drug delivery systems that have been developed and developing are the mucoadhesive drug delivery systems, drug patches, transdermal patches etc. Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. Various sites for the mucoadhesive drug delivery system are ocular, buccal cavity, GIT, vaginal, rectal, nasal etc. The nasal route is an important mode of drug delivery, with a growing number of products available for administration through the route for systemic and local administration. An in-situ gel is a new dosage form. In situ gel has been applied in nasal drug delivery recently. Compared with other liquid nasal formulation nasal in-situ gels are administered as low viscosity solution into the intranasal cavity which upon contact with the nasal mucosa, the polymer changes conformation making a gel. So that it not only increases the contact time between the drug and the absorptive site but also releases the drug slowly in the nasal cavity. A gel is a state between liquid and solid, which consists of physically cross-linked networks of long polymer molecules, with liquid molecules trapped within a three-dimensional polymeric network swollen by a solvent. Before administration, the in-situ gelling system is a liquid aqueous solution and it changes into a gel at the physiological condition. Prolonged and sustained release of the

drug is reproducible, and in-situ gel is biocompatible, with magnificent stability and reliable quantities of medication, making it more accurate. There are various routes for in situ gel drug delivery, for, example, oral, ocular, vaginal, rectal, intravenous, intra peritoneal, etc. Gelation happens through crosslinking of the polymer chain, which can be attained through covalent bond formation (chemical crosslinking) or non-covalent bond formation (physical crosslinking). A different mechanism exists which produce the formation of in-situ gels, like depend on physiologic stimuli (e.g. temperature modifications, pH-triggered systems), those based on physical changes in biomaterials (e.g. Solvent exchange and swelling), and those depend on chemical reactions (e.g. UV radiation, ionic copolymerization agents, or a directly applied trigger for gelation. In-situ gel formulation is carried out for targeted delivery through the vaginal and rectal routes, and the nasal mucosa, circumventing the hepatic first-pass metabolism, which his important for the proteins and peptides delivery that is usually administered via the intravenous route because of their susceptibility to the gastrointestinal protease.

Nasal Drug Delivery:

Intranasal route is considered for the drugs that are ineffective orally and are used chronically where rapid entry into the Circulation is desired and they require small doses. The absorption of drugs from the nasal mucosa most probably takes place via the aqueous channels of the membrane. Therefore, as long as the drug is in the form of solution and the molecular size is small, the drug will be absorbed rapidly via the aqueous path of the membrane. The absorption from the nasal cavity decreases as the molecular size increases. Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the time allowed for drug absorption to occur. However, mucoadhesive preparations had been developed to increase the contact time between the dosage form and mucosal layers of nasal cavities.

Nasal Anatomy and Physiology:

The nose is divided into two nasal cavities via the septum. The volume of nasal cavity is approximately 15 ml with a surface area of around 150 cm^2. The three distinct functional regions are present in the nose – vestibular, respiratory, and olfactory regions . Amongst these, the respiratory region is the most important for systemic drug delivery. The respiratory epithelium consists of basal cells, mucus containing goblet cells, ciliated columnar and non-ciliated columnar cells. The cilia move in a wavelike fashion to transport particles to the pharynx area for ingestion . Additionally, the cells in this region are covered by nearly 300 microvilli, providing a large surface area for absorption. Below the epithelium is the lamina propria, where blood vessels, nerves, serous glands, and mucus secretory glands may be found. The lamina propria also houses a dense network of capillaries, through which drug absorption takes place.The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min. The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children. The mucus layer entraps particles, which are then cleared from the nasal cavity by the cilia. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min. The nasal cavity also houses numerous enzymes..

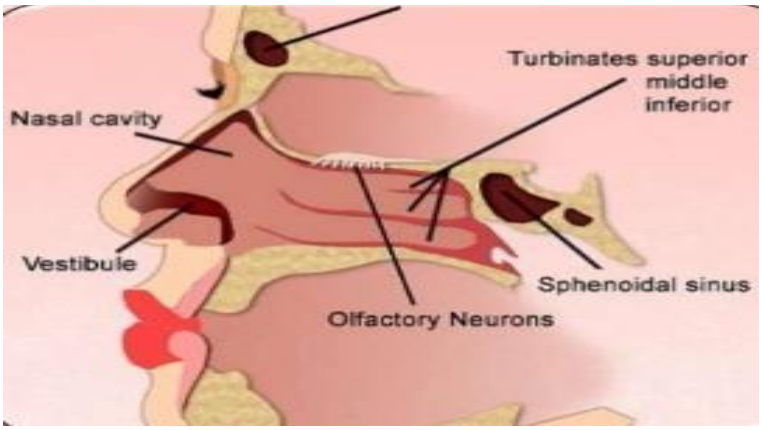

FIG.1: PARTS OF NASAL CAVITY CONSISTS OF NASAL VESTIBULE, INFERIOR TURBINATE, MIDDLE TURBINATE, SUPERIOR TURBINATE AND OLFACTORY NEURONS

Advantages of In Situ Gel Nasal Formulation

- Increased residence time of drug in nasal cavity.

- Decreased frequency of drug administration.
- Results in rapid absorption and onset of effect.
- Avoids degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
- Low dose required.
- Minimized local and systemic side effects.
- Improved bio-ability of drug.
- Direct transport into systemic circulation and CNS, is possible
- Offers lower risk of overdose of CNS acting drug
- Improved patient compliance.
- Needle-free (painless)
- Non-invasive
- User -friendly
- Ease of administration
- Self-medication possible
- The nasal route is suitable when compared with a parenteral route for long term therapy
- The risk of transmission of infectious disease reduces Rapid absorption and onset of pharmacologic action
- Highly vascularized mucosa
- Easy accessibility to blood capillaries
- Large nasal mucosal surface area

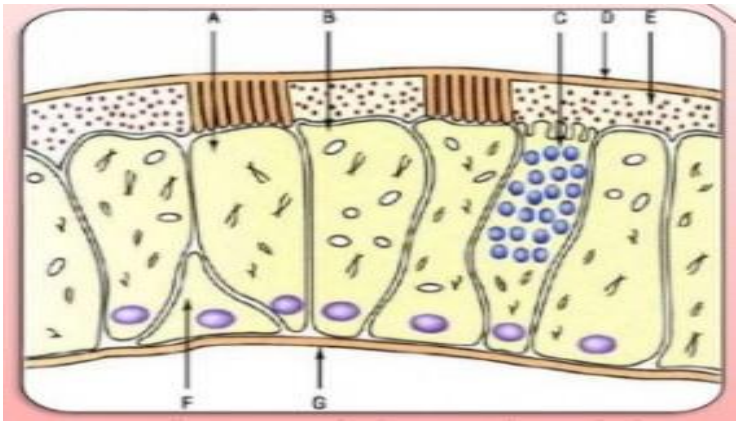

FIG.2: CELL TYPE OF THE NASAL EPITHELIUM SHOWING CILIATED CELL (A) NON CILIATED CELL (B) GOBLET CELLS (C) GEL MUCUS LAYER (D) SOL LAYER (E) BASAL CELL (F) BASEMENT MEMBRAN

Barriers for nasal drug delivery

Low bioavailability, muco-ciliary clearance, and enzymatic degradation act as major barriers for nasal drug delivery. Some important characteristics of various barriers which mainly affect the nasal drug delivery are discussed below.

Low bioavailability

• Bioavailability of polar drugs is mainly low (about 10% for low molecular weight drugs and 1% for peptides such as calcitonin and insulin).

• With a large molecular weight, polar drugs have limited nasal absorption.

• Drugs can cross the epithelial cell membrane by the transcellular and paracellular routes between cells.

• Polar drugs with a molecular weight below 1000 Da will pass the membrane by the latter routes.

• Nasal absorption of polar drugs is enhanced by coadministration of absorption-enhancing agents. • Polarity lipophilic:

1. LMW lipophilic -100% bioavailability

2. HMW amphipathic -10% bioavailability

3. Peptides

1% Examples

• Surfactants (Sodium lauryl sulfate, sodium dodecyl sulfate, phosphatidylcholines)

• Bile salts (Sodium glycocholate, sodium taurocholate, sodium deoxycholate)

• Fatty acids and their derivatives (linoleic acid)

• Phospholipids (lysophosphatidylcholine)

• Various cyclodextrin and cationic compounds like chitosan, poly-L-arginine, and poly-L-lysine

• Fusidic acid derivatives (sodium tauradihydrofusidate)

Muco-ciliary clearance

It is an essential factor which involves the combined action of the mucus and cilia, which defend against inhaled foreign particles in the respiratory tract.

• Across the nasal mucosa, it leads to decreased transport of drugs because of high clearance.

• It has also been shown that for liquid and powder formulations which are not bioadhesive, the half-life for clearance is of the order of 15–30 min.

- ❖ The bioadhesive excipients are used in the formulations as an approach to overcome the rapid mucociliary clearance.

• The clearance may also be decreased by depositing the formulation in the anterior and less ciliated part of the nasal cavity, thus leading to improved absorption.

Enzymatic degradation

• When peptides and proteins cross the nasal mucosa, there is the possibility of an enzymatic degradation of the molecule in the lumen of the nasal cavity or during passage through the epithelial barrier, which can limit the bioavailability of the drug.

• These two sites contain exopeptidases such as mono and diamino peptidases, that can cleave peptides at their N and C termini, and endopeptidases such as serine and cysteine, which can attack internal peptide bonds. The use of enzyme inhibitors, cosolvents, and prodrugs may be the approaches to overcome this barrier.

MECHANISM OF NASAL ABSORPTION

1. **First mechanism:**

   It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 daltons having drugs shows poor bioavailability.

2. **Second mechanism:**

   It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that shows a rate dependency on their lipophilicity. Drug also cross cell membrane by an active transport route via carrier- mediated means or transport through the opening

METHOD OF FORMULATION

Generally, two methods are used for the preparation of in-situ nasal gel,

- ❖ Cold Method
- ❖ Hot Method

Cold Method:

In this method the drug is stirred with sufficient quantity of double distilled water and kept overnight at 4 ˚ C in a refrigerator. The in-situ gelling polymer is added slowly with continuous stirring. The dispersion is then stored in a refrigerator until clear solution is formed and finally volume is adjusted. This method is selected when poloxamer, chitosan or carbopol is used as a gelling polymer. Considering the fact that polymeric

dispersion of poloxamer remains as solution at lower temperature and gets converted into gel at higher nasal temperature because the solubility of polypropylene oxide chain of poloxamer decreases at high temperature which results in precipitation or salting out of polymer. Similarly, chitosan also requires low temperature to remain as solution at room temperature, its hydrophobicity increase with increase in temperature.

Hot Method:

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

FACTORS AFFECTING NASAL DRUG DELIVERY SYSTEM

1.Physicochemical properties of a drug

a) Molecular weight: Nasal delivery is expected to decrease with an increasing molecular weight of the drug molecule. A linear inverse correlation within the absorption of drugs and the molecular weight of the drug has been reported and the molecular weight of the drug is greater than 1000 Da except by using of absorption enhancers. With the use of permeation enhancers, good bioavailability to at least 6000 Daltons can be achieved.

b) Chemical form: It is an important factor for drug absorption. By changing the drug into salt or an ester form can change its absorption; e.g. in situ absorption of carboxylic acid esters of L-tyrosine was significantly greater than that of unmodified L-Tyrosine.

c) Size: Particle size and morphology of a drug are important tools for the design of nasal drug delivery. Generally, particles in the 5-10 microns range should be deposited in the nostrils. Too fine particles, less than five microns may be inhaled into lungs and should be avoided for nasal products while

particles greater then 10µm are deposited with the upper respiratory tract.

d) Solubility: Solubility is not only limited the drug absorption, but it can also limit a formulators ability to formulate a formulation if the drug is not sufficiently soluble in the desired vehicles. From a mechanistic and thermodynamic standpoint of view, it is important to learn about the relationship between a drug's saturation solubility and its absorption.

e) Lipophilicity : Lipophilic compounds tend to readily cross biological membranes via the transcellular route and these compounds can partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Some examples of lipophilic drugs like naloxone, buprenorphine, testosterone, and 17a-ethinylestradiol, are completely or almost completely absorbed by the nasal route in animal models. The permeation of the compound normally increases through nasal mucosa by increasing lipophilicity.

f) Pka and partition coefficient: According to the pH partition theory, unionized species are absorbed better compared with ionized species and the same holds in the case of nasal absorption.

g) Polymorphism: It can affect the rate of drug dissolution, solubility, and absorption through biological membranes.

2. Physicochemical properties of a formulation

a) Drug concentration, dose, and dose-volume: Drug concentration, dose ,and dose-volume of administration are three interlinked parameters that affect the performance of the nasal delivery system. If the drug concentration formulations increasing by increasing formulation volume there may be a limit as to what extent nasal absorption will drain out of the nasal cavity. 0.05-0.15ml is the ideal dose volume with an upper limit of 0.20ml.

b) pH and mucosal irritation: In addition to the properties of the nasal surface, the pH of the formulation can affect a drug's permeation. Both the pH and pKa of a drug are considered to rationalize systemic absorption. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5. Nasal secretions contain lysozyme, which destroys certain bacteria at acidic pH .Lysozyme is inactivated and the nasal tissue is susceptible to microbial infection under alkaline conditions.

c) Buffer capacity: Nasal formulations are administered in little volumes ranging from 25 to 200µL. Hence, nasal secretions may change the pH of the administrated dose. This can affects the concentration of unionized drugs available for the absorption. Therefore, an appropriate formulation buffer capacity may be required to maintain the pH in-situ.

d) Solubilizers: Aqueous solubility of the drug is always a limitation for nasal drug delivery in solution. Co-solvents are usedfor increasing solubility like glycols, alcohol, Transcutol, medium-chain glycerides and Labrasol can be used to enhance the solubility of drugs.

e) Preservatives: Nasal formulations mostly contain preservatives to protect them from microbial contamination. Some generally used preservatives are parabens, benzalkonium chloride, and benzoyl alcohol. Preservatives are used in small quantities and are not likely to affect drug absorption

f) Antioxidants: Antioxidants have not any effect on drug absorption or cause nasal irritation. Example-sodium metabisulfite, sodium bisulfate, butylated hydroxyltoluene, and tocopherol.

g) Humectants: Intranasal moisture is important for preventing dehydration. Therefore, humectants can be added mostly in gel-based nasal products to avoid irritation of the nasal cavity. Humectants do not affect drug absorption. Examples like glycerin, sorbitol, and mannitol.

h) Absorption enhancer: Absorption enhancers could also be needed when a drug has poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation. Once a suitable enhancer is identified, its optimal concentration should be experimentally determined. Generally, higher concentrations of absorption enhancers are probable to result in nasal irritation and damage to the nasal mucosa. On the other hand, lower enhancer concentrations would generally provide lower or no improvement of absorption.

i) Osmolarity: Isotonic solutions are administered for shrinkage of the nasal epithelial mucosa, because of the effect of osmolarity on the absorption, this results in increased permeation of the compound because of structural changes in the compound. Isotonic solutions also are known to inhibit ciliary activity.

j) Viscosity: The higher viscosity of the formulation increases contact time between the drug and therefore the nasal mucosa, thereby increasing permeation time. At the same time, formulations with high viscosity can affect the normal functions like ciliary beating or muco-ciliary clearance and thus changes the permeability of drugs.

3. Physiological factors

a) Blood flow/ supply: Nasal mucosa has a larger surface area and rich with blood supply which makes nasal an optimum place for drug absorption. The blood flow influences significantly the systemic nasal absorption of the medicines that because it enhances more drug passes through the membrane, reaching the overall circulation

b) Nasal secretion: The mucus layer probably exists as a double layer (5 mm thick) consisting of a periciliary sol phase in which the cilia beat and a superficial blanket of gel a removed forwards by the tip of the cilia. The permeability of drug through the nasal mucosa is suffering from viscosity of nasal secretion. Approximately 1.5-2.1 ml of mucus is produced daily in the nasal cavity. It is reported that if the sol layer of mucus is too thin, the viscous surface layer will inhibit the ciliary beating, and if the sol layers too thick, mucociliary clearance is impaired because contact with cilia is lost. The solubility of a drug in nasal secretions: a drug needs to be solubilized before it permeates. Various studies revealed that the secretion ad clearance rates are reduced at night thus altering the permeation of drug. In such cases, chronokinetics will dictate the pattern and rate of permeation.

c) Nasal cycle: In this process congestion and relaxation regulate the rise and fall in the amount of drug permeation process

d) pH of the nasal cavity: Nasal cavity pH in the adult is 5.5-6.5 and 5.0-7.0 in infants. A greater drug permeation is usually achieved at a nasal pH that is lower than the drugs pKa because under such conditions the penetrant molecules exist as unionized form. A change in the pH of mucus can affect the ionization and thus increase or decrease the permeation of drugs, depending on the nature of the drug. The ideal pH of a formulation should be within 4.5–6.5 and if possible the formulation should also have the buffering capacity.

e) Effect of mucociliary clearance: The main function of the mucociliary clearance system is to remove foreign substances (bacteria, allergens and so on) and particles from the nasal cavity, thus preventing them from reaching the lower airways. Normal mucociliary transit has been reported to be 12 to 15 min. Transit times of more than 30 min are considered to be abnormal and are indicative of impaired mucociliary clearance. Reduced Mucociliary clearance (MCC) and ciliary beating (MCC) increases the time of contact between a drug and the mucous membrane and subsequently enhances drug permeation; whereas, increased MCC decreases drug permeation. Some factors affecting MCC like drugs, hormonal changes of the body, pathological conditions, environmental conditions, and formulation factors.

Effect of deposition on absorption: Deposition of the formulation in the anterior portion of the nose provides an extended nasal residence and better absorption, and this is an area of low permeability, whereas ,in the posterior portion of the nose, where the drug permeability is generally higher, the deposited drug is eliminated by mucociliary clearance and therefore has a shorter residence time.

g) Effect of enzymatic activity: Many enzymes might affect the stability of drugs that are present on the nasal mucosa. For example, proteins and peptides are subjected to degradation by proteases and aminopeptidases at the mucosal membrane.

4. Biological Factors: Efforts have been made to modify and explore the structural features and mechanism of nasal mucosa to increase its permeability, this is usually not available in the normal physiology of the nasal cavity, mainly during chronic application. These alterations could cause unintended adverse effects and result in pathological implications.

a) Structural features: Nasal epithelium mainly consists of different types of cells that show variety in nasal absorption and because of other factors such as presences of microvilli, cell density, surface area ,and several cells. The respiratory region is most accurate and suitable for permeation of the compounds.

b) Biochemical changes: A large number of enzymes such as oxidative and conjugative enzymes, peptidases and proteases are mainly actedon nasal

mucus which is an enzymatic barrier for the delivery of drugs. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in the creation of a pseudo-first-pass effect, which hampers the absorption of drugs. Some example like the nasal P450-dependent mono oxygenase system has been implicated in nasal metabolism of nasal decongestants, alcohols, nicotine, and cocaine.

5. Pathological condition: Diseases such as the common cold, rhinitis, atopic rhinitis and nasal polyposis are usually associated with mucociliary dysfunctioning, hypo or hyper secretions, and irritation of the nasal mucosa, which can influence drug permeation.

a) Environmental condition: Temperatures in the range of 24°C cause a moderate reduction in the rate of MCC.A linear increase in ciliary beat frequency occurs with an increase in temperature, which in turn influences the properties of the mucous membrane.

DIFFERENT METHODS TO IMPROVE NASAL ABSORPTION

1)Permeation enhancers:

A variety of permeation enhancers have been investigated to improve the nasal absorption, like fatty acids, bile salts, phospholipids, surfactants, cyclodextrin, etc., which act via different mechanisms such as inhibition of enzyme activity, reduction of mucus viscosity, decreasing muco-ciliary clearance, opening tight junctions, and solubilizing or stabilizing the drug.

2) Prodrug approach: Pro drugs are the inactive chemical moiety that becomes active at the target site. This approach is mainly used to improve physicochemical properties such as taste, solubility ,and stability of the formulation. This approach includes the derivatization of C and N termini, esters, and cyclic prodrugs.

3) In situ gel: The conversion into a gel by the influence of stimuli including temperature, pH, and ionic concentration, is possible with substances like Carbopol, cellulose derivatives, lecithin, chitosan, etc. These formulations generally control the problems of administration.

4)Nasal enzyme inhibitors: Enzyme inhibitors like protease and peptidase are used as inhibitors for the

formulation of peptide and protein molecules. Other examples are bile salts, amastatin, bestatin, boroleucine, fusidic acids, etc.

5) Structural modification: Drug structure can be modified without changing the pharmacologic activity, to improve nasal absorption. Chemical modifications are mainly used to modify the physicochemical properties of the drug such that they lead to improved nasal absorption of the drug.

6) Mucoadhesion: Mucoadhesion is defined as the state in which two materials are held together for a long period. Muco adhesive polymers make contact with the biological membrane, and after the establishment of contact, they penetrate the tissue surface. Natural polymers can be easily obtained from natural sources, and require an environmentally-friendly method of processing ata low cost. Some examples include potato starch, rice starch, maize starch, wheat starch, guar gum, tragacanth, xanthan gum, etc. Synthetic polymers have high cost of production and also produce environmental pollution during synthesis. These polymers include polyethylene oxide, polyvinyl alcohol, methylcellulose, ethylcellulose, hydroxyl propylmethylcellulose, etc.

IN SITU GEL

In Latin, in situ means ‘in position’ or ‘in its original place .For the past 30 years, greater attention has been directed towards the development of controlled and sustained drug delivery systems. A vast amount of research has been carried out in designing polymeric systems such as in situ gels .In situ gel formation of drug delivery systems can be defined as a liquid Formulation generating a solid or semisolid depot after administration. In situ activated gel ,forming Systems are those which are when exposed to physiological conditions that will shift to a gel phase. This new concept of manufacturing a gel in situ was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or Non-covalent bond formation (physical cross-linking).The routes of administration for in situ gel could be oral, ocular, rectal, vaginal, injectable and intra-peritoneal. “Gel” is that the state which exists in between liquid and solid, which consists

of physically crosslinked networks of long polymer molecules, with liquid molecules trapped within a three-dimensional polymeric network swollen by a solvent. This system is a liquid aqueous solution before the administration and a gel at physiological conditions. Prolonged and sustained release of the drug is reproducible, and the in situ gel is biocompatible, with magnificent stability and reliable quantities of medication, making it more accurate. There are various routes for in situ gel drug delivery, for example, oral, ocular, vaginal, rectal, intravenous, intraperitoneal, etc .In situ gel is a new dosage form that has been applied in nasal drug delivery recently. Compared with other liquid nasal formulations, nasal in situ gels are administered 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 also the absorptive sites within the cavity but also release drug slowly and continuously, hence ,it especially useful for those drugs used chronically. The phase transition can be induced by a shift in pH, a shift in temperature or by the presence of cations.

IMPORTANCE OF IN SITU GELLING SYSTEM

The major importance is that the possibility of administering accurate and reproducible quantities compared to already formed gel. It increases the exposure time of drugs with that of mucus at the site of absorption and has better bioavailability, increases patient compliance.

PRINCIPLE OF IN SITU GELLING SYSTEM

The principle of in situ gelling system is of solid nasal formulations are that the nasal formulations absorb the nasal fluid after administration and form a gel within the cavity. The foreign body sensation can avoid by the formation of nasal gel within the cavity. Due to bioadhesive nature, the gel adheres to the nasal mucosa. It acts as a release controlling matrix and thus acts as a sustained drug delivery system.

TRIGGERED IN SITU GELLING FORMATION

1. **Temperature triggered in situ gel :**

   There are some polymers which undergo large and unexpected physical

and chemical changes in response to small external changes in their environmental conditions. Such polymers are called Stimuli-responsive polymers. They are also called as stimuli-sensitive, intelligent, smart or environmentally sensitive polymers. These polymers recognize a stimulus as a signal, judge the degree of the signal and then transform their chain confirmation in response. Temperature sensitive polymers are most extensively studied class of environmentally responsive polymer systems in drug delivery. This is because temperature is relatively easy to control and also easily applicable to both in vitro and in vivo. In this system, gelling of solution is triggered by alteration in temperature, thus sustaining the drug release. These hydrogels exists in liquid form at room temperature (20-25°C) and undergo gelation when comes in contact with body fluid (35-37°C). The use biomaterial whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach in situ formation. The best critical temperature range for such systems is ambient and physiologic temperature; such that clinical manipulation is facilitated and no external source of heat other than that of body is required to trigger gelation. Temperature sensitive polymers may be,

1. Positive thermosensitive gels: This system has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling UCST. E.g. Polymer networks of poly (acrylic acid)
2. Negative thermosensitive gels: This system have a lower critical solution temperature (LCST) and contract upon heating above the LCST. E.g. poly (N-isoprophylacrylamide)
3. Thermo reversible gels E.g. poloxamers/pluronics, tetronics

2. pH triggered in situ gel : Another physiological stimulus that induces formation of in situ gel is pH. Polymers included in this class contain an acidic or a basic group that either accept or release protons when they are exposed to different environmental pH. Hence these are called pH sensitive polymers. Most of the pH sensitive polymers containing anionic group are based on PAA (Carbopol®, Carbomer) and its derivatives.

2. **Ion- activated in situ gel:** In this type of gelation, polymer that undergoes phase transition in presence of ions. Gellan gum is an anionic polysaccharide that undergoes phase transition in the presence of monovalent and divalent cations like Ca2+, Mg2+, K+, and Na+ present in the nasal secretion.

VARIOUS POLYMERS USED IN TRIGGERED SYSTEM

Poloxamer : Poloxamers are tri block copolymers with a center block of hydrophobic polypropylene oxide (PPO) flanked by two hydrophilic polyethylene oxide (PEO) blocks. Among this family of copolymers, poloxamer 407 is a non-ionic surfactant with reversible gelation properties above a particular polymer concentration and a particular temperature. The gelation phenomenon is reversible and characterized by a solgel transition temperature (sol-gel). Below sol-gel, poloxamer407 aqueous solutions remain fluid and the solution turns to a semi-solid material above this temperature which is shown in the The thermo gelation is due to hydrophobic interactions between the poloxamer 407 copolymer chains. By elevating the temperature, the poloxamer 407 copolymer chains start to aggregate into a micellar structure. The formation of micelle structures is a result of the dehydration of the hydrophobic PPO repeat units and defines the initial step of gelation. sol-gel is concentration dependent and increases by a reduction of the poloxamer 407 concentration in aqueous solution until a lower level is reached at which point poloxamer 407 does not gel anymore.

• Chitosan : Chitosan, an amine-polysaccharide is a pH dependent, cationic polymer. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. Adding poly salts, bearing a single anionic head, like glucose phosphate salts to chitosan aqueous solution can transform the cationic polysaccharides solution into thermally sensitive pH dependent gel.

• Carbopol: Carbopol is a polyacrylicacid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. Carbopol

(poly acrylic acid) is a well-known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH.

• Pectin : Pectins are a family of polysaccharides. Low methoxypectins readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains. Although the gelation of pectin will occur in the presence of H+ ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery.

• Gellan gum : Gellan gum is an anionic deacetylated, exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of 1b-l-rhamnose, 1b D-glucuronic acid and 2b D-glucose. The mechanism of gelation involves the formation of double-helical junction zones followed by aggregation of the double helical segments to form a 3-D network by complexation with cations and hydrogen bonding with water. Because human nasal mucosa is covered with approximately 0.1 ml mucus, which consists of sodium, potassium and calcium ions.

• Ethyl (Hydroxyethyl) Cellulose: Ethyl (hydroxyethyl) cellulose (EHEC) is a non-ionic amphiphilic polymer containing ethylene oxide (EO) groups, having mixed hydrophobic (low amount) and hydrophilic structural units. EHEC shows macroscopic phase separation when the temperature is raised above the lower critical solution temperature (LCST), as the result of the intermolecular aggregation of hydrophobic domains. The presence of hydrophilic segments in more amounts in relation to hydrophobic units renders EHEC water-soluble. Semi-dilute aqueous solutions of a certain, rather hydrophobic type of the nonionic cellulose derivative EHEC have been shown to exhibit thermogelling properties in the presence of ionic surfactants

APPLICATION OF IN-SITU POLYMERIC DRUG DELIVERY SYSTEM

Depending on the route of drug delivery in-situ drug delivery may be,

1. **Oral drug delivery system:** Pectin, xyloglucan and gellan gum are the

natural polymers used for in situ forming oral drug delivery systems. Although the gelation of pectin will occur in the presence of H+ ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. The potential of an orally administered in situ gelling pectin formulation for the sustained delivery of paracetamol has been reported.

2. **Ocular drug delivery system:** For in situ gels 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. Aqueous solution of gellan dropped into the eye undergoes transition into the gel state due to the temperature and ionic condition (Ca++) in the tear fluid. Much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug delivery. Drug release from these in situgels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops.

3. **Nasal drug delivery system:** In the recent years, nasal route has been identified as promising drug delivery route for systemic therapy. Mucoadhesive in situ nasal gel formulations have demonstrated increase in the residence time in the nasal cavity as well enhancement of the permeation characteristics of the drug.

4. **Rectal drug delivery system:** In situ gels also possess a potential application for drug delivery by rectal and vaginal route. Miyazaki et al. investigated the use of xyloglucan based thermoreversible gels for rectal drug delivery of indomethacin.

5. **Vaginal drug delivery system**: For a better therapeutic efficacy and patient compliance, a mucoadhesive,

thermosensitive, prolonged release vaginal gels are also used.

6. **Injectable drug delivery system:** 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.

Conclusions

In the recent years, nasal route has been identified as promising drug delivery route for systemic therapy. Mucoadhesive in situ nasal gel formulations have demonstrated increase in the residence time in the nasal cavity as well enhancement of the permeation characteristics of the drug.In situ gel formation based on chemical reactions Ionic crosslinking, enzymatic crosslinking, and photo polymerization etc. .chemical reactions mainly cause gelation. It is predictable that intranasal formulations will go on to achieve market potential. The nasal mucosa offers controlled-release drug delivery, but due to certain limitations, the use of the intranasal route for administration of drugs is limited. To decrease these limitations, the mucoadhesive polymeric system is used. The first requirement for controlled drug delivery is to focus on patient comfort, which is offered here by the in situ gelling system. In situ gels also offer a number of other advantages, such as prolonged or sustained release of drug. For the past few decades, extraordinary and novel research on pH-induced, temperature-sensitive, and ioninduced gel-forming formulations have been described in literature. Use of good biodegradable biocompatible, and water-soluble polymers to formulate in situ nasal gels can make them further suitable and excellent as drug delivery systems.

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