Review Article

A Review on *in situ* Gel: A Novel Drug Delivery System

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ABSTRACT

The 'in situ gel' system has emerged as one of the best novel drug delivery systems; it helps for the sustained and controlled release of the drugs by its special characteristic feature of 'Sol to Gel' transition. In situ gelling system is a formulation that is in solution form before entering in to the body, but it will change to gel form under various physiological conditions. There are various polymers which under go in situ gel forming and potentially used for various routes of drug administration. There are several applications and advantages of in situ gelling system in today's life. This review mainly focus on introduction to in situ gel, its mechanism, various polymers used and its applications.

Keywords: in situ gel, novel drug delivery system, polymers.

INTRODUCTION

The '*in situ* gel' system has emerged as one of the best novel drug delivery systems, the in situ gelling system helps for the sustained and controlled release of the drugs, improved patient compliance and comfort[1] by its special characteristic feature of 'Sol to Gel' transition. In situ gelling system is a formulation that is in solution form before entering in to the body, but it will change to gel form under various physiological conditions. The sol to gel transition depends on various factors like temperature, change in pH, solvent exchange, UV radiation, and presence of specific molecules or ions. The drug delivery systems having the above mentioned properties 'sol to gel transition' can be widely used for sustained delivery vehicle preparation of bioactive molecules. There are several advantages in 'in situ gelling system' which includes ease of application of dosage, reduced frequency of administration and even protection of drug from change in environmental conditions.

Various natural and synthetic polymers undergo *in situ* gel forming and potentially can be used[2] for oral, ocular, transdermal, buccal, intraperitonial, parenteral, injectable, rectal and vaginal routes. Recent advances in in situ gels have made it possible to exploit the changes in physiological uniqueness[3, 4] in different regions of the Gastrointestinal tract for improved drug absorption as well as patient's convenience and compliance. Pectin, gellan gum, chitosan, alginic aicd, guar gum, carbopal, xyloglucan, xantham gum, HPMC, poloxamer etc are some of natural polymers used for in situ gelling system. There are several applications[5] and advantages of in situ gelling system in today's life. This review mainly focus on introduction to in situ gel, its mechanism, various polymers used and its applications.

Importance of *in situ* gelling system[7, 8]

- It helps for the controlled and sustained release of the drug by its special 'Sol Gel transition.'
- It helps for the reduced frequency of drug administration of the drug in the body.
- Low dose of the drug is required and there will be no drug accumulation and no side effects.
- The bioavailability of the drug will be more.
- There will be increased residence time of the drug due to gel formation.
- The in situ gel system decreases wastage of the drug
- Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.

Advantages of *in situ* gel system [9-11]

- Controlled and sustained release of the drug
- Ease of the drug administration
- It can be administered to unconscious patients
- More patient compliance and comfort

- Minimizing the dose frequency and drug toxicity
- Increased bioavailability
- Use of natural polymers provide biocompatibility and biodegradation
- Natural polymers have inherent properties of biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities
- Synthetic polymers usually have well-defined structures that can be modified to yield tolerable degradability and functionality.
- In situ gels can also be engineered to exhibit bioadhesiveness to facilitate drug targeting, especially through mucus membranes, for non-invasive drug administration.
- In situ gels offer an important "stealth" characteristic in vivo, owing to their hydrophilicity which increases the in vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities.

Disadvantages of in situ gel system [12, 13]

- It requires high level of fluids.
- The sol form of the drug is more susceptible for degradation.
- Chances of stability problems due to chemical degradation.
- After placing the drug eating and drinking may become restricted up to few hours.
- The quantity and homogeneity of drug loading into hydrogels may be limited, particularly for hydrophobic drugs.
- Only drugs with small dose requirement can be given.
- Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel from a targeted local site.

Ideal characteristics of polymers for preparation of *in situ* gel[14, 15]

- The polymer should be capable of adhering to the mucous membrane.
- It should be well compatible and should not provide any toxic effects.
- It should have pseudo plastic behavior.
- The polymer should be capable of decreasing the viscosity with increase in shear rate.
- Preferred pseudo plastic behavior of polymer.
- Good tolerance and optical clarity is more preferred.
- It should influence the tear behavior.

Mechanism of in situ gel

The in situ gel system's formation is done by two mechanisms such as physical mechanism and chemical mechanism.

Physical Mechanism:

In situ formation based on physical mechanism consists of the following:

Diffusion

Diffusion[17] is a type physical approach that is used in in-situ gel formulation. In this method involves the diffusion of solvent from polymer solution into surrounding tissue which results in formation of precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been commonly used polymer in formation of in-situ gelling system.

Swelling

Swelling is a type of physical approach that is used in in-situ formulation. In this method the polymer are surrounding the polymer imbibe and the fluids that are present in exterior environment and swell from out to inside and drug releases slowly. myverol (glycerol mono-oleate) is a substance which is used as polar lipid that swells in water to form Lyotropic liquid crystalline phase structures. This substance has some bioadhesive properties and it can degrade in vivo by enzymatic action.

Chemical Mechanism[18]:

In situ gelling formation based on chemical reactions mechanism

Chemical reactions that results in situ gelation may involve the following processes

Enzymatic cross-linking

Enzymatic cross linking is the most suitable method used in formation of in situ gelling system. In this method, gel is formed by cross linking with the enzymes which are present in body fluids. In situ formation induce by natural enzymes and that are not been investigated widely but appear to have some advantages over chemical and photochemical methods. For example, an enzymatic process handles efficacy under physiologic conditions and no need for possibly destructive chemicals such as monomers and initiators. Hydrogels are used in intelligent stimuli-responsive delivery systems that can release insulin have been investigated. Modify the amount of enzyme also maintain a suitable mechanism for controlling the rate of gel formation, which confess the mixtures to be injected before gel formation.

Photo-polymerization

In photo-polymerization method[19] electromagnetic radiations are used during formation of in situ gelling system. A solution of reactive macromere or monomers and invader can be injected into a tissues site and the application of electromagnetic radiation used to form gel. The most suitable polymers for photo polymerization are the polymers which undergo dissociation by polymerisable functional group in the presence of photo initiator like acrylate or similar monomers and macromers that are typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet are not used often because they are limited penetration of tissue and biologically harmful. In this method, ketone, such as 2,2 dimethoxy-2-phenyl acetophenone, is used as the initiator for ultraviolet photo- polymerization. camphorquinone and ethyl eosin initiators are used in visible light systems.

Ionic cross linking

In this method, the ion sensitive polymer is used. Ion sensitive polymers may undergo phase transition in presence of various ions like Na^{+}, K^{+}, Ca^{+}, and Mg^{+}. Some polysaccharides are also in the class of ion-sensitive ones. While k-carrageenan forms rigid, small amount of K+ are reply in brittle gels, elastic gels are forms in i-carrageenam mainly in the presence of Ca2+. Gellan gum mainly available as Gelrite. It is an anionic polysaccharide, in the presence of mono and divalent cations that undergoes in situ gelling system[20, 21].

Various approaches of *in situ* gelation

Various approaches are made in order to get in situ gelation system

Temperature triggered in situ gel

Temperature is the most widely used stimulus in environmentally responsive polymer systems in in-situ gelling formulation. The change of temperature used in easy to control, and also easily applicable both in vitro and in vivo. In this system, gelation is caused due to body temperature and no need of external heat. These hydrogels are liquid at room temperature (20–25°C) and undergo gelation when in contact with body fluids (35–37°C), due to an increase in temperature. There are three types of temperature induced systems. They are negatively thermo sensitive type Eg: Poly (N-isopropylacrylamide) positively thermo sensitive type Eg: polyacrylic acid thermally reversible type Eg: poloxamer, pluronics, Tetronics.

In this system, thermo responsive or temperature responsive polymers are used that show a drastic and discontinuous change in their physical properties with temperature. These polymers show a miscibility gap at high or low temperature an upper or lower critical solution temperature exists.

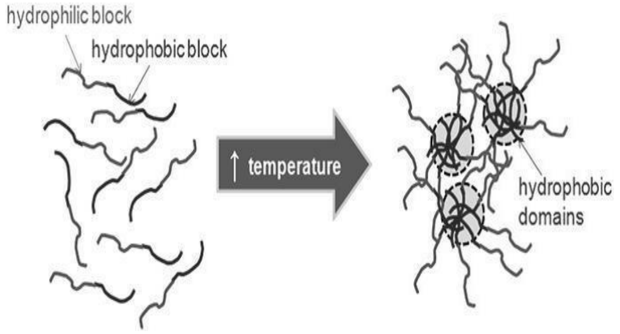

Figure 1: Mechanism of temperature sensitive system

pH triggered in situ gelation

In this system gel is formed due to pH changes. In this method pH sensitive polymers or pH responsive are used. In pH sensitive polymers includes pendant acidic or basic groups that may accept or release protons in counter to changes in environmental[22] pH. The large number polymers of ionizable groups are known as poly electrolytes. The poly electrolytes are present in the formulation causes increase in external pH that leads to swelling of hydrogel that forms in situ gel. Some suitable polymers for this approach those polymers having anionic groups. Some are cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes and poly methacrilic acid (PMC) etc.

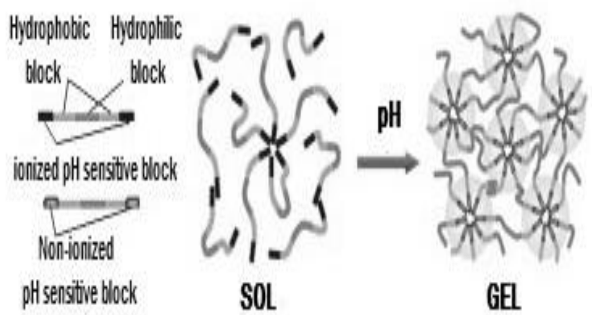

Figure 2: Mechanism of pH triggered in situ gel system

Ion activated in situ gelation

In this method, gelling of the solution instilled is triggered by change in the ionic strength[23,24]. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The polymer which shows osmotically induced gelation is Gelrite or Gellan gum, Hyaluronic acid and Alginates etc.

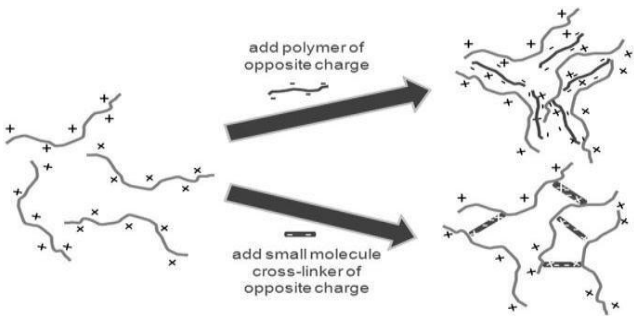

Figure 3: Mechanism of temperature sensitive system.

Polymers used as in situ gelling agents

Pectin

Pectins are a family of polysaccharides, in which the polymer contains mainly, comprises α- -(1-4)--D galacturonic acid residues. In the presence of free calcium ions, Low methoxy pectins (degree of esterification <50%) readily forms gels in aqueous solution, which crosslink the galacturonic acid chains in a manner described by egg-box model. In the presence of H+ ions the gelation of pectin will occur, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. Pectin used mainly for these formulations is that it is water soluble, so organic solvents are not used in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is orally[25] administered.

Guar gum

Properties

Guar gum is also called as guaran of naturally occurring gum which is obtained from the endosperm of the seed. Guar gum is insoluble in hydrocarbons, fats, esters, alcohols and ketones but soluble in water. These show its dispersibility in both cold and hot water that it is soluble in both cold and hot water to form colloidal solution at low amount. Guar gum has derivatives are used in targeted delivery systems in the formation of coating matrix systems, nano-microparticles and hydrogels. Guar gum also has derivatives such as graft polymers like polyacrylamide grafted guar gums that have good colon targeting[26] properties. It can also be used as a polymer in matrix tablets which shows controlled release.

Carbopol

Properties

Carbopol is a polyacrylic acid (PAA) polymer, which changed to gel as the pH is raised from 4.0 to 7.4. Carbopol remains in solution form at acidic pH but transform into a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol which enhance viscosity of carbopol solution, while reducing the acidity of the solution. Comparing different types of poly (acrylic acid) (Carbopol 940-934-941and 910) 47 concluded that Carbopol 940 showed superior[27] appearance and clarity.

Xyloglucan

Properties

Xyloglucan is also called as tamarind gum which is a polysaccharide obtained from the endosperm of the seed. Xylogulcan consists of three different oligomers like heptasaccharide, octasaccharide, nonsaccharide, which differ in number of galactose side chain. It is mainly used in oral, rectal, ocular drug delivery due to its non- toxic, biodegradable and biocompatible property. Like, poloxamer it exhibits gelation[28] on heating refrigerator temperature or cooling from a higher temperature.

Gellan gum Many natural, biodegradabl

Properties

Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid and linked together to obtained a tetrasaccharide unit. Gelrite[29] is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Due to instillation, gelrite forms gel because in presence of calcium ions. The gelation includes the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks[30] by complexaton with cations and hydrogen bonding with water. In food industry, gellan gum is used as suspending and stabilizing agent.

Alginic acid

Properties

It is a linear block copolymer polysaccharide consists of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. In each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of diandtrivalent metal ions by a cooperative process involves consecutive glucuronic residues in the α-L glucuronic acid blocks of the alginate chain[31].Alginic acid used as a vehicle for ophthalmic formulations, since it exhibits favorable biological properties such as biodegradable and non toxic[32].

Xanthum gum

Properties

Xanthan gum has high molecular weight extra cellular polysaccharide which is produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β- D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain[33]. Xanthan gum is soluble in cold and hot water as well as alkaline and acidic conditions. It exhibits good stability at alkaline conditions.

Chitosan

Properties

Gelling of chitosan occurs by two changes such as pH responsive change and temperature change. Chitosan is a natural component of shrimp and crab shell which consist of biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin. Chitosan is a biocompatible pH dependent cationic polymer, which can remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to precipitation by the formation of a hydrated gel[34, 35].

HPMC

Properties

Cellulose is consists of glucan chain which has repeating β-(1, 4)-D-glucopyranose unit. Some natural polymers like HPMC, MC and EC these exhibit temperature sensitive sol-gel phase transition. Cellulose material will increases its viscosity when temperature is decreases while its derivatives like HPMC, MC, will also increase its viscosity when temperature is increased. MC is a natural polymer composed of native cellulose with alternate methyl substitution group on its chain. At low temperature (30^{0}C) solution is in liquid form and when temperature is increases (40-50^{0}C) and gelation[36] occurred.

Poloxamer

Poloxamer are water soluble tri-block copolymer. It consists of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration[37].

Properties

Poloxamer is commercially available as Pluronic and has good thermal setting property and increased drug residence time. It mainly used as gelling agent, emulsifying agent and solubilizing agent. Poloxamer gives colourless, transparent gel. It depends upon the ratio and distribution of hydrophilic and hydrophobic chain several molecular weights available, having different gelling property[38].

Applications of *in situ* polymeric drug delivery system[39, 40]

Oral drug delivery system

The pH-sensitive hydro gels have a potential use in site-specific delivery of drugs to specific regions of the GI tract. Hydro gels built of varying proportions of cross linked PEG and PAA derivatives allowed in preparing silicone microspheres, which produce prednisolone in the gastric medium or showed gastro protective property. Cross-linked dextran hydro gels with a faster swelling under high pH conditions, whereas other polysaccharides such as amidaded pectin's, inulin and guar gum were investigated in order to improve a potential colon-specific drug delivery system. The formulations of gellan and sodium alginate both contain a complexed calcium ion that undergoes a process of gelation by releasing of these ions in the acidic environment of the stomach.

Ocular drug delivery system

In ocular delivery system natural polymers like alginic acid, inulin, & xyloglucan, inulin are most commonly used. For local ophthalmic delivery system different compounds such as autonomic drugs, anti-inflammatory agent & antimicrobial agent,are used to release intra ocular tension in glaucoma. Conventional delivery system often result in poor availability & therapeutic response due to high tear fluid turn over & dynamics leads rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel were developed. To improve the bioavailability viscosity enhancers such as Carboxy Methyl Cellulose, Hydroxy Propyl Methyl Cellulose, Carbomers, Poly Vinyl alcohol used to improve the viscosity of formulation in order to prolong the precorneal residence time & increases the bioavailability, easy to manufacture. Penetration enhancer such as preservatives, chelating agent, surfactants are used to develop corneal drug penetration.

Nasal drug delivery system

In nasal in-situ gel system xanthan gum and gallan gum are used as in-situ gel forming polymers Momethasone furoate used to evaluate for its efficacy for the treatment of allergic rhinitis. Animal study is used to conduct allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed. In-situ gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%).

Rectal and vaginal drug delivery system

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Acetaminophen an anti inflammatory drug formulated as rectal in situ gel by using polycarbophil and poloxamer F188 and poloxamer 407 as synthetic polymer forming in situ gelling liquid suppository which is considered as an synthetic polymers forming in situ gelling liquid suppository which is considered as an effective method shows enhance bioavailability.

Injectable drug delivery system

In this drug delivery system are also formulated as in situ gels which obtained over the last decade due to its uses as there is no surgical procedure is required and also patient compliance. Mostly synthetic polymers and block copolymers are used in the formulation of

Injectable *in situ* gel. One example of inflammatory drug is Bupivacaine which is formulated as a injectable in situ gel using poly(D,L-lactide), poly (D,L-lactide coglycolide) and PLGA as polymer shows prolong action drug in gel conditions.

Dermal and transedermal drug delivery

Pluronic F127 in thermally reversible gel was evaluated as vehicle for the percutaneous administration of Indomethacin. In-vivo studies suggest that 20% w/w aqueous gel may be it is used as practical base for topical administration of the drug. The combination of iontophoresis and chemical enhancers resulted in synergistic enhancement of insulin permeation.

CONCLUSION

The present review concludes that 'in situ gel' system has emerged as one of the best novel drug delivery systems, the in situ gelling system helps for the sustained and controlled release of the drugs, improved patient compliance and comfort, Various natural and synthetic polymers undergo in situ gel forming and potentially can be used for oral, ocular, transdermal, buccal, intraperotonial, parenteral, injectable, rectal and vaginal routes. There is high scope for research work on in situ gel system in order to provide advanced techniques in drug delivery systems.

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