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Review Article

In-Situ Gelling System: A Review

*Sarada K, Firoz S, Padmini K

Sree Vidyanikethan College of pharmacy, Sree Sainath Nagar, Chandragiri (M), Tiruapti, Andhra Pradesh, India-517102.

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ABSTRACT

Current review on in-situ gelling system explains about gels which are defined as intermediate state of matter consists of liquid and solid components. Hydrogels are also briefly discussed in the review that is defined as three dimensional structures which has capacity to retain bulk amount of water and also biological fluids to swell. In-situ gels are type of hydrogels that are solution in form and undergo gelation in contact with body fluids or change in pH. Some of the polymers that are used in in-situ gelling system are guar gum, gellan gum, xanthan gum, carrageenan, xyloglucan, pectin, chitosan and thiolated chitosan. In this review on in-situ gelling system, some of the approaches through which in-situ gels can be obtained are also discussed. It also focuses on the applications of in-situ gels that are the type of novel drug delivery systems in which these systems can be formulated. Some of the novel drug delivery systems are oral, nasal, injectable and ophthalmic drug delivery systems.

Keywords: Gels, in-situ gel, Hydrogels, polymers, gelling mechanism.

INTRODUCTION

Gels: Gels are an intermediate state of matter containing both liquid and solid components. It consists of three dimensional solid networks. As it has three dimensional solid network, gels are classified into two types based on the nature of the bonds. They are

- Physical gels arise when weak bonds like hydrogen bonds, electrostatic bonds and vanderwaal bonds constitute together to maintain the gel network.

**Author for correspondence*

- Chemical gels arise when strong covalent bonds[1] constitute to maintain the gel network. The network indicates the presence of cross-links which helps to avoid the dissolution of the hydrophilic polymer in an aqueous medium.

Hydrogels: Hydrogels are the three dimensional structures that has polymeric networks which has the capacity to absorb and retain large amounts of water and biological fluids to swell.

Classification of hydrogels: Hydrogels are of two types. They are

Preformed hydrogels are defined as simple viscous solutions which do not undergo any modification after administration.

In-situ gels are the solutions or suspensions that undergo gelation after reaching the particular site due to physico- chemical changes.

In-situ gelling system: In-situ gelling system has become one of the most prominent among novel drug delivery systems due to many advantages such as improved patient compliance, reduced frequency of drug administration. 'In-situ' is a Latin word which means 'in position'[2]. There are many triggering mechanisms in in-situ gel formation some of them are pH change, temperature modification and solvent exchange[3].As the gel formed from in-situ gelling system, being lighter than gastric fluids float over stomach contents due to the presence of bio adhesive nature of polymers resulting in prolonged gastric retention time[4]. In-situ gels are the formulations that are in sol form before administration in the body, but once administration undergo gelation to form gel. Various routes administration of in-situ gelling systems is oral, nasal, ophthalmic, vaginal, injectable, intraperitoneal and rectal route.

Advantages of *in-situ* gelling system:

- In-situ gels shows ease of administration and good patient compliance.
- It shows increased gastric retention with slow drug release[4].
- It reduces dosing frequency.
- It shows local action and site specificity by acting directly onto the targeted site.
- It shows less adverse effects compared to other pharmacological dosage forms[5,6.]

Disadvantages of *in-situ* gelling system:[7]

- It is more susceptible to stability problems due to chemical degradation.
- It requires high level of fluids.
- It leads to degradation due to storage problems.

Mechanism involved in formation of *in-situ* gels: In-situ gels are the hydrogels that are liquids at room temperature but undergo gelation when in contact with body fluids or change in pH. The in-situ gelling systems utilises various polymers that converts from solution and gel due

to change in physicochemical properties. In this system when low viscosity solution comes in contact with body fluids undergo changes in confirmation of polymers and a viscous gel of density lower than gastric fluid is formed.

Approaches of in-situ gelling system: Approaches of in-situ gelling system are of three types

Based on physiological stimuli:

Temperature induced in-situ gelling system: Temperature induced systems are most widely used systems in in-situ gelling formulations. In this type of systems, no external heat other than body temperature is required to cause gelation. There are three types of temperature induced systems. Some of them are

- Negatively thermo sensitive type Eg: poly(N-isopropylacrylamide)
- Positively thermo sensitive type Eg: Polyacrylic acid
- Thermally reversible type[8] Eg: Poloxamer, Pluronics, Tetronics.

In temperature induced gelling system, temperature responsive polymers or thermo responsive polymers are used that exhibit a drastic and discontinuous change in their physical properties with temperature. This type of polymers belongs to the category of stimuli responsive materials that change their properties continuously with environmental conditions. These polymers exhibit a miscibility gap at high or low temperatures an upper or lower critical solution temperature exists.

The range at which the solution exists at upper critical solution temperature is 0°-100°C. In this approach, the solution is liquid at room temperature and when reaches the body fluid due to exposure to body temperature it converts into gel. As the body cannot maintain upper critical solution temperature, lower critical solution temperature suitable polymers are used that undergo polymer-polymer interaction that causes sudden change in polymer solubility. As the solution is in liquid form, at lower critical solution temperature the hydrogen bonding between polymer and water cause an abrupt changes and leads to the formation of gel.[9]

pH triggered systems: In this system change in pH causes formation of gel. In this approach, pH responsive or pH sensitive polymers are used. pH sensitive polymers have acidic or alkaline ionisable functional groups which are called as polyelectrolytes. The polyelectrolytes those are present in the formulation causes increase in external pH that leads to the swelling of hydrogel that leads to the formation of in-situ gel.

Suitable polymers for pH triggered systems are the polymers that are having anionic groups. Some of them are cellulose acetate phthalate (CAP), Carbomer and its derivatives, Polyethylene glycol (PEG), Pseudo latexes and poly methacrilic acid (PMC) etc.

Physical changes:

Swelling: Swelling is a type of physical approach that is used in the formation of in-situ gel. In this approach, the polymers that are surrounding the polymer imbibe the fluids that are present in the external environment and swell from inside to outside and slowly release the drug.

Diffusion: Diffusion is a type of physical approach that is used in in-situ gel formation. In this approach, solvent gets diffused out from the polymer solution into surrounding tissues which results in the formation of precipitate or solidification of polymer matrix. The most commonly used polymer in diffusion approach of formation of in-situ gelling system is N-methyl pyrrolidone (NMP)[10].

Chemical induced systems: In this approach, chemical reactions are involved to form in-situ gel. The formation of in-situ gel includes ionic cross linking, enzymatic cross linking and photo polymerization.

Ionic cross linking: In this approach, the ion sensitive polymers are used. The ion sensitive polymers induce gelation in the presence of ions like Na^+, K^+, Ca^{2+} and Mg^{2+}. The ion sensitive polymers undergo phase transition to form gel.

Enzymatic cross linking: Enzymatic cross linking is the most convenient approach used in formation of in-situ gelling system. In this approach, gel is formed by cross linking with the enzymes that are present in the body fluids.

Photo polymerisation: In this approach, electromagnetic radiations are used during formation of in-situ gel[11]. The most suitable polymers for photo polymerisation are the polymers that have polymerisable functional groups which undergo dissociation in the presence of photo initiators like acrylates or other polymers that usually have long wavelength ultraviolet and visible wavelengths are used[12]. Short wavelengths are not used because they are biologically harmful. In this approach, ketones such as 2,2-dimethoxy-2-phenyl acetophenone is used as the initiator for ultraviolet photo polymerization. Camphorquinone and ethyl eosin initiators are used as visible light systems.

In-situ gelling system polymers:

Gellan gum: Gellan gum is a type of temperature dependant or cation induced polymer that causes gelation which involves the formation of double helical zones which forms a three dimensional network by complexation with cations and hydrogen bonding with water [13]. Divalent cations such as Ca^{2+} or Mg^{2+} induce gelation by cross-linking to form a gel network. When the liquid solution comes in contact with mucosal layer that is present in the stomach region causes rapid gelation even at low polymer concentrations. As the gellan gum has swelling nature, it gives good bio adhesive nature in the GIT region[14]. Gellan gum is

commercially available as a pharmaceutical excipient named as gelrite® which is marketed by merck as a controlled release glaucoma formulation[15].

Xyloglucan: Xyloglucan is also called as tamarind gum which is a polysaccharide obtained from the endosperm of the seed. As xyloglucan is obtained from tamarind seeds, it is partially degraded by β-galactosidase. The product that is obtained after degradation undergoes gelation by thermo responsive process [16]. The phase transition from sol to gel varies with the degree of galactose elimination. Though in-situ gels those are formed by using xyloglucan involves thermo reversible process, they are also formed on warming at body temperature. Xyloglucan when used in oral delivery shows slow gelation time upto minutes and allows in-situ gelation in stomach in chilled condition.

Gelling of xyloglucan occurs by four methods like enzymatic degradation with β-galactosidase, addition of alcohols, addition of polyphenols and addition of iodine solution. Xyloglucan has gelling ability in the presence of sugar or alcohol. It forms gel in the presence of 40-65% sugar over a wide pH range. By addition of 20% alcohol, the amount of sugar needed to form a gel can be substantially reduced. To form a gel, heating is required to dissolve polysaccharides and upon cooling to room temperature the gel will form which shows slow water release. During enzymatic degradation, β- galactosidase causes formation of gel. At elevated temperatures, due to loss of β- galactosidase causes fluctuation in melting points leading to aggregation of cross linked domains causing the gel to melt and forms straight chains.

Guar gum: Guar gum is a naturally occurring gum which is also called as guaran which is obtained from the endosperm of the seed.Guar gum is soluble in water but insoluble in hydrocarbons, fats, esters, alcohols and ketones. It shows its dispersibility in both hot and cold water that is it is soluble in both hot and cold water to form colloidal solution at low amount[17]. As guar gum has the capability of forming high viscous solution at low concentrations, the galactose side chains that are attached to mannose backbone interact with water molecules that are present in the solution leading to the formation of inter molecular chain which causes entanglement of gaur gum molecules that are present in the aqueous phase causing the formation of gelling or thickening of the solution[18]. As guar gum is soluble in both hot water and cold water, temperature plays a key role in the formation of gelling in the solution. So, increase in temperature causes reduction in gelling property of guar gum. As the temperature reduces and causes the formation of sol. So, temperature causes reversible change in gelling of gaur gum[19]. Guar gum has derivatives that are used in targeted delivery systems in the formation of coating matrix systems, nano-microparticles and hydrogels[20]. Guar gum also has

derivatives such as graft polymers like polyacrylamide grafted guar gums that have good colon targeting properties. Guar gum can also be used as a polymer in matrix tablets which shows controlled release[21,22].

The semi synthetic form of guar gum is carboxy methyl guar(CMG) which is anionic in nature that are used in formulation of transdermal drug delivery systems because it shows good release rate profile, safety and stability[23]. Guar gum is also available in various cross linked forms that are used in various novel formulations i.e, glutyraldehyde cross linked guar gum, hydroxyl ethyl guar gum, poly acrylic acid conjugate guar gum, hydroxyl methyl gum; 4-vinyl pyridine conjugated guar gum[24,25,26]. The modified guar gum has potential to prevent cancer by inhibiting carcinogen activating enzymes and promoting the carcinogen detoxification enzyme glutathione-s-transferase[27].

Xanthan gum: Xanthan gum is soluble in hot water and cold water as well as acidic and alkaline conditions. Xanthan gum exhibits good stability at acidic and alkaline conditions. It exhibits anionic nature due to the presence of both glucuronic acid and pyruvic acid groups that are present in the side chain[28]. It is pharmaceutically used in the formulation of emulsions or suspensions which prevents the separation of insoluble ingredients. It is also used as a polymer in formulation of in-situ gelling systems. In most of the formulations, xanthan gum is used as an agent that combines with other hydrocolloids[29].

Xanthan gum when dissolved in water at room temperature forms lumps due to binding of water molecules and xanthan gum molecules. When these partially dissolved solution is annealed i.e. undergoes heat treatment lumps containing molecular chains get rearrange among themselves. As it reaches moderate temperature, the molecular chains move freely and forms clear solution which is allowed to cool to form firm and stiff gels. Due to formation of homogenous solution the gel appears clearly[30].

Carrageenan: Carrageenan is a natural polysaccharide that is given importance as gelatin as a home remedy to cure cough and cold. Based on number and position of ester sulphate groups and also in the arrangement of 3, 6- anhydro galactose, carrageenan is classified into:

- Iota carrageenan has the capability to form gels in the presence of potassium or calcium ions. It forms elastic gel in which there is no draining of water occurs. It forms the stable by using the process of freeze thaw method. It shows complete solubility in hot water.
- Kappa carrageenan has the capacity to form gels in the presence of potassium salts. The gel that is synthesised from carrageenan is brittle in nature. Kappa-carrageenan has similar properties to that of locust bean gum and it is soluble in hot water and is a good gelling agent.

- Lambda carrageenan does not induce gel formation instead, it forms highly viscous solutions. Lambda carrageenan shows its solubility in cold water.

Due to presence of higher levels of ester sulphate groups, these groups lower the solubility temperature of the carrageenan which causes gel inhibition that leads to lowering the strength of the gels[31]. Hot aqueous solution of kappa and iota carrageenans has the ability to form thermo-reversible gels upon cooling. This phenomenon occurs due to the formation of a double helix structure that is present in carrageenan. At temperatures above the melting point of the gel, carrageenan polymers exist as random coils. On cooling, a three-dimensional polymer network builds up in which double helices form the junction points of the polymer chains. Further cooling causes aggregation of junction points to form a three-dimensional gel. The presence of links in the chain, quantity, type and position of ester sulphate groups has important effects on gelling. In kappa and iota carrageenan solutions gelling is basic in nature. To obtain water gel, the solution should contain calcium or potassium salts.

When the drug is insoluble it forms stable emulsions and enhances homogeneity in colloidal suspension. It acts as a film forming agent in formation of crystal clear soft capsules. It acts as a gelling agent in formation of antacid gels. In antibiotic suspensions, it prolongs shelf life and improves stability[32,33].Carrageenan is used in the production of semi-synthetic antibiotics and those are useful for industrial purpose. Eg: Tetracycline and chlortetracycline for industrial production[34].

Semi synthetic antibiotics are produced by enzymatic hydrolysis of penicillin G by fermentation process[35] by using kappa carrageenan type. It is also used in the production of aminoacids like D-aspartic acid which is used as a component of synthetic penicillin[36].

Chitosan: Gelling of chitosan occurs by two changes such as pH responsive change and temperature change. Chitosan consists of ionic pendant groups which ionize and form network with electrostatic forces. The gelling mechanism based on temperature changes at low critical solution temperature. At this temperature due to extreme hydrophobic interactions gels are formed. At upper critical solution temperature due to cooling of polymer solution gels are formed. So, low critical solution temperature exhibiting polymers are used for gelation process of chitosan.[47]

Thiolated chitosan: Nowadays, polymers with thiol groups exhibit much higher adhesive properties than other polymers with mucoadhesive properties. These types of polymers are also called as “thiomers” which interact with cysteine rich sub domains of mucus glycoprotiens via disulfide exchange reactions or simple oxidation process[38]. Thiolated chitosans exhibit strong

cohesive nature that makes them highly suitable for controlled drug release dosage forms[39,40]. It also exhibit in-situ gelling nature at physiological pH values[41].

In thiolated chitosan, the oxidation of thiol groups at physiological pH results in the formation of inter and intra molecular disulfide bonds. The presence of disulfide bonds causes cross linking which leads to the formation of gel when reaches physiological environment[42].

The formation of covalent bonds between thiol groups of the polymer and cysteine rich subdomians of glycoproteins in the mucus layer exhibits mucoadhesive nature of the thiolated chitosan[43]. Thiolated chitosans acts as a permeation enhancer as it has positive charges which interact with the cell membrane causing a structural reorganisation of tight junction associated proteins. Thiolated chitosans show more permeation enhancing nature than chitosan due to its size limited diffusion or competitive charge interactions with mucin[44].

Apart from mucoadhesive property and permeation enhancing property, it also exhibits cohesive nature. Due to reduction of thiol functions, the chitosan backbone makes thiolated chitosans to form disulfide bonds with mucus glycoprotiens and form intern and intramolecular disulfide bonds[45].

Pectin: As pectin is cationic in nature, the monovalent cations (alkali metal) salts of pectinic and pectic acids are soluble in water. But, divalent and trivalent cationic salts are weakly soluble or insoluble in water. When water is added to dry powdered pectin, clumps are formed due to its tendency to hydrate. These clumps consist of semi dry packets of pectin contained in an envelope of highly hydrated outer coating. The clumps can be solubilised by mixing the pectin powder with water soluble carrier [46].

Based on degree of esterification, pectin is of two types. They are

- Low methoxy pectins
- High methoxy pectins

The esterification of galacturonic acid residues with methanol or acetic acid is a very important structural characteristic of pectic substances. The degree of methylation (DM) is defined as the percentage of carbonyl groups esterified with methanol. If more than 50% of the carboxyl groups are methylated the pectins are called high-methoxy pectins (HM), and less than that degree of methylation are called low methoxy (LM) pectins.

Gelling property of pectin depends upon the molecular size and degree of esterification. Presence of hydrogen bonds between free carboxyl groups causes gel formation. The presence of divalent cations like calcium ions can cause gelling of low methoxy (LM) pectins. The intermolecular junction zones between homo galacturonic smooth regions of different chains

cause gelation. The initial strong association of two polymers form a dimer which is followed by the formation of weak inter dimer aggregation by electrostatic interactions. The presence of acetyl groups prevents gel formation with calcium ions but gives the pectin emulsion stabilising properties.

High Methoxy (HM) pectins have the ability to two dimensional network gels with sugar and acid which are called as low water activity gels or sugar-acid-pectin gels. The molecules of pectin in which the solvent (water) with the co-solutes sugar and acid are immobilised. The build up of the 3-d network is based on the formation of junction zones in which there are chain associations stabilised by hydrogen bonding between un dissociated carboxyl and secondary alcohol groups and by hydrophobic interaction between methyl esters.

Applications:

Oral drug delivery systems: As oral route is the most compatible and easy route of administration of drugs, in-situ gelling type of systems are also formulated to deliver through oral route. Formulations of different categories of drugs are reported. Some of the examples are clotrimazole an antimicrobial drug is formulated as an in-situ gelling system by using carbopol 934P, gellan gum and HPMC as polymers showing zero order kinetic release with 8 hours of sustain action of drug[48]. Paracetamol an anti-inflammatory drug is formulated as an in-situ gelling system using xyloglucan a natural polymer showing diffusion controlled release of drug[49].

Ophthalmic drug delivery systems: Ophthalmic drug delivery systems are used in the treatment of intraocular tension during glaucoma. Conventional dosage forms show poor bioavailability due to heavy draining of tear fluids from eye leads to rapid elimination of drug. To enhance the bioavailability problems ophthalmic drug delivery systems are used.

Various natural polymers are used in formulation of ophthalmic in-situ gelling systems. Ofloxacin an anti microbial drug is formulated as an in-situ gelling system by using carbopol and HPMC as polymers due to triggering of pH forms in-situ gel by showing sustain release for a period of 8 hours[50]. Levofloxacin is formulated as an ophthalmic in-situ gel by using gellan gum which is most commonly used polymer in ophthalmic delivery systems showing good drug release with 90.2% [51]. Ciprofloxacin is formulated as an ophthalmic in-situ gel using carbopol 940 P, pluronic F-127, gellan gum and 1.5% HPMC as polymers showing drug release of 6 hours[52].

Injectable drug delivery systems: Injectable drug delivery systems are also formulated as in-situ gels which received much more interest over the last decade due to its advantages 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 gels. Bupivacaine an anti inflammatory drug is formulated as an injectable in-situ gel using poly (D,L-lactide), poly (D, L-lactide co-glycolide) and PLGA as polymers showing prolong action of drug in gel conditions[53]. It is investigated that injectable in-situ gels are also used in the treatment of tumours. Paclitaxel is formulated as injectable in-situ gel using implanted EMT-6 tumours subcutaneously in albino mice.

Nasal drug delivery systems: Nasal route of drug delivery is the most accepted route of administration of drugs as it has many advantages like patient compliance, avoids first pass metabolism and also provides high degree of absorption as well as transport of substances. Nasal drug delivery is the most suitable route for administration of CNS drugs because the drug shows its effect through olfactory neurons which is considered as the most potential route[54,55]. Radix bupleri an anti inflammatory drug is formulated as nasal in-situ gel by using gellan gum as natural polymer which shows longer anti pyretic effect[56]. Curcumin a natural anti inflammatory drug which is formulated as nasal in-situ gel by using capryol 90 and transcutol HP as polymers showing results as better route than intravenous route of administration[57].

Rectal and vaginal drug delivery systems: In-situ gels are also administered through rectal and vaginal routes. Acetaminophen an anti inflammatory drug formulated as rectal in-situ gel by using polycarbophil and poloxamer F188 and poloxamer 407 as synthetic polymers forming in-situ gelling liquid suppository which is considered as an effective method showing enhance bioavailability[58]. Itraconazole is an anti inflammatory drug is formulated as vaginal in-situ gel by using poloxamer 407, 188 and HPMC as polymers in the treatment of vaginal candidiasis [59]. Clotrimazole is given through vaginal route is also reported[37].

CONCLUSION

In this review on in-situ gelling system definition of gels and in-situ gels are discussed. Various approaches in which in-situ gels can be produced are briefly discussed. Polymers that are used in synthesis of in-situ gels along with its gelling mechanism are included. Applications of in-situ gels in various drug delivery systems are included along with examples.

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