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A REVIEW ON IN SITU GELS

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ABSTRACT
Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. The *in situ* gel forming polymeric delivery systems have shown benefits such as ease of administration and reduced frequency of administration, improved patient compliance. Various approaches like physiological stimuli, ion-activated system etc result in the formation of *in situ* gels. Generally, two methods are used for the preparation of *in situ* gels such as cold method and hot method. Both natural and synthetic biodegradable polymers are used for the formulation of *in situ* gels such as pectin, alginic acid, gellan gum, xyloglucan, carbopol etc. *In situ* gels are evaluated for their physical strength, appearance, viscosity, spreadability and *in vitro* studies**.** Mainly *in situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. Overall, this review focuses on the introduction to *in situ* gels, various approaches utilized, various polymers used, its evaluation, and applications.

KEYWORDS: *In situ* gels, Ion activated system, Cold method, hot method etc.

INTRODUCTION

A gel is a soft, stable, or solid-like material which consists of at least two components, one of them being a liquid, present in substantial quantity. Gels are a transitional state of matter containing both liquid and reliable ingredients (Semisolids or semi-liquids). Gels combine the cohesive properties of solids and the diffusive transport characteristics of fluids. It consists of a three-dimensional, stable, and secure component network.[1]

Gels are harder than jellies because they have more cross links, higher physical density or simply less liquid. Gel-forming polymers form materials of different hardness, starting from sols to slimes, jellies, gels and hydrogels. Some gel systems are as clear as water, while others are cloudy because the material is not completely molecularly dispersed (Soluble or insoluble) or does not form light-scattering aggregates. With some exceptions, the concentration of gelling agent is usually less than 10% and is usually in the range of 0.5% to 2% more.[2]

Based on nature of solvent, gels are classified into three types i.e., organogels, xerogels and hydrogels.

Organogel is a non-crystalline, non-glassy thermoreversible solid material composed of a liquid organic phase trapped in a 3D cross-linked network. Xerogel is a solid formed from a gel by drying with unrestricted shrinkage. It typically retains high porosity (15-50%) and a huge surface area (150-900 m2/g), along with very small pore size (1-10nm). When solvents are removed from under supercritical condition, the network does not shrink, and a highly porous, low density material known as an aerogel is produced. Heat treatment of a xerogel at higher temperatures produces viscous sintering and efficiently transforms the porous gel into the thick gels.[3]

Hydrogel is that it is a polymeric material that exhibits the ability to swell and retain a significant fraction of water within its structure, but will not dissolve in water.[4] Hydrogels are further classified into two groups i.e., preformed hydrogels and *in situ* gels.[5]

Preformed hydrogel

Preformed particle gel (PPG) is a particle superabsorbent crosslinking polymer that can swell up to 200 times its original size in brine. The use of PPG as a fluid-diverting agent to control conformance is a novel process designed to overcome some distinct drawbacks inherent in *in situ* gelation systems.[5]

***In situ* gels**

The "*in situ* gel" system has emerged as one of the best new drug delivery systems. The *insitu* gelling system helps to improve the sustained and controlled release of the drug, patient compliance, and comfort due to the special features of the "Sol to Gel" transition. An *insitu* gelling system is a formulation that is in the form of a solution before it enters the body, but it transforms into a gel under one or combinations of a variety of physiological conditions. The sol-to-gel transition depends on a variety of factors, including temperature, pH changes, solvent exchange, UV radiation, and the presence of specific molecules or ions. Drug delivery systems with the above "sol-to-gel" properties can be widely used in the preparation of sustained delivery vehicles for bioactive molecules.[6]

The development of *in situ* gel systems has received considerable attention over the past few years. Increasing number of *in situ* gel forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported.[7] This interest has been sparked by the advantages shown by *in situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort.[8]

Advantages of *in situ* gel

- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by Conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug
- To provide better housing of delivery system.[9]

Characteristics of polymers for preparation on *in situ* gel

- The polymer should be capable of adhering to the mucous membrane.
- It should be well compatible and should not provide any toxic effects.
- The polymer should be capable of decreasing the viscosity with increase in shear rate.
- Good tolerance and optical clarity is more preferred.
- It should influence the tear behavior.[10]

Approaches of *in situ* gel drug delivery

There are 4 mechanisms for triggering the *in situ* gel formation

1. *In situ* gel formation due to physiological stimuli:
a) Temperature triggered *in situ* gel systems
b) pH triggered *in situ* gelling systems
2. *In situ* gel formation due to ion-activated system
3. *In situ* gel formation due to physical mechanism
a) Swelling
b) Diffusion
4. *In situ* gel formation due to chemical reactions
a) Ionic cross-linking
b) Enzymatically cross linking
c) Photo-polymerization

1. *In situ* gel formation due to physiological stimuli

There are a few polymers which go through enormous and sudden physical and chemical changes because of little outer changes in their environmental conditions. Such polymers are called Stimuli-responsive polymers. They are likewise called as smart, intelligent, stimuli responsive polymers. These polymers perceive an upgrade as a sign, judge the level of the signal and afterward change their chain confirmation accordingly.

a. Temperature triggered *in situ* gel system: Thermo sensitive polymers are most widely considered class of naturally responsive polymer frameworks in medication conveyance. In this system, gelling of solution is set off by modification in temperature, consequently sustaining medication discharge. These hydrogels exist in fluid structure at room temperature (20-25°C) and converts in gel when interacts with body fluids (35-37°C). The utilization of biomaterial whose change from sol-gel is set off by increment in temperature is an alluring method to approach *in situ* formulations. The best basic temperature range for such system is surrounding and physiologic temperature; with the end goal that clinical control is encouraged and no outer heating source other than that of body is needed to trigger gelatin. Three primary procedures are utilized in designing the thermo sensitive sol-gel polymeric framework. Consequently, they are ordered into:

a. Negatively thermo sensitive, which contract upon heating
b. Positively thermo sensitive, which contract upon cooling
c. Thermo-reversible gel

Polymers which show temperature incited gelation are poloxamers/Pluronic, cellulose subsidiaries [HPMC, ethyl (hydroxy ethyl) cellulose (EHEC), methyl cellulose], xyloglucan, tectonics, and so forth.

b. pH triggered *in situ* gelling systems: Another physiological improvement that prompts arrangement of *in situ* gel is pH. Polymers remembered for this class contain an acidic or an alkaline group that either accept or donate protons when they are presented to various environmental pH. Henceforth these are called pH responsive polymers. This kind of mechanism is generally utilized for ocular drug delivery system. The increment in the precorneal time of residence of medication and thus better bioavailability can be accomplished by utilizing *in situ* gel systems. The polymers having an enormous number of ionisable gatherings are called as polyelectrolyte. If there

should arise an occurrence of pitifully acidic groups (anionic), increment in swelling of hydrogel with increment in external pH is noticed, though polymers containing essential (cationic) groups shows reduced swelling. The greater part of the pH delicate polymers containing anionic gathering depend on PAA polyacrylic acid (Carbopol®, Carbomer) and its derivatives. Different polymers which show pH incited gelation are cellulose acetic acid derivation phthalate (CAP) latex, polymethyl mathacrylic (PMMA), polyethylene glycol (PEG), pseudo latexes, and so forth.

2. *In situ* gel formation due to ion-activated system

Here, gelling of the imparted solution is prompted by the adjustment in ionic strength. It is accepted that the osmotic gradient across the surface of the gel decides the pace of gelation. In presence of mono and divalent cations commonly present in the tear liquids, the watery polymer solutions shape **I**a reasonable gel. The electrolyte present in the tear liquid, particularly Na^+, Ca^{2+} and Mg^{2+} cations assume a significant job in inception of gelling when the arrangement is ingrained in the conjunctival cul-de-sac. Polymers that display osmotically initiated gelation include gelrite or gellan gum, hyaluronicacid, alginates, and so on.[11]

3. *In situ* gel formation due to physical mechanism

a) Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to give desired space. One such substance is myverol (Glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded *in vivo* by enzymatic action.

b) Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.[12]

4. *In situ* gel formation due to chemical reactions

a) Ionic cross-linking

There are some ion sensitive polysaccharides, for example, gellan gum, gelatine, sodium alginate which go through phase change in presence of different ions. An anionic polysaccharide, Gellan gum, goes through *in situ* gelling in event of mono-and divalent cations, for example $Ca^{2+,}$ Mg^{2+}, K^+ and Na^+.

b) Enzymatic crosslinking

In this group of *in situ gels*, the sol-to-gel transition is catalyzed by natural enzymes. They have not been investigated broadly but seem to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates capably under physiologic conditions without the need for potentially harmful chemicals such as monomers and initiators. Gradual dissolution of the polymer, increased micellar aggregation, and the improved embarrassment of the polymeric network.

c) Photo-polymerization

For over more than decade, *in situ* photo-polymerization has been used in biomedical applications. Monomers (reactive macromeres) and initiator solution can be injected into a tissue site. The application of electromagnetic radiation is used to form a gel. Acrylate or similar functional groups are typically used as the polymerizable groups on the individual monomers and macromere because they rapidly go through photo polymerization in the presence of a suitable photo initiator. Classically long wavelength UV and visible wavelengths are used; short UV wavelength is not used because of incomplete penetration of tissue and bio-logical risk.[13]

Polymers used in the *in situ* gel

Classification of *in situ* gel polymers

Based on their origin or based on the mechanisms of gelation, polymers are classified. According to a source, *in situ* gelling agents classified into two types:

- **Natural polymers:** Pectin, Gellan gum, Xyloglucan, Xantham gum, Chitosan etc.
- **Synthetic or semi-synthetic polymers:** Hydroxymethylcellulose (HPMC), N-Propylacrylamide Copolymers, Carbapol, Polaxomer etc.

Natural polymers

Pectin

These are plant origin anionic characteristics can be divided into two polysaccharides isolated from the cell wall of most plants and consist of -(1-4) -D-galacturonic acid residues. Pectin undergoes gel formation in the presence of the medium; a stiff gel is produced. Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an a-(1-4) chain. On the basis of methyl esterification of galacturonic acid, there are two different types of pectin- high methoxy and low methoxy gelation. Gelation of high methoxy pectin usually occurs at pH<3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content.

Gellan gum

Gellan gum is a water soluble anionic polysaccharide, commercially known as Phytagel or Gelrite. Gellan gum secreted by the Sphingomonas elodea (*Pseudomonas elodea*) and chemically is anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of â-D-glucuronic acid (1 unit), á-L-rhamnose (1 unit) and â-D-glucose (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to the presence of cations (e.g., Na^+, K^+, Ca^{2+} and Mg^{2+}). Gellan gum can be applied pharmaceutically as a

water-soluble polymer acts as a potential carrier for different oral floating sustained delivery dosage forms.

Xyloglucan

It is a plant-based polysaccharide obtained from seeds of tamarind. Chemically, this polysaccharide composed of a chain of (1-4)-D-glucan having (1-6)-D xylose units as branches which have partial (1-2)- D-galactoxylose substitution. Xyloglucan is composed of heptasaccharide, octasaccharide, and nonasaccharide oligamers, which differ in the number of galactose side chains. Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a sol to gel at a transition temperature. It is used for rectal, oral and ocular delivery of pilocarpine and timolol.

Xanthan gum

Xanthan gum is a high molecular weight extracellular polysaccharide produced by xanthomonas campestris. It is a long chain polysaccharide with large number of trisaccharide side chains. The main chain consists of two glucose units. The side chains are composed of two mannose units and one glucuronic acid unit. Xanthan gum can form strong gel when mixed with positively charged polymers. This gum develops a weak structure in water, which creates high viscosity solutions at low concentration.

Chitosan

Chitosan is a natural and versatile polycationic polymer obtained by alkaline deacetylation of chitin. It is a biodegradable, thermosensitive and non-toxic polymer. Chitosan is a biocompatible pH dependent cationic polymer, which 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 the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions by addition of polyol salts, without any chemical modification or cross linking.

Synthetic or semi-synthetic polymers

Hydroxypropyl Methyl Cellulose (HPMC)

Hydroxypropyl Methyl Cellulose (HPMC) as a partly O-methylated (OCH3) and O-(2-hydroxypropylated) (OCH_2CH (OH) CH_3) cellulose conforming to the limits for the various types of HPMC. It is available in several grades that vary in viscosity (50-100000 cps), and Molecular weight is approximately 10000- 1500000 Da. It is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations as coating agent, controlled-release agent, dispersing agent, dissolution enhancer, extended-release agent, film forming agent, modified-release agent, release modifying agent, solubilizing agent, stabilizing agent, sustained-release agent, thickening agent, and viscosity-increasing agent.

N-Propyl acrylamide copolymers

Poly (N-isopropylacrylamide) (pNiPAAm) is a non-biodegradable polymer with a LCST, 32ºC in water, and cross-linked gels of this material collapse around this temperature. Recent developments on pNiPAAm based hydrogels include their use for drug delivery cell encapsulation and delivery and cell culture surfaces.

Carbopol

It is a well-known pH-dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. In combination with HPMC, impart the viscosity of carbopol solution while reducing the acidity of the solution.

Poloxamer

These polymers are ABA-type triblock copolymers composed of PEO polyethylene oxide (A) and PPO polypropylene oxide units (B). The poloxamer series covers a range of liquids, pastes, and solids, with molecular weights and ethylene oxide-propylene oxide weight ratios varying from 1100 to 14,000 and 1:9 to 8:2, respectively. Concentrated aqueous solutions of poloxamer form thermoreversible gels. Poloxamer 407 (Pluronics F127) was found to gel at a concentration of 20%wt at 25^{o}C, which is less than that of the other members of the poloxamer series. At room temperature (25^{o}C), the solution behaves as a mobile viscous liquid, which is transformed into a semi-solid transparent gel at body temperature (37^{o}C).[10, 14, 15]

Methods of preparation

Generally, *in situ* gelling systems are prepared by two methods namely:

1. Cold Method and
2. Hot Method

1. Cold method

The cold method involves stirring a drug with enough distilled water and storing it overnight at 4°C in a refrigerator. The solution is then gradually supplemented with the *in situ* gelling polymer while being continuously stirred. The mixture is then kept in a refrigerator until it transforms into a clear solution. The volume is finally adjusted. When chitosan, Carbopol, and poloxamer are utilized as gelling polymers, this approach is typically employed.

2. Hot method

The hot method is usually utilized when pectin or gellan gum are employed as a gelling polymer. During the procedure, the gellan gum chains progressively dissolve in water at high temperatures and adopt a random-coil configuration with high segmental mobility. When this solution cools while being surrounded by ions like K^+ or Ca^{2+}, it progressively begins to gel. The demethoxylation of pectin, which aids in its solubilization, also requires high temperatures.[16]

Evaluation of *In situ* gel

1. Determination of visual Appearance and Clarity

The appearance and clarity is determined visually against a white and black background for presence of any particulate matter.[17]

2. pH

The pH will be checked by using a calibrated digital pH meter immediately after preparation.[18]

3. Texture analysis

The formulation's purity and durability is assessed using a texture analyzer, which largely displays the sol's syringe ability, allowing the formulation to be delivered *in vivo* with ease. To maintain tight contact with a tissue-like surface, higher adhesive values for gels are required.[19]

4. Sol-Gel transition temperature and gelling time

For *in situ* gelling systems with thermo reversible polymers, the sol-gel transition temperature may be defined as the temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specific rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube.[20]

5. Viscosity

Brook field Viscometer is used to determine the viscosities of the prepared formulations. A volume of 50 ml of the sample was measured and taken into Nessler's cylinder and sheared at a rate of 50 and 60 rpm using spindle number 63 at room temperature. Each sample's viscosity measurement is done in triplicate.[21]

6. Spreadability

For the determination of Spreadability, 1 gm of sample is applied between the two glass slides and was compressed to uniform thickness by placing 1000 gm weight for 5 min. Weight (50 gm) added to the pan the time required to separate the two slides, i.e. the time in which upper glass slide moves over the lower plate was taken as measure of spreadability (S).[22]

$S=M\times L/T$

Where M= weight tied to upper slide,
L= length moved on the glass slide,
T= time taken.

7. Drug content

Take 1ml of formulation and adjust to 10ml in volumetric flask and then dilute with 10ml of distilled water, 1ml from this solution again diluted with distilled water up to 10ml. After this take absorbance of prepared solution at a particular wavelength of the drug by using UV visible spectroscopy.[23]

8. *In vitro* diffusion studies

Franz diffusion cell is used to determine *in vitro* diffusion study of *in situ* gel. In this instrument two compartments are present, in which formulation is placed in donor compartment and freshly prepared medium is placed in receptor compartment. The dialysis membrane is placed (0.22 µm pore size) between receptor and donor compartments. The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature is maintained at 37ºC± 0.5ºC. 1 ml sample is withdrawn at specified time interval for six hours. This sample is diluted to 10 ml volumetric flask with suitable solvent and analyzed by UV spectrophotometer.[24]

9. Gelation temperature

Gelation temperature is assessed using a modified Miller and Donovan technique. 2ml aliquots of the gel are transferred to test tubes sealed with parafilm and immersed in a water bath at 4°C. The temperature of the bath was increased in increments of 1°C and left to equilibrate for 15 min at each new setting. The samples were examined for gelation, which was deemed to have occurred when the meniscus would no longer move upon tilting through 90°C.[25]

Applications of *in situ* gel

1. Oral drug delivery system

Potential uses of pH-sensitive hydrogels for site specific delivery of drugs to specific regions of GI tract have been widely studied. Polymers used for oral *in situ* gel delivery system are pectin, xyloglucan and gellan gum. The potential of an orally administered *in situ* gelling pectin formulation for the sustained delivery of paracetamol have been reported. *In situ* gelling gellan formulation as vehicle for oral delivery of theophyllin has been reported. Hydrogels made of varying proportions of PAA (polyacrylic acid) derivatives and cross-linked PEG assist in preparation of silicone microspheres, which released Prednisolone in the gastric medium and showed protective property.[26]

2. Ocular- 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 eye. So, to overcome bioavailability problems, ophthalmic *in situ* gels were developed Much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug deliver. Drug release from these *in situ* gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops. Miyazaki *et al.* attempted to formulate *in situ* gels for ocular delivery using Xyloglucan (1.5% w/w) as the natural polymer. These *in situ* forming polymeric systems were observed to show a significant mitotic response for a period of 4h when instilled into lower cul-de-sac of rabbit eye. The

formulation and evaluation of an ophthalmic delivery system for indomethacin for the treatment of uveitis was carried out. A sustained release of indomethacin was observed for a period of 8 hr *in vitro* thus considering this system as an excellent candidate with the water-soluble Carbopol system has been reported.[27]

3. Nasal drug delivery system

In the nasal gel system *in situ* xanthan gum and gallan gum are used as *in situ* polymers forming the gel Momethasone furoate which is used to test its effectiveness in treating infectious rhinitis. Animal studies have been used to model rhinitis allergies and the effect of *in situ* gel on antigen-treated nose signals in sensitive mice was observed. An *in situ* gel was found to prevent an increase in nasal symptoms compared to nosonex for marketing preparation (suspension of Momethasone furoate 0.05%).[28]

4. *In situ* forming polymeric systems for Rectal and Vaginal delivery

In situ gels could also be used to administer drugs via the rectal and vaginal routes. Miyazaki *et al*., looked into the utilization of xyloglucan-based thermoreversible gels for indomethacin rectal medication administration. When rabbits were given indomethacin-loaded xyloglucan-based systems, they showed a broad drug absorption peak and a longer drug residence time than when they were given a commercial suppository. Furthermore, after delivery of the *in situ* polymeric system, there was a considerable reduction in drug Cmax, indicating that the deleterious effects of indomethacin on the nervous system were avoided. For the treatment of vaginitis, a mucoadhesive, thermosensitive, extended release vaginal gel including the clotrimazole-cyclodextrin complex was developed. To achieve long residence time at the application site, Pluronic F-127 was employed as an *in situ* gel forming polymer in conjunction with mucoadhesive polymers such as Carbopol 934 and hydroxylpropylmethylcellulose.[29]

5. Injectable drug delivery system

In this drug delivery system, these 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.[30]

6. Dermal and Transdermal 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.[30]

CONCLUSION

The conclusion drawn on *in situ* gel formulations highlights the significance advantages, evaluation and potential applications of *in situ* gelling systems in drug delivery. These systems offer benefits such as improved patients compliance, reduced dosing frequency, increased gastric retention, site-specific drug delivery, ease of administration, and minimized adverse effects compared to other dosage forms, and enhanced bioavailability. Various triggering mechanisms, including pH change, temperature modification, and solvent exchange, play crucial roles in the gelation process of *in situ* gelling systems. Overall, *in situ* gels have emerged as promising and versatile drug delivery system with the potential to revolutionize pharmaceutical research and development.

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