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Review Article

Review On In-Situ Gel: A Novel Approach To Sustained And Controlled Release Form

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ABSTRACT

The 'in situ gel' system can be used to deliver both controlled and sustained delivery of drug. Due to its special feature of 'Sol to Gel transition' it is widely accepted as a novel drug delivery system with improved patient compliance. The sol to gel transition occurs at various physiological conditions thereby provide sustained drug release. The various polymers helps in this transition at targeted site. The 'in situ gel' has a wider application in ocular, oral, rectal, vaginal, nasal, transdermal delivery of drugs.

INTRODUCTION

The in situ gel is a novel approach to sustained and controlled release formulation. Due to its special characteristic of 'Sol to Gel transition' it is widely accepted. The sol to gel transition i.e., the solution (before application) gets transformed to gel form occurs at various physiological conditions like change in temperature, pH, due to special ions etc. Various polymers like guar gum, pectin,carbapol, poloxomer etc are used in this system. This system is used to deliver drugs to oral, ocular, transdermal, buccal, intraperitonial, parenteral, injectable, rectal and vaginal routes.[1,2] Increased bioavailability, reduced dosing frequency and dose and increased residence time are the characteristic of the system. More over system shows better patient compliance especially in unconscious patients.Stability issues ,homogeneity in drug loading ,mechanical strength are the critical parameters that may affect the system.

MECHANISM:

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There are two ways that the in situ gel system forms:

1. Physical mechanism
2. Chemical mechanism.

1. Physical mechanism:

a.Diffussion:

One kind of physical method employed in insitu gel formulation is diffusion. This approach creates precipitation or solidification of the polymer matrix by allowing solvent from the polymer solution to diffuse into the surrounding tissue. One polymer that is frequently employed in the creation of in-situ gelling systems is N-methyl pyrrolidone (NMP).[3]

b.Swelling:

Another form of physical method employed in insitu formulation is swelling. Applying this technique,the polymer absorb the fluids from the external environment, swells from the outside inward, and releases the medication gradually. Glycerol monooleate, or myverol, is a polar lipid that forms Lyotropic liquid crystalline phase structures as it swells in water. This material can break down in vivo by enzymatic action and has certain bioadhesive qualities.

2. Chemical mechanism:

The following chemical processes may be involved in in situ gelation:

a. Enzymatic cross linking:

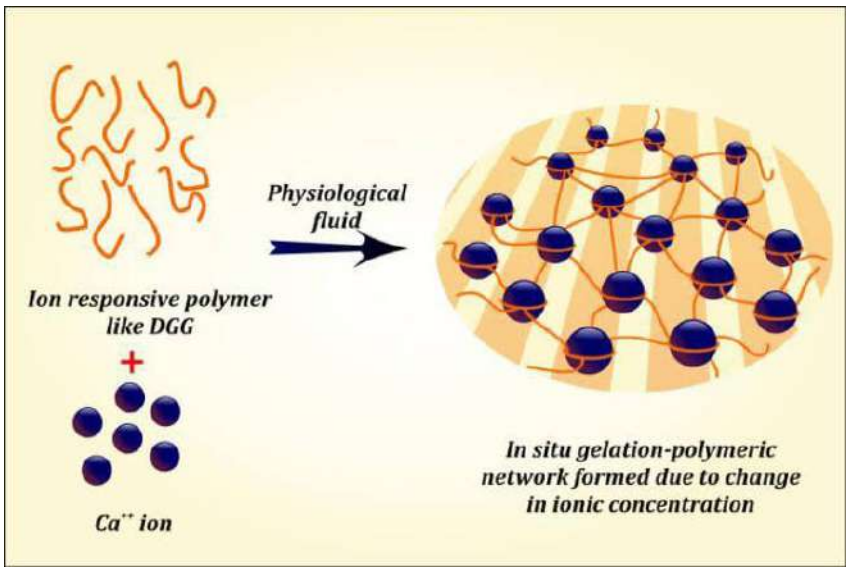
In situ gelling system creation is best achieved via enzymatic cross-linking. Using this technique, gel is created by creating cross links with the enzymes found in body fluids. Although they haven't been studied extensively, in situ creation caused by natural enzymes seems to have certain benefits over chemical and photochemical processes. The enzymatic method, for instance, manages effectiveness under physiological settings and eliminates the need for potentially hazardous substances like initiators and monomers. Altering the enzyme's concentration while maintaining a suitable established mechanism that regulates the rate at which gel forms, ensuring that the mixtures are injected prior to gel formation.[4]

b.Photopolymerization:

Electromagnetic radiations are used in the photo-polymerization method to form the in situ gelling system. An invader and reactive macromere or monomer solution can be injected into a tissue site, and gel can be formed by applying electromagnetic radiation. The best polymers for photo polymerization are those that can be broken down by a polymerisable functional group when exposed to a photoinitiator such as acrylate or a similar monomer. Long wavelength ultraviolet and visible macromers are usually employed in photopolymerization. Because short wavelength ultraviolet light has a limited tissue penetration and is biologically harmful, it is not used frequently. This technique uses ketone as the ultraviolet photo-polymerization initiator, such as 2,2 dimethoxy-2-phenyl acetophenone. ethyl eosin initiators and camphorquinone are utilized in visible light.[5]

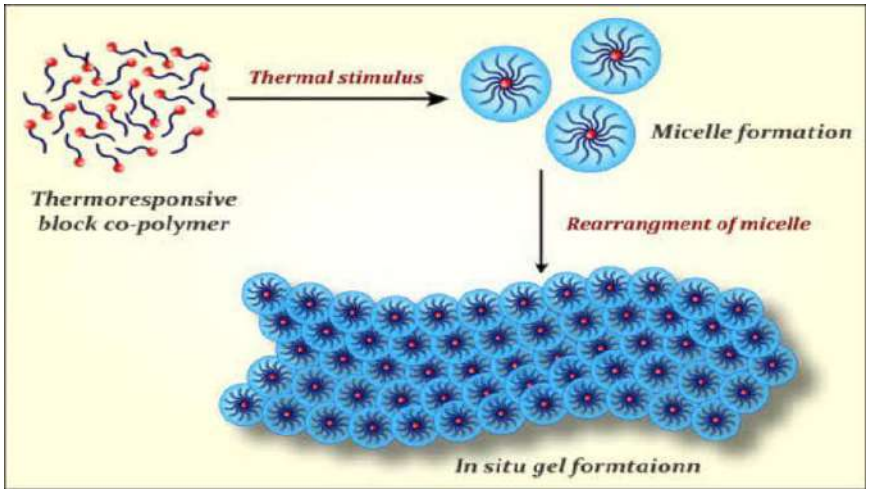
c.Ion gellation method:

This technique makes use of an ion-sensitive polymer. Phase transitions can occur in ion-sensitive polymers when they come into contact with different ions such as Na+, K+, Ca+, and Mg+. Ion-sensitive polysaccharides include a category of polysaccharides. I carrageenam forms elastic gels primarily in the presence of Ca2+, whereas k-carrageenan forms rigid, even small amounts of K+ are responding in brittle gels. The most common form of gellan gum is Gelrite. It is an anionic polysaccharide that goes through an in situ gelling system when mono- and divalent cations are present.



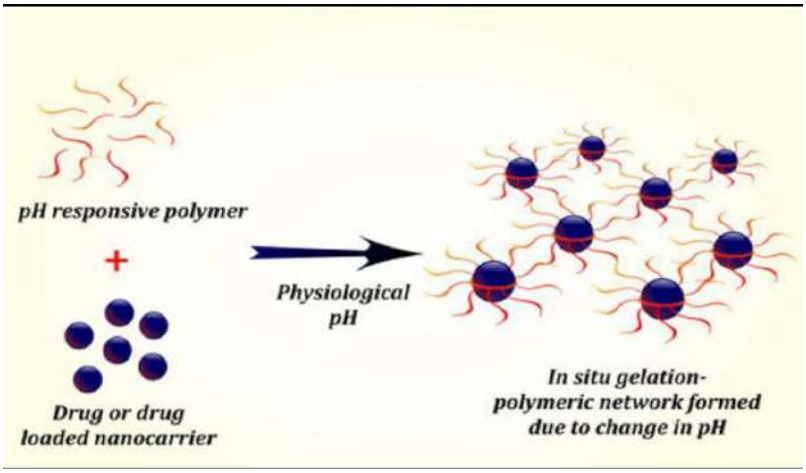
d. Temperature triggered gellation:

In the formulation of in-situ gelling, temperature is the most frequently utilized stimulus in environmentally responsive polymer systems. The technique used for temperature change is simple to apply in both in vitro and in vivo settings, and it is also easy to control. In this system, body temperature triggers gelation; external heat is not required. When these hydrogels come into contact with body fluids, their liquid form(in room temperature) changes to a gel state (35–37°C) as a result of the rise in temperature. Temperature-induced systems can be found in varieties. For example, poly (Nisopropylacrylamide) is a negatively thermosensitive type; polyacrylic acid is a positively thermosensitive type that is thermally reversible. Such as Tetronics, Pluronics, and Poloxamer. Thermoresponsive or temperature-responsive polymers—which exhibit abrupt, sharp changes in their physical characteristics with temperature—are employed in this system. These polymers exhibit an upper or lower critical solution temperature and a miscibility gap at high or low temperatures. Pluronic F-127 is a nonionic triblock copolymer that gels firmly when the temperature is changed.[6,7]



e. pH trigerred in situ gellation:

Changes in pH cause gel transition in this system. This technique uses pH-responsive or pH-sensitive polymers. pH-sensitive polymers contain pendant basic or acidic groups that may absorb or release protons in response to pH variations in their surroundings. Poly electrolytes are large-scale polymers of ionizable groups. As the formulation contains poly electrolytes, the rise in external pH , leads the hydrogel to swell and form in situ gel. Anionic polymers are among the appropriate polymers for this strategy. Among them are polyethylene glycol (PEG), pseudo latexes, carbomer and its derivatives, cellulose acetate phthalate (CAP), poly methacrilic acid (PMC), and so on. The well-known polymer carbopol, also known as polyacryl acid, is pH dependent. At acidic pH levels, it remains in solution, but at alkaline pH levels, it gels with low viscosity.



Polymers employed in "in situ gelling" system:

1.Xanthum Gum:

Gram-negative bacteria Xanthomonas campestris undergoes fermentation to produce high molecular weight extra cellular polysaccharide, which is what gives xanthan gum its texture. This naturally occurring cellulose derivative's fundamental structure consists of a cellulosic backbone (β-D-glucose residues) connected to an alternative glucose residue of the main chain33 by a trisaccharide side chain consisting of β-D-mannose, β-D-glucuronic acid, and α-D-mannose. Both hot and cold water, as well as alkaline and acidic environments, will dissolve xanthan gum. In alkaline circumstances, it shows good stability.

2. Pectin:

A family of polysaccharides known as pectins mostly composed of α- -(1-4)--D galacturonic acid residues in their polymer structure.. Low methoxy pectins (degree of esterification <50%) easily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a way explained by the egg-box model. Pectin forms gels in the presence of H+ ions. Typically, calcium ions are required as a source of divalent ions to create gels that can be used as drug delivery vehicles. Since pectin is water soluble, organic solvents are not used in the formulation process. When pectin is taken orally, divalent cations found in the stomach facilitate the gel-forming process.[8].

3.Alginate:

This polysaccharide is a linear block copolymer, made up of β-L-glucuronic acid and β-D-mannuronic acid residues connected by 1,4-glycosidic bonds. Depending on the algal source, there are variations in each block and the order of blocks along the molecule. When di and trivalent metal ions are added to diluted water solutions of alginates, the alginate chain's α-L glucuronic acid

blocks' consecutive glucuronic residues work together to create solid gels. Because alginic acid has advantageous biological qualities such being nontoxic and biodegradable, it is employed as a carrier for ophthalmic preparations.

4.Carbopol:

Carbopol is a popular pHsensitive polymer. The polyacrylic acid (PAA) polymer carbopol get turned to gel when the pH was increased from 4.0 to 7.4. At acidic pH levels, carbopol stays in solution; at alkaline pH levels, it gels into a low viscosity state. When HPMC and carbopol are combined, the viscosity of the carbopol solution is increased while its acidity is decreased. After comparing several poly (acrylic acid) varieties (Carbopol 940, 934, 941, and 910) , it was determined that Carbopol 940 had better look and clarity. [9]

5.Chitosan:

Two factors, such as variation in temperature and pH , causes gelling of chitosan. The naturally occurring chitosan found in shrimp and crab shells is made up of a thermosensitive, biodegradable polycationic polymer that is produced by alkaline deacetylation of chitin. Chitosan is a pH-dependent cationic polymer that is biocompatible and may dissolve in aqueous solutions up to 6.2. Precipitation occurs when a hydrated gel is formed if chitosan aqueous solution is neutralized to a pH higher than 6.2. [10]

6.Gellan gum:

The microorganism Sphingomonas elodea secretes gellan gum, an anionic heteropolysaccharide. It is made up of glucuronic acid, rhamnose, and glucose that have been joined to form a tetrasaccharide molecule. Deacetylated gellan gum, or Gelrite29, is produced by subjecting gellan gum to an alkali solution, which eliminates the acetyl group from the molecule. Gelrite crystallizes as a result of instillation because calcium ions are present. As a result of complexation with cations and hydrogen bonding with water, double helical segments aggregate to form three-dimensional networks30 during the gelation process. This is followed by the creation of double helical junction zones. Gellan gum is used as a stabilizing and suspending agent in the food business.

7.Cellulose derivatives:

The glucan chain that makes up cellulose has repeated -(1, 4)-D-glucopyranose units. Temperature-sensitive sol-gel phase transition is exhibited by certain natural polymers, such as HPMC, MC, and EC. When the temperature drops, cellulose material will become more viscous, whereas as the temperature rises, its derivatives, such as HPMC and MC, will also become more viscous. MC is a naturally occurring polymer made up of native cellulose chains that have been alternately substituted with methyl groups. A solution is liquid at low temperatures (3000C), while gelation occurs at higher temperatures (40–5000C).

8.Poloxamer:

Poloxamer is a tri-block copolymer that dissolves in water. It is made up of two ABA-configured cores made of polyethylene oxide (PEO) and polypropylene oxide (PPO). Pluronic, a commercially available form of poloxamer, offers longer drug residence times and good thermal setting properties. Its primary applications are as a solubilizing, emulsifying, and gelling agent. A translucent, colorless gel is produced by poloxymer. The distribution and ratio of hydrophilic and hydrophobic chains, with varying molecular weights and gelling properties, are the determining factors .

9.Xyloglucan:

Tamarind gum, also known as xyloglucan, is a polymer that is extracted from the seed's

endosperm. Three distinct oligomers, heptasaccharide, octasaccharide, and nonsaccharide, which vary in the quantity of galactose side chains, make up xylogulcan. Due to its non-toxic, biodegradable, and biocompatible qualities, it is mostly employed in oral, rectal, and ocular medication delivery. Similar to poloxamer, which gelates at refrigerator temperature when heated, or when cooled from a higher temperature.

Application of in situ gelling system:

1.In transdemal system:

Because of the composition and structure of the skin, pharmaceutical research has found it extremely difficult to deliver medication molecules across the skin barrier.

The efficacy of Pluronic F127 in thermally reversible gel as a vehicle for the subcutaneous delivery of Indomethacin was assessed. According to in-vivo research, a 20% w/w aqueous gel could serve as a useful foundation for topical medication administration. Iontophoresis and chemical enhancers worked in collaboration to increase insulin penetration in a synergistic manner. By developing cyclodextrin complexes, Cur's solubility and stability were increased. The Cur-loaded ISGs demonstrated effective melanoma therapy and high transdermal efficiency with the use of Poloxamer polymer.[11]

2. Oral drug delivery system:

The pH-sensitive hydro gels may be used to deliver medications to particular GI tract locations. Hydrogels composed of different ratios of cross-linked PEG and PAA derivatives facilitated the creation of silicone microspheres that either exhibited gastroprotective properties or produced prednisolone in the stomach media. While various polysaccharides such amidaded pectins, inulin, and guar gum were researched to improve a potential colon-specific drug delivery method, cross-linked dextran hydro gels swell more quickly at high pH levels. The complexed calcium ions included in the gellan and sodium alginate formulations undergo a process of gelation upon release into the stomach's acidic environment.

3.Ophthalmic drug delivery system:

To increase ocular bioavailability and extend the precorneal residence period of the medication, in situ gels generating technology have been established.Natural polymers including xyloglucan, alginic acid, and inulin are the most often utilized in ocular delivery systems. Various chemical compounds, including autonomic medications, anti-inflammatory agents, and antibacterial agents, are utilized in local ophthalmic delivery systems to relieve intraocular tension in cases of glaucoma. As an in situ gelling vehicle for ophthalmic drug delivery systems, Pluronic F127-g-poly(acrylic acid) copolymers were investigated for their capacity to extend the precorneal residence time and enhance ocular bioavailability of the drug. Doxycycline niosomal thermoresponsive in situ gel for ophthalmic application were developed using Poloxamer 407 to increase the residence time of dosge form.[12].

4.Nasal drug delivery:

There are multiple factors that lead to the declining acceptance of nasal dose forms: Low bioavailability is frequently caused by mucociliary clearance, enzymatic degradation, and low penetration. The in-situ gel generating polymers in the nasal in-situ gel system are xanthan and gallan gum. An amoxicillin-loaded albumin nanoparticle in situ ionic-sensitive nasal gel with a suitable retention and controlled-release profile on the nasal mucosa for possible efficacious therapy of ABR was conducted.[13]

5. Rectal and vaginal drug delivery system:

Several medication forms that are manufactured as liquid, semisolid (ointments, creams, and foams), or solid dose forms (suppositories) can be

administered via the rectal route. In order to create a rectal in situ gel, acetaminophen, an anti-inflammatory medication, was combined with polycarbophil and poloxamer F188 and 407, two synthetic polymers that form an in situ gelling liquid suppository. This method is thought to be effective and enhances bioavailability.

6. Injectable delivery system:

Since there is no need for surgery and patient cooperation, in situ gels, which have been developed specifically for this drug delivery system, have gained popularity during the past ten years. When creating injectable in situ gel, block copolymers and synthetic polymers are the most common materials used. A medication that is used to treat inflammation is bupivacaine, which is made as an injectable in situ gel with poly(D,L-lactide), poly(D,L-lactide coglycolide), and PLGA as the polymer that exhibits a prolonged duration of action in gel state.

CONCLUSION

The present research finds that the "in situ gel" system has become one of the most effective innovative drug delivery methods; it facilitates controlled and sustained release of medications while enhancing patient comfort and compliance. Through the process of in situ gel formation, a variety of natural and synthetic polymers may find application in the oral, ophthalmic, transdermal, buccal, intraperotonial, injectable, rectal, and vaginal routes. Research on the in situ gel system has a lot of potential to offer innovative approaches for drug delivery systems.

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