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In-Situ Gelling System: A Review

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ABSTRACT

One of the most well-known and widely available systems is In-situ gels. By reducing the frequency of drug administration through their special characteristic features of sol to gel transition, these systems provide a number of benefits including simple production, ease of use, increased adherence, and patient comfort. In-situ gels are a particular class of hydrogel that are in solution form and go through a gelation process depending on the physiological circumstances. The gel's development is influenced by variables including temperature swings, pH shifts, ion exposure, UV light, electrical sensitivity, and a crucial enzyme from which the drug is continuously and carefully released. This review primarily focuses on an introduction to in situ gel, its advantages and disadvantages, its mechanism, different approaches to in situ gel formation, the mechanism of drug release from the system, different polymers used in formulations, general methods of preparation, different uses for in situ gel systems in drug delivery, and evaluation of in situ gel.

INTRODUCTION

The researchers have spent the last two decades working to create a new strategy that can overcome the challenges associated with traditional formulations. The primary benefit of these activities is unquestionably the creation of in-situ gel.[1]Every drug delivery system's primary goal is to change the drug's pharmacokinetic characteristics and tissue distribution in a beneficial way. Much focus has been placed on the development of controlled and sustained release medication delivery devices over the past 60 years. One of the greatest innovative medication delivery systems has been identified as the "in situ gel" technique. In situ gels are the solutions or suspensions that undergo gelation after reaching the particular site due the solutions contact with body fluids or physicochemical changes (i.e., pH, temperature, ionic concentration, and UV radiation, presence of specific molecules or ions, external trigger). Many research have been carried out using the oral, ocular, nasal, rectal, vaginal, injectable, parenteral, and intraperitoneal methods. Several polymeric drug delivery systems have been created. Once subjected to physiological stimuli, these polymers go through a sol-gel transition. In situ gel drug delivery systems are created using a variety of organic and synthetic polymers.[2]

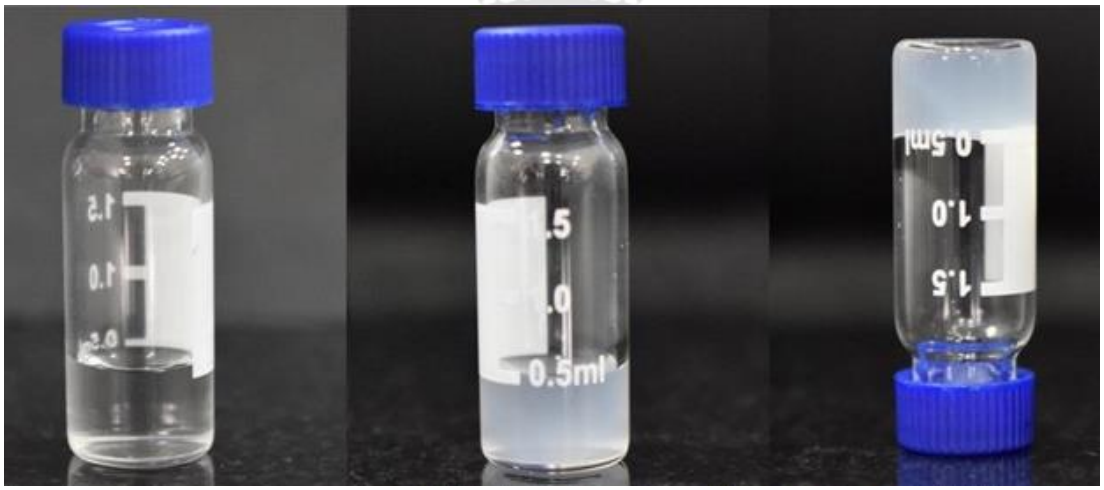

Fig 1.sol state (at low temperature) → gel state (at high temperature)

IMPORTANCE OF IN-SITU GELLING SYSTEM [3]

1) Its specific "Sol Gel transition" contributes to the drug's controlled and sustained release.

2) It helps in lowering the frequency of drug administration to the body.

3) There won't be any drug formation and no adverse effects because only a small amount of the medication is needed.

4) The medicine will have a higher bioavailability.

5) Due to gel formation, the drug's residence period will become longer.

6) The in situ gel method reduces drug wastage.

7) The best dosage form for drugs is a liquid that can maintain drug release and stay in touch with the cornea of the eye for a long time.

8) A medicine drained through the nasolacrimal duct may have less systemic absorption, which could have certain unwanted side effects.

APPLICATION OF IN-SITU GEL

1. Oral: Theophylline is given orally to mice and rabbits in the form of in situ gels with gellan gum serving as the sustained release carrier. In an acidic environment like the stomach, gel production takes place. Theophylline's in situ gel forms boost bioavailability in mice by four to five times and in rabbits by as much as three times. Environmental factors can affect oral in situ gel. In situ gel is present at the moment of administration as a low viscous solution, but in a delicate environment, the polymer changes conformation to become a gel. By slowly releasing the medicine, in situ gel may increase the interaction time between the drug and its stomach-based absorption site. As a result, in situ gel is extremely beneficial for treating chronic disorders. [4]

2. Ocular: The sustained release profile of the brimonidine tartrate in situ gel formulation, along with carbopol composition polymer 974P and hidroxy propyl methyl cellulose (HPMC) K4M, significantly affects the drug's duration of action and enhances the activity of reducing intraocular pressure more effectively than drop treatments for glaucoma.[4]

3. Nasal: Xanthan gum and gallan gum are use as in-situ gel polymers in the nasal in-situ gel system to investigate the efficacy of momethasonefuroate in the treatment of allergic rhinitis. The influence of in-situ gel on nasal antigen signals in rat consciousness and the modelling of allergen rhinitis using animal studies. As opposed to Nosonex marketing

changes (Momethasonefuroate suspension 0.05%), in-situ gel has been observed to reduce the occurrence of nasal symptoms.[5]

4. Rectal: When administered to rabbits, in situ gel Ibuprofen of solid dispersion is found to be more effective than a solid suppository when combined with poloxamer 407 (thermosensitive), HPMC E5, and sodium alginate (mucoadhesive). Moreover, it results in increased plasma peak and bioavailability concentrations.[4]

5. Vaginal: Gellan gum, an active gelling polymer, and HPMC (0.1%) ions, a bioadhesive that has been shown to generate non-irritating, bioadhesive preparations with good retention qualities, are given to clindamycin HCl during the in situ gel formation process.[4]

6. Injection: Because it may be used without requiring surgery and has high patient compliance, this medication delivery system has also been developed as a gel over the past ten years. Injectable in situ gel injection is made of a variety of block copolymers and synthetic polymers. One illustration of an anti-inflammatory medication is bupivacaine, which is created as an injectable in situ gel using the polymers poly (D, L-lactide, poly (D, L-lactidecoglycolide), and PLGA.[5]

7. Dermal and transdermal: As a vehicle for administering indomethacin, pluronic F127 in heat-releasing gel has undergone testing. A 20% weight/weight aqueous gel may work well as a basis for topical medication administration, according to in-vivo study. Interactions between insulin permeation and chemical improvements have been developed as a result of iontophoresis**.**[4]

PRINCIPAL OF IN-SITU GEL

In order to create an in-situ gel system, a stable suspension system including the dispersed medication and other excipients must first be created. Due to a pH change, this sol/suspension system must gel in the gastrointestinal environment. The formulation used is a sodium alginate or gellan gum solution containing calcium chloride and sodium citrate, which complexes free calcium ions and only releases them in the stomach's acidic environment. Gellan gum or sodium alginate is used as a gelling agent, and the free calcium ions are trapped in their polymeric chains, causing the chains to crosslink and create a matrix structure. Through complexation with cations and hydrogen bonding with water, this

gelation entails the production of a double helical junction followed by the reassembly of double helical segments to form a three-dimensional network.[6]

ADVANTAGES [7]

1. It makes administration simple.
2. It increases bioavailability.
3. It reduces medication wastage.
4. Increases patient comfort and compliance, and reduces local and systemic toxicity.
5. It was given to elderly and unconscious patients.
6. It aids in the prolonged or extended release of medications.
7. Due to the low dose, it prevents drug buildup.
8. It displays bio-adhesiveness to aid in drug targeting;
9. It allows for drug targeting primarily through mucous membranes.
10. Provide acceptable functionality and degradability utilising synthetic polymers.
11. to decrease the medications discharged through the nasolacrimal duct's systemic absorption

DISADVANTAGES: [3, 7]

1. It needs more fluids than usual.
2. Very little amounts can be provided for administration.
3. There is a possibility for instability because of chemical deterioration.
4. After taking the medication, decrease your intake for a few hours.
5. Due to its low mechanical strength, it could dissolve too soon.
6. The quantity and uniformity of drug loading were restricted for hydrophobic medicines.

IDEAL CHARACTERISTIC OF POLYMERS

A polymer is a necessary component in the creation of any gel. The following list includes some of the essential polymer properties for in situ gels.[5, 7]

1. It should be compatible.
2. It shouldn't affect how tears behave.
3. It shouldn't have any harmful side effects.
4. It should have pseudo-plastic behaviour.
5. It should be optically clear and have acceptable tolerance.
6. It should be able to adhere to the mucous membrane and decrease viscosity while increasing shear rate.

MECHANISM OF IN-SITU GEL: [2, 3, 5,10,13,15]

Here are 4 mechanisms for triggering the in-situ gelling formation of biomaterials. These include**:**

1. In situ gel formation due to physiological stimuli: A small number of polymers experience significant and rapid physical and chemical changes as a result of external environmental changes. Stimuli-responsive polymers are those that respond to stimuli. They are also referred to as intelligent, smart, and stimuli-responsive polymers. These polymers read an upgrade as a sign, evaluate the strength of the signal, and adjust their chain confirmation as necessary. In situ gel system that is temperature controlled.

a. Temperature triggered in situ gel systems

Thermosensitive polymers are the most commonly used class of naturally responsive polymer frameworks in drug delivery. This is because temperature is quite easy to manage and also useful for both in vitro and in vivo research. With this technology, a change in temperature triggers the gelling of the solution, which sustains the release of the drug. These hydrogels are fluid at room temperature (20–25 °C), but when they interact with bodily fluids (35–37 °C), they become gel. An unusual way to approach *In--situ* formulations is to use biomaterials whose transformation from sol-gel is triggered by increase in temperature.

In order to encourage clinical control and ensure that no external heating source other than the body is required to cause gelatin, the surrounding and physiological temperature range is the optimum fundamental temperature range for such a system. The thermosensitive sol-gel polymeric framework is designed using three main techniques. As a result, they are divided into:

1) Negatively thermo sensitive, which contract upon heating

2) Positively thermo sensitive, which contract upon cooling

3) Thermo-reversible gel

Poloxamers/Pluronic, cellulose derivatives such as xyloglucan and ethyl (hydroxy ethyl) cellulose (EHEC), and tectonics are examples of polymers that undergo temperature-induced gelation.

b. pH triggered in situ gelling systems: pH is another physiological enhancement that promotes the application of in situ gel. Remembered polymers have an acidic or an alkaline group that, depending on the pH of the environment, either accepts or donates protons. They are now referred to as pH responsive polymers. It is common practice to use this type of mechanism for ocular medication delivery systems. Using in situ gel systems will increase the medication's precorneal time of residence, improving its bioavailability. The formulation is present as a normal solution at pH 4.4, but at pH 7.4.

2. In situ gel formation due to ion-activated system: The change in ionic strength in this case causes the imparted solution to gel. It is widely acknowledged that the rate of gelation is controlled by the osmotic gradient across the gel's surface. The aqueous polymer solutions form a reasonable gel when monovalent and divalent cations, which are frequently present in tear liquids, are present. When the arrangement is embedded in the conjunctival cul-de-sac, the electrolyte present in the tear liquid, particularly Na+, Ca +, Ca^{2}+, and Mg^{2}+ cations, play a key role in the beginning of gelling. Gel rite or gellan gum, hyaluronic acid, alginates, and other substances are all found in polymers that exhibit osmotically induced gelation.

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

a. Swelling: In in-situ formulation, one type of physical technique is called swelling. In this technique, the polymer is surrounded by the polymer wrap, and the fluids in the

surrounding environment inflate from the outside to the inside, allowing the medication to slowly escape. Myverol, also known as glycerol monooleate, is a polar lipid that expands in water to create lyotropic liquid crystalline phase structures. This material can degrade *in-vivo* by enzymatic action and exhibits certain bioadhesive characteristics.

b. Diffusion:is a kind of physical method utilised in the creation of in-situ gels. This approach calls for the solvent from the polymer solution to diffuse into the tissue around it, causing the matrix to precipitate or solidify. In-situ gelling systems frequently use the polymer N-methyl pyrrolidone (NMP).

4. In situ gel formation due to chemical reactions

a. Ionic cross-linking: Some ion-sensitive polysaccharides, such as gellan gum, gelatin, and sodium alginate, undergo phase changes when certain ions are present. Gellan gum, an anionic polysaccharide, undergoes in situ gelling in the presence of monovalent and divalent cations such Ca^{2}+, Mg^{2}+, K+, and Na+.

b. Enzymatically cross linking: Even though in-situ development using ordinary catalysts has not received much attention, it does have some advantages over chemical and photochemical methods. For instance, an enzymatic cycle operates effectively in physiologic settings without the requirement for potentially hazardous chemicals like monomers and initiators. Adjusting the amount of enzymes provides an effective method for regulating the rate of gel formation, allowing the mixture to be infused prior to gel formation.

c. Photo-polymerization: Photo-polymerization is typically used for in situ conversion of biomaterials. Electromagnetic radiation is used to create gel after injecting a combination of a monomer or reactive macromer and an initiator into a tissue location. Since they easily undergo photo-polymerization in the presence of the proper photo initiator, acrylates and related polymerizable groups are frequently used as the polymerizable groups on the individual monomers and macromers. In particular, UV and visible wavelengths are used. Because of its limited tissue penetration and negative effects, short wavelength UV isn't widely used. After being introduced to the ideal location through infusion, photo-polymerizable frameworks are photocured in place with the aid of fibre optic linkages and then release the medication over a delayed period of time. The photo-responses provide rapid polymerization rates when the temperature is physiological. Sawhney et al. explain the

use of a photo-polymerizable, biodegradable hydrogel as a tissue-reaching substance and controlled delivery carrier.

CLASSIFICATION OF IN-SITU GEL POLYMERS [2, 3, 4, 7, 8, 9, 13, 14]

Polymers are categorized according to their origin or the way that form gel. A source on the ground claims that there are two different sorts of gelling systems.

I. Natural polymers: E. g., Alginic acid, Carrageenan, chitosan, Guar gum, gellan gum, pectin, sodium alginate, xanthan gum, xyloglucan, etc.

II. Synthetic or non-synthetic polymers: E. g., Cellulose acetate phthalate, hydroxypropyl methylcellulose, methylcellulose, polyacrylic acid, poly (lactic-co-glycolic acid, poloxamers.

- **Natural polymer are as follows:**

1) Sodium alginate: Is a polymer that comes from nature. In terms of chemistry, sodium alginate is an alginic acid salt that includes residues of -D-mannuronic and -L-glucuronic acids connected by 1,4-glycosidic bonds. In the presence of divalent or trivalent ions, an alginates solution in water solidifies into files. For the preparation of gel-based solutions and the transport of proteins, peptides, and medicines, sodium alginate is frequently utilised. Because of its decomposing and non-toxic characteristics as well as additional adhesive capabilities, alginate salt is regarded as being very desirable. Research has demonstrated that where the ionic radical below is low, alginates form cohesive structures. When preparing oral administration fluids continuously, sodium alginate, a water-soluble polymer used in pharmacies, is highly helpful since it acts as a stabilising and viscosity-increasing agent.

2) Pectin: These polysaccharides, which include - (1-4) -D-galacturonic acid residues, have anionic characteristics of plant origin and can be split into two groups according to their polysaccharide structure. In the presence of a moderate amount of gel, pectin prevents the creation of a strong gel. A complex polysaccharide called pectin binds to D-galacturonic acid residues mostly in the series (1-4). The two forms of pectin—high methoxy and low methoxy gelation—are based on the methyl esterification of galacturonic acid. At pH 3.5, high methoxy pectin can typically mature. Low-methoxy pectin has a lot of calcium ions and doesn't require an acid or solid substance to function.

3) Gellan gum: A water-soluble anionic polysaccharide called gellan gum is also marketed as Phytagel or Gel rite. Gellan gum (FDA-approved) is a chemically anionic deacetylated polysaccharide duplicating tetra saccharide units made of -D-glucuronic acid (1 unit), -L-rhamn (1 unit), and -D-glucose residues. It is recommended by Sphingomonas elodea (Pseudomonas elodea) (2 units). Changes in temperature or the presence of cations (such as Na + K +, Ca2 +, and Mg2 +) cause gellan gum to form. Gellan gum is a water-soluble polymer that can be found in pharmacies and used as a potential carrier for a number of solid oral float types.

4) Xyloglucan: Tamarind seeds contain a plant-based polysaccharide. This polysaccharide's chemical structure is made up of a succession of (1-4) -D-glucan units (1-6) Particles of xylose with partial selections, -D (1-2) -D galactoxyloseXyloglucan is made up of oligamers with varying numbers of galactose side chains, including heptasaccharide, octasaccharide, and nonasaccharide. Xyloglucan does not employ gel, however solutions of xyloglucan that have been partially deteriorated by galactosidase exhibit a sol to gel in the hot area. Pilocarpine and timolol are delivered through the rectal, oral, and ocular routes.

5) Xanthan gum: A high molecular weight extracellular polysaccharide produced by Xanthomonascampestris is called xanthan gum. A trisaccharide that has a long chain polysaccharide on one side. Two glucose units are found in the main chain. Two mannose units and one glucuronic acid unit make up the side chains. In the presence of highly charged polymers, xanthan gum can solidify into a gel. By weakening the structure of water, this gum produces high viscosity solutions at low concentrations.

6) Pluronic: A group of difunctional copolymers called Poloxamers or Pluronic (marketed by BASF Company) are available for purchase in non-ionic organisms. They are made up of a block of hydrophobic polypropylene oxide in the centre and blocks of hydrophilic polyethylene oxide on either side. When these molecules are concentrated in aqueous solvents, they form micellar structures above the critical micellar concentration because of the PEO / PPO ratio of 2:1. They are thought of as PPO-PEO-PEO copolymers. Pluronictriblock copolymers come in a range of molecular weights and body composition phases. In accordance with the body location of the designated marks, such as F of flakes, P paste, and L liquid. Pluronics or Poloxamers can also experience temperature variations as a result of changes in temperature.

7) Chitosan: Chitosan is a natural and flexible polymeric polymer derived from the alkaline deacetylation of chitin. It is scalding, non-toxic, and rotting. Chitosan is a cationic biocompatible polymer that is continuously distributed in acidic solutions up to a pH of 6.2. A hydrated gel-like precipitate forms when chitosan in an aqueous solution becomes neutral at a pH level higher than 6.2. Without any chemical alteration or bonding, the addition of polyol salt transforms the pH-gelling cationic polysaccharide solution into a potent gel-based pH solution that forms a gel.

8) Carbopol: Carbopol is a pH-based polymer that, at alkaline pH, forms a thin gel of viscosity while remaining in solution at acidic pH. In order to increase the viscosity of the Carbopol solution and lessen its acidity, HPMC is used in conjunction with Carbopol. Many water copolymers undergo melting and temperature fluctuations**.**

- **Synthetic or non-synthetic polymers are as follows:**

1) Cellulose acetate phthalate (CAP): Pseudo-latex is another name for CAP. It is synthetic latex that has been created in an aqueous media through the dispersion of an earlier polymer. Due to the fact that latex is a free-running solution with a pH of 4.4 and undergoes coagulation tear fluid, raising the pH to pH 7.4, it is a cross-linked polyacrylic polymer with pH sensitivity that may have useful qualities for prolonged medication delivery to the eye. In -scintigraphy, CAP is used to measure the ocular residence duration of an ophthalmic solution, and no organic solvents are employed in the manufacturing process.

2) Hydroxypropyl Methylcellulose (HPMC): This polymer is mucoadhesive, thermoreversible, and biocompatible. Due to its great swellability, thermal gelation capabilities, use as hydrophilic matrices, and use in oral drug delivery systems, it is a form of cellulose ether. When combined with carbopol, HPMC increases the viscosity while lowering the acidity of the solution. The interaction between the polymer's hydrophobic elements causes HPMC to gel at higher temperatures. It was actively contributing to the creation of an aqueous solution for topical eye therapy. Vaginal mucoadhesive film formulation with CR of S-nitroso glutathione and effects on the gelling behaviour turned out to be crucial.

3) Methylcellulose: It also functions as an in situ gelling polymer and is a cellulose derivative. When heated, a number of cellulose derivatives that remain liquid at low temperatures turn into gels. A phase transition into gels, for instance, occurs in the aqueous

solutions of MC and HPMC between 40°and 50°C and 75° and 90°C, respectively. However, the phase transition temperature for MC and HPMC is lower than the physiological temperature due to chemical and physical modifications made to the polymers, which are greater than the physiological temperature. Solutions of HPMC and MC gel due to hydrophobic contact between molecules with methoxy groups. Due to macromolecule hydration at a lower temperature, polymer-polymer interaction occurs between them. When the heat rises, the hydration progressively evaporates, resulting in a decrease in viscosity. The polymers begin to associate and their thickness begins to rise at the transition when there has been sufficient dehydration of the polymers, indicating the establishment of a network structure. The solution is liquid at low temperatures (30°C), but when the temperature rose (40–50°C), gelation took place.

4) Polyacrylic acid (PAA): Commercially, PAA is referred to as carbopol. It is frequently applied in ophthalmology to improve pre-corneal retention. When compared to other cellulose derivatives, it can have exceptional mucoadhesive characteristics. Comparing other grades such carbopol 910, 934, 940, 941, etc., it was determined that 940 exhibited the superior one.

5) Poloxamaers: Thermosensitive in situ gels use poloxamers, also commercially know n as pluronic. It lengthens medication residence time and has excellent thermal setting properties. Two polyethylene oxide (PEO) and two polypropylene oxide make up this water-soluble tri-block copolymer (PPO). Due to its ability to make clear, colourless gels, pluronic F127 is the poloxamer polymer that is most frequently employed in pharmaceuticals. PEO and PPO make up 70% and 30% of it, respectively. For enhanced absorption and to extend the residence period of the ocular medicines, a copolymer pluronic F127-g-poly (acrylic acid) was utilised as an in situ gelling vehicle.

Evaluation and characterizations of In-situ gel: [4, 5, 10, 12, 16]

Following parameters are used for In-situ gel:

1) Clarity: Visual examination against a black and white background gives us information about the solution's clarity.

2) Texture analysis: Using a texture analyzer that identified the sol's syringe ability so that the structure could not be easily manipulated in vivo, the stability and consistency of the

hydrogel were examined. Gels must have high adhesion ratings in order to keep in close contact with the surface.

3) pH of gel: The composition is determined using a pH metre after 1ml of NaOH has been added by subtraction while the mixture is continuously stirred in a beaker.

4) Sol to gel transition temperature and gelling time: The temperature at which the sol gel phase transformation is first noticed in in-situ systems with thermosensitive polymers after being stored at a specific temperature and then heated to a specific level can be referred to as the sol-gel transition temperature. The lack of meniscus movement in the tube's tilt is a sign that the gel has formed.

5) Stability study: Based on research, stability testing sought to determine how long a substance should be stored and used. For about a month, the sample is kept in a climate room with a temperature of 40 °C and a relative humidity of 75%. The material was examined for related pH, viscocity, clarity, drug content, rheological properties, and in vitro dissolution after a period of time.

6) Drug content: A micropipette was used to transfer 1g of the mixture to 25-mL volumetric flasks after manually shaking the vials containing the preparation for two to three minutes. The total volume was then made up with phosphate buffer pH 6.6 (IP) and measured using a UV spectrophotometer at 272.5 nm.

7) Spreadability: Spreading coefficient was determined by a device or an apparatus. The device consist of a ground glass slide that was fixed on the wooden block. Each formulation of In-situ gel weighting about 2 g was placed and study on this ground slide. Gel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook. Weight of 1 g was placed on the top of the two slides for 5 min to expel air and to provide a uniform film of gel between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (in seconds) required by the top slide to separate from ground slide was noted. A shorter interval indicates better spreading coefficient

The result is calculated by using following formula

$$S = \frac{(M \times L}{T}$$

S= Spreading coefficient

M = Weight tied to upper slide

L = the length of the glass slides

T = Time taken to separate the slides.

8) Viscocity: This is an important aspect to consider while evaluating in situ gels. Viscosity and rheological properties of in situ forming drug delivery systems can be tested using a Brookfield rheometer or another kind of viscometer. Particularly when administered parenterally and topically, these formulations' viscosities should be such that no problems are anticipated during patient administration.

9) Gelling capacity: it is determined by using the drop of the formulation and 2ml of simulated salivary fluid (ph-6.8) at 37°C and observed the gel formulation and noting time for gelation and the time taken for the gel formed to dissolve.

CONCLUSION

In this review on in-situ gelling system definition of gels and in-situ gels are discussed. Briefly mentioned the number of methods for producing in-situ gels. Included polymers and the technique by which they are employed to create in-situ gels. Numerous drug delivery methods utilize in-situ gels in their operations. For the in-situ gel formulations, the use of biodegradable and water-soluble polymers can increase acceptance and make them an excellent drug delivery technique.

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