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A REVIEW ARTICLE ON IN SITU GELS

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INTRODUCTION

In situ gelling systems are polymeric formulations that are in sol forms before entering in the body, but change to gel forms under the physiological conditions. The sol-gel transition depends on one or a combination of different stimuli, like pH change, temperature modulation, solvent exchange, ultra violet irradiation and the presence of specific ions or molecules. Drug delivery systems having such properties can be widely used for sustained delivery vehicle preparation of the bioactive molecules.

Various natural and synthetic polymers undergo in situ gel forming and potentially can be used for oral, buccal, rectal, vaginal, ocular, intraperitoneal and parenteral drug delivery.[29]

Importance of in situ gelling system

- In-situ gel helps for the controlled and sustained release of the drugs by its Sol-Gel transition.
- It helps in reducing frequency of drug administration in the body.
- Low doses of the drugs are required and there will be no drug accumulation and side effects.
- It increases bioavailability of drugs.
- Residence time of drug will be increased due to gel formation.[30,31]

Advantages of in situ gelling system

- Ease of the drug administration
- Can be administered to unconscious patients

- Increased patient compliance and comfort
- Decrease the dose frequency and drug toxicity
- Increased bioavailability
- Provide biocompatibility and biodegradation due to use of natural polymers.[32-34]

Disadvantages of in situ gel system

- It requires high level of fluids.
- The sol form of the drug is more susceptible for degradation.
- Chances of stability problems due to chemical degradation.
- After placing the drug eating and drinking may become restricted up to the few hours.[35,36]

Preparation of in situ gel

The polymer may differ based on the development of in situ gelling systems. The polymeric solution was prepared by dispersing required quantities of polymers and copolymers in distilled water using a magnetic stirrer until the polymers completely dissolve. After the preparation of an aqueous drug solution, transferred to a primarily prepared polymeric solution with continuous stirring until to get a homogeneous solution, and then add excipients based on the delivery system. Finally, make up the volume with distilled water.[37]

Ideal characteristics of polymers for preparation of 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.
- It should have pseudo plastic behaviour.
- The polymer should be capable of decreasing the viscosity with increase in shear rate.
- Good tolerance and optical clarity are more preferred.[38,39]

Classification of in situ gel polymers

Based on their origin, polymers of in situ gels are classified into two types

1. **Natural polymers** (E. g., Alginic acid, Carrageenan, chitosan, Guar gum, gellan gum, pectin, sodium hyaluronate, xanthan gum, xyloglucan, etc.)
2. **Synthetic or semi-synthetic polymers** (E. g., Cellulose acetate phthalate, hydroxypropyl methylcellulose, methylcellulose, polyacrylic acid, poly (lactic-co-glycolic acid, poloxamers).[40,41,42]

1) Natural polymers

- **Alginic acid or sodium alginate:** A biodegradable, hydrophilic, non-toxic, linear block copolymer polysaccharide consists of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. It is used as a vehicle for ophthalmic formulations. Alginate transforms into a stable gel upon exposure to divalent cations (Ca+2, Mg+2) by cross-linking the carboxylate groups, which is not easily eroded by tear fluid.[43,44]

- **Carrageenan:** It is used as a home remedy to cure a cold and cough as gelatine. Depending on the sulfate group number and position classified into three types:

a. Iota carrageenan: It forms an elastic gel in the presence of calcium or potassium ions and completely soluble in hot water.

b. Kappa carrageenan: It forms a 'gel' in the presence of potassium ions and shows similar properties of locust bean gum, like soluble in hot water.

c. Lambda carrageenan: It does not induce gel formation, but it forms highly viscous solutions and is completely soluble in cold water.[45,46,47]

- **Chitosan:** It is a biodegradable, biocompatible, thermosensitive, pH dependent, cationic, amino polysaccharide obtained by alkaline deacetylation of chitin. Gelling of chitosan occurs by pH and temperature changes. It has excellent mucoadhesive properties due to the electrostatic interaction between positively charged chitosan and negatively charged mucosal surfaces.[48,49]

- **Guar gum or guaran:** It is soluble in water but insoluble in hydrocarbons, fats, ester, alcohols, and ketones. It shows better dispersibility and forms high viscous colloidal solutions with hot and cold water with small amounts. Temperature changes cause a reversible shift in gel formation.[50]

- **Gellan gum:** It is commercially known as Gelrite or Kelcogel, and it is a linear, water-soluble, temperature-dependent, extracellular, hetero, anionic polysaccharide; like alginate, this gellan gum form gel in the presence of metal cations (mono or divalent). Monovalent cations such as Na+or K+ and divalent cations such as Ca+2 or Mg+2 induce cross-linking gelation. The gelation includes the formation of double helical junction zones followed by aggregation of the double-helical segment to form 3-D networks by complexation with

cations and hydrogen bonding with water. In the preparation of in situ gels, it is one of the most commonly used polymers.[51]

- **Pectin:** A family of cationic, linear polysaccharides comprises α-(1, 4)-D galacturonic acid residues. In the presence of H+ions, the gelation of pectin will occur, a source of mono, divalent, and trivalent ions. The degree of methylation (DM), defined as the percentage of carbonyl groups esterified with methanol. Based on the degree of esterification, pectins classified into two categories

a. Low methoxy pectins; less than 50% of the carboxyl groups methylate the pectins.
b. High methoxy pectins; more than 50% of the carboxyl groups methylate the pectins.[52,53,54]

- **Sodium hyaluronate:** It is a water-soluble form of the sodium salt of hyaluronic acid. It is a natural, endogenous polysaccharide that supports producing collagen and maintains elasticity in the body. It also increases formulation stability and reduces the probability of oxidation.[55,56]

- **Xyloglucan or tamarind gum:** Xyloglucan is an abundant, hemicellulosic polysaccharide due to the non-toxic, biocompatible, and biodegradable nature, potentially using in several delivery systems. It is partially degraded by β galactosidase and undergoes gelation by the thermoresponsive process. Xyloglucan has the gelling ability in the presence of sugars (40-65%) or alcohols over a wide pH range. Still, in the combination (20% alcohols), the sugars are substantially reduced to form a gel.[57,58]

- **Xanthan gum:** Xanthan gum shows good stability at both acidic and alkali conditions and soluble in cold and hot water. It exhibits anionic nature due to the presence of both glucuronic and pyruvic acid groups.[59]

2) **Synthetic or semi-synthetic polymers**

- **Cellulose acetate phthalate (CAP):** CAP also knows as pseudo latex. It is artificial latex prepared in an aqueous medium by dispersion of a pre-existing polymer. It is pH sensitive, cross-linked polyacrylic polymers with potentially useful properties for sustained drug delivery to the eye because latex is a free-running solution at a pH of 4.4, which undergoes coagulation tear fluid, raises the pH to pH 7.4. CAP is used to monitor the ocular residence time of an ophthalmic preparation in γ-scintigraphy, and the production doesn't require the use of organic solvents.[60]

- **Hydroxypropyl methylcellulose (HPMC):** This is a biocompatible, thermoreversible, mucoadhesive polymer. It is a type of cellulose ether due to high swellability, thermal gelation properties, and used as hydrophilic matrices and used for oral drug delivery systems. HPMC used in combination with carbopol, enhancing the solution's viscosity while reducing the solution's acidity. HPMC goes for gelation at higher temperatures due to the interaction between hydrophobic components of the polymer.[61,62,63]

- **Methylcellulose (MC):** It is also a cellulose derivative, used as in situ gelling polymer. Several cellulose derivatives stay on liquid at low temperatures and become gel upon heating. Hydrophobic interaction among molecules with methoxy groups causes gelation of HPMC and MC solutions.[64,65]

- **Polyacrylic acid (PAA):** PAA is commercially known to be carbopol. It is widely used in ophthalmology for enhancing pre-corneal retention. It can exhibit excellent mucoadhesive properties to compare with other cellulose derivatives. Comparing different grads such as carbopol 910, 934, 940, 941, etc. concluded that 940 showed superior one.[66]

- **Poly (lactic-co-glycolic acid) or PLGA:** It is a biocompatible and biodegradable polymer. It is a synthetic copolymer of polylactic acid (PLA) and polyglycolic acid (PGA). These systems are applied to controlled drug delivery and are available as implants, microparticles, and in situ implants in the market. PLGA is one of the most capable polymers used to fabricate drug delivery and tissue engineering applications because of its long clinical experience.[67,68]

- **Poloxamers:** Poloxamers are commercially known as pluronic and used in thermosensitive in situ gels. It has excellent thermal setting properties and increases drug residence time. It is a water-soluble tri-block copolymer and consists of two polyethylene oxide (PEO) and polypropylene oxide (PPO). Pluronic F127 is the most commonly used poloxamer polymer in pharmaceuticals due to its colorless and transparent gels forming character.[69]

MECHANISM

There are two ways that the in situ gel system forms

1) Physical mechanism.
2) Chemical mechanism.

1. Physical mechanism

a) Diffusion: 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).[70]

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.[71]

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. 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.[72]

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.

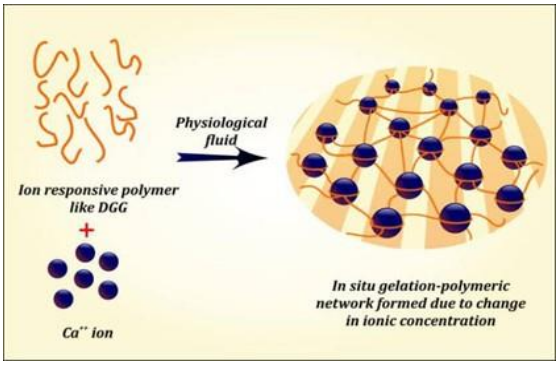

Figure 10: Ion gelation method.

d) Temperature triggered gelation: 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.[73,74]

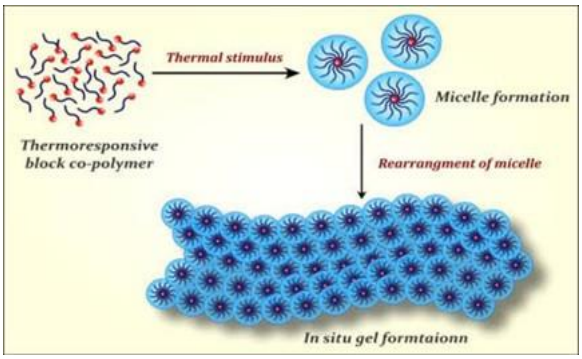

Figure 11: Temperature triggered gelation.

e) pH triggered in situ gelation: 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.

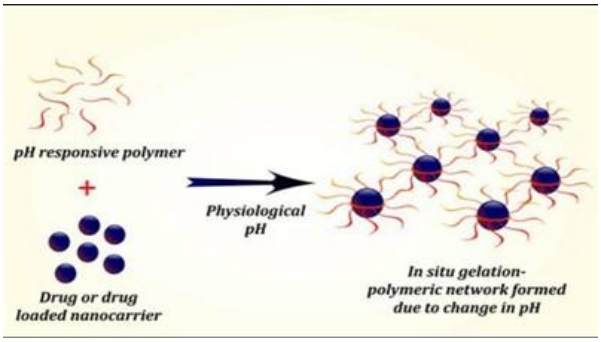

Figure 12: PH triggered in situ gelation.

EVALUATION AND CHARACTERIZATION OF IN-SITU GELLING SYSTEM

Clarity: The clarity of the formulations before and after gelling is often determined by visual examination of the formulations under light alternatively against white and black backgrounds.[75] Additionally, the contents are often set in motion with a swirling action. Also, it is observed for the formation of turbidity or any unwanted particles dispersed within the solution.[76]

pH: pH affects both the solubility and stability of the drug in the formulation. The formulation should remain stable at its pH and at the same time be non-irritating to the patient at the time of administration. The pH is measured by a digital pH meter.[77] It should be pre calibrated using standard buffers of pH 4 and pH 7 according to established procedures.[78]

Texture analysis: Texture analysis provides information about the mechanical properties of a sample: hardness, compressibility, and adhesion. These properties can directly correlate with sensory parameters in vivo, helping to develop products with desirable attributes that contribute to patient acceptability and compliance.[79]

Gelling capacity: Gelling capacity is determined for in-situ gels for ophthalmic formulations. The in-situ gel is mixed with simulated tear fluid to examine the gelling ability of ophthalmic products. This is determined by visual observation of a drop of formulation during a vial

containing 2.0 ml of freshly prepared simulated tear fluid. Gelation was visually assessed by recording the time and time it took for the formed gel to dissolve.[80,81]

Gel-Strength: This parameter can be evaluated using a rheometer. Depending on the gelation mechanism of the gelling agent used, a specific amount of gel is prepared from the form of the sol in the beaker. This gel, in the beaker, rises at a constant rate, so slowly push the probe into the gel. Changes in the load on the probe can be measured as a function of the probe immersion depth below the gel surface.[82]

Rheological studies: Rheology studies should be performed on in-situ gels, as we know from our previous knowledge that gels exhibit thixotropic behavior.[83] Viscosity and rheological properties of polymer formulations in solution or gel can be measured with Brookfield rheometers or other types of viscometers such as research rotators and Oscillatory rheometers.

Gelation temperature: The gelation temperature or sol-gel transition temperature is the temperature at which the liquid-to-gel phase transition occurs. Gelation temperature is determined for an in-situ gel formation system incorporating a thermoreversible polymer and was described by Miller & Donovan technology.[84] The formation of the gel is indicated by the lack of movement of the meniscus when the tube is tilted. This is known as the gelation temperature when the meniscus would no longer move upon tilting to 90°.[85]

Drug-polymer interaction study and thermal analysis: Interaction studies should be performed with Fourier Transform Infrared (FTIR) spectroscopy. During the gelation process, the nature of the interacting forces can be evaluated using techniques that employ the KBr pellet method. Thermogravimetric analysis (TGA) can be performed on in-situ polymer systems to quantify the proportion of water in hydrogels. Differential scanning calorimetry (DSC) was performed to observe if there was a change in the thermogram compared to the pure active ingredient used for gelation.[86]

In vitro drug release studies: For in-situ gel formulations intended to be administered by the oral, ocular, or rectal route, evaluation studies must be performed to determine drug release from the formulation in vitro. The study is performed using a plastic dialysis cell or Franz diffusion cell.[87]

Accelerated stability studies: The sterile formulations are subjected to stability testing to assess shelf life. The sterile formulation is replaced in amber-coloured glass vials, closed with grey butyl rubber closures, and sealed with aluminum foils. The vials containing formulation are kept in a stability chamber, maintained at 40 ± 2°C, and 75 ± 5 % RH for one month as per the International Conference of Harmonization (ICH) State Guidelines. Samples could be withdrawn weekly and analyzed for drug content, pH, visual appearance, gelling capacity, and in vitro drug release.[88]

APPLICATIONS OF IN SITU GELLING SYSTEM

According to the route of administration, these in-situ polymeric systems may be classified as illustrated in the following sections.

✓ **Ocular drug delivery system:** The unique properties of the ocular cavity and its effective clearance mechanism make ocular administration of the drug a difficult target with low therapeutic response. New generation ophthalmic formulations are tasked with improving the availability of drugs administered by the ocular route and thus improving their therapeutic efficacy. This can be achieved by using in-situ gelling formulations that increase pre-corneal retention time and achieve optimal drug concentrations at the target site.[89]

✓ **Nasal drug delivery system:** The nasal cavity has emerged as an attractive route for multi-site targeting for the administration of a wide variety of drugs, from small compounds to biopolymers such as peptides, proteins, and vaccines. The nasal route is a natural choice for topical administration of drugs aimed at treating local disorders affecting the nose and sinuses, such as allergic or infectious rhinitis, sinusitis, nasal sinusitis, and nasal sinus lesions.[90]

✓ **Buccal drug delivery system:** Over the last decade, administration of the intraoral in-situ gelation system has been used primarily for the topical treatment of oral mucositis, controlling pain, regulating the inflammatory response, enhancing the wound healing process, and treating bacterial infections. It has emerged as a valuable strategy to prevent fungal infections. Oral mucositis represents the most common and clinically significant complication of systemic chemotherapy and/or radiation therapy in patients with head and neck cancer. Such pathological conditions are generally characterized by thinning of the oral epithelium leading to mucosal inflammation and ulceration, mainly associated with severe pain and bleeding.[91]

✓ **Gastrointestinal drug delivery system**: The pH-sensitive hydrogels have the potential to be used for site-specific delivery of drugs to specific areas of the gastrointestinal tract.[92] Some studies have taken multiple approaches, leading to the development of formulations based on a mixture of ionic, temperature, and/or pH-sensitive polymers. Pectin, xyloglucan, and gellan gum are natural polymers used to form oral drug delivery systems in-situ. The possibility of orally administered in-situ gelling pectin preparations for sustained drug delivery has been reported.[93]

✓ **Vaginal drug delivery system:** In addition to being an important organ of the reproductive pathway, the vagina is also a suitable pathway for the administration of drugs with local and systemic effects. Antibiotics, hormones, spermicides, and anti-inflammatory drugs have traditionally been administered topically via the vaginal pathway. Besides, the vagina exhibits several features such as abundant blood supply, large surface area, and the potential to bypass the first-pass metabolism, creating a vaginal pathway suitable for systemic administration of drugs such as calcitonin.[94]

✓ **Rectal drug delivery system:** The rectal route can be used to deliver many types of drugs prescribed as liquids, semi-solids (ointments, creams, and foams), and solid dosage forms (suppositories). Traditional suppositories often cause discomfort when inserted. Also, the suppository cannot be adequately held in a particular location in the rectum and can sometimes move upwards into the colon, allowing the drug to undergo the first-pass effect. Choi has developed a new in-situ gelling liquid suppository with a gelling temperature of 30-36°C. Poloxamer 407 and/or poloxamer 188 were used to confer temperature-sensitive gelling properties. In-situ gels have the potential to be applied to the rectal pathways. Miyazaki et al. investigated the use of xyloglucan-based thermoreversible gels for rectal drug delivery of indomethacin.[95,96]

✓ **Intravesical drug delivery system:** In-situ gelling formulations have attracted some interest as an ideal topical and sustained delivery system for chemotherapeutic agents. After intratumoral or peritumor injection, such a system, in the sol state before administration, turns into a hydrogel in response to a particular stimulus and releases the drug locally in a controlled manner. Increased drug levels at the target site (tumor) maximize anticancer activity and at the same time minimize systemic toxicity. Also, the three-dimensional structure of hydrogel ensures sustained drug release that prolongs tumor exposure to chemotherapeutic agents.[97]

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