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Review Article

IN SITU GEL POLYMERS: A REVIEW

MOUNIKA KONATHAM[1], MOUNIKA TEJASWI GORLE[1], NAVEEN PATHAKALA[1,2], VASUDHA BAKSHI[1], YASO DEEPIKA MAMIDISETTI[3], PRIYANKA CHINTHAKINDI[4], RAJENDRA KUMAR JADI[1,2*]

[1]School of Pharmacy, Anurag University (Formerly Anurag Group of Institutions), Venkatapur, Medchal, Hyderabad 500088, Telangana State, India, [2]Department of Pharmacy, University College of Technology, Osmania University, Hyderabad 500007, Telangana, India, [3]Career Point University, Kota, Aalniya, Rajasthan 324005, India, [4]Department of Biotechnology,Chaitanya College of Pharmacy Education and Research, Kakatiya University, Kishanpura, Hanamkonda, Warangal 506001, Telangana, India
Email: rajendra.rajaji@gmail.com

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ABSTRACT

In situ gels have become one of the most prominent and accessible systems. These systems have several advantages like simple manufacturing, easy to use, improved adherence, and patient comfort by minimizing drug administration frequency by its unique characteristic features of sol to gel transition. In the 'sol-gel' method, the precursor goes through hydrolysis and polymerization or condensation to produce a colloidal suspension or solution. As they can administer in solution form, these in situ gelling systems undergo gelation at the achievement site. Some researchers recently developed in situ gelling systems of liposomes, microspheres, nanoemulsions, nanospheres, etc. This review mainly focused on the introduction, advantages, disadvantages, types of polymers, and suitable characteristics for preparing in situ gels.

Keywords: In situ gels, Polymer, Sol-gel, Gelation, Transition

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INTRODUCTION

In situ gels are the solutions or suspensions that undergo gelation after reaching the particular site due to contact with body fluids or physicochemical changes (i.e., pH, temperature, ionic concentration, UV radiation, presence of specific molecules or ions, external triggers, etc.) [1, 2]. In situ, gels have been potentially used for buccal, intraperitoneal, nasal, ocular, oral, parenteral, rectal, subcutaneous, transdermal, and vaginal routes [3, 4]. The gel formulations enhance the local and systemic exposure of potential lead compounds in the discovery phase, ideal for establishing animal models for various conditions quickly and cost-effectively [5]. Despite the massive diversity of gels, a particular class of gels, namely smart polymer gels, are in pharmaceutical research focus during the last decades [6, 7]. These intelligent polymers change their physicochemical properties in response to an altered environment [8, 9]. In recent advancements, in situ gels have made it possible to exploit physiological uniqueness [10, 11]. Comprehensive research has been carried in designing in situ gels, emerged as one of the best novel drug delivery systems (NDDS) [12, 13]. In this review, we try to explain about introduction, advantages, disadvantages, types of polymers, and suitable characteristics for the preparation of in situ gels. It also focused on marketed preparation as well as recent developments and advancements of in situ gels.

Advantages

- It offers ease of administration [14]
- It provides more bio-availability [15]
- It decreases the wastage of drug [16]
- It reduces the frequency of administration [14, 17]
- It allows patient compliance and comfort [14, 18]
- It minimizes local and systemic toxicity [19]
- It administered to unconscious and old patients [20]
- It helps in the extended or prolonged release of drugs [21]
- It doesn't permit drug accumulation (due to low dose) [22]
- It exhibits bio-adhesiveness to facilitate drug targeting [23]
- To enable drug targeting mainly through mucus membranes [24]
- By using natural polymers, provides biocompatibility and biodegradation [25]
- By using synthetic polymers, yield tolerable degradability and functionality [26]
- To reduce the systemic absorption of drugs drained through the nasolacrimal duct [27]

Disadvantages

- It requires an elevated level of fluids [28]
- Only small doses can be administered [29]
- The solution form of the drug is more susceptible to degradation [30]
- Due to chemical degradation, there is a chance of instability [31]
- After drug administration, eating and drinking limited for a few hours [32]
- It may result in premature dissolution due to low mechanical strength [33]
- For hydrophobic drugs, the quantity and homogeneity of drug loading limited [34]

Suitable characteristics of polymers

An essential ingredient in the manufacture of any gel is a polymer. Some of the relevant polymer characteristics for in situ gels given below: [14, 17, 35-41]

- It should be compatible
- It should influence tear behavior
- It should not provide any toxic effects
- It should have pseudo-plastic behavior
- It should have good tolerance and optical clarity
- It should be capable of adhering to the mucous membrane
- It should be capable of declining the viscosity with a boost in shear rate [41].

Classification of in situ gel polymers

Based on their origin, polymers are classified or the mechanism of gelation. According to a source in situ, gelling systems classified into two types: [42-45].

i. **Natural polymers** (E. g., Alginic acid, Carrageenan, chitosan, Guar gum, gellan gum, pectin, sodium hyaluronate, xanthan gum, xyloglucan, etc.)

ii. **Synthetic or semi-synthetic polymers** (E. g., Cellulose acetate phthalate, hydroxypropyl methylcellulose, methylcellulose, polyacrylic acid, poly (lactic-co-glycolic acid, poloxamers).

i. 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 [46-47].

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: [48-50]

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.

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. At low critical solution temperatures due to extreme hydrophobic interactions, gels formed with electrostatic forces. At upper critical solution temperature, exhibiting polymers are used for the gelation process of chitosan. Due to availability, non-toxic, inexpensive, etc., this is the second most abundant polysaccharide using after cellulose [51-55].

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 [47, 56].

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 [57].

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. It is only applicable to water-soluble formulations and not for the organic solvents. Monovalent cations (alkali metal) salts of pectin and pectic acids are soluble in water. But di and trivalent cationic salts are weakly soluble or insoluble in water. When the addition of water to dry powdered pectin, clumps (i.e., semi-dry packets) formed due to its tendency to hydrate and solubilization of cluster's done by mixing with a water-soluble carrier. 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: [58-62].

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.

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 [63-65].

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. When used in oral delivery shows gelation time up to minutes and allows gelation in the stomach in chilled condition. Like, poloxamer it exhibits gelation on heating/refrigerator temperature or cooling from higher heat. 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 [66-68].

Thiolated chitosan or thiomers

Nowadays, thiol groups exhibit much higher adhesive (mucoadhesive) properties than other polymers. Thiomers interact with cysteine-rich sub-domains or mucus glycoproteins via cross-linking intra-and inter-disulfide bonds by the simple oxidation process that leads to gel formation reaching the physiological environment. These are the most promising multi-functional, cationic, hydrophilic macromolecules, and they also act as permeation enhancers than chitosans. It has positive charges which interact with the cell membranes causing a structural reorganization of tight junction-associated proteins. Apart from this, it also exhibits a robust, cohesive nature [69-72].

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 [73, 74].

ii. Synthetic or semi-synthetic polymers

Cellulose acetate phthalate (CAP)

CAP also known 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 [75].

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. It was playing an active role in aqueous solution formation for topical treatment of the eye. It proved to be essential to formulate vaginal mucoadhesive film with CR of S-nitroso glutathione and effects on the gelling behavior. [14, 17, 76-78].

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. For example, MC and HPMC's aqueous solution undergoes a phase transition into gels between 40-50 °C and 75-90 °C, respectively. However, MC and HPMC's phase transition temperature is higher than the physiological temperature but lowered by making chemical and physical changes in the polymers. Hydrophobic interaction among molecules with methoxy groups causes gelation of HPMC and MC solutions. Polymer-polymer contact occurs between macromolecules due to hydration at a lesser temperature. The hydration is lost gradually on increasing the heat consequential in lower viscosity. At the transition where enough dehydration of the polymers takes place, they start associating, and the thickness starts rising, showing a network structure formation. At low temperature (30 °C) solution is in liquid form, and when the temperature increased (40-50 °C) and gelation occurred [76, 79-81].

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 [77, 82-84].

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 [85-87].

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. It consists of PEO (70%) and PPO (30%). A copolymer pluronic F127-g-poly (acrylic acid) was used as in situ gelling vehicles to prolong the residence time and better bioavailability of the ocular drugs [88-90].

Poloxamines

Poloxamines are commonly known as tetronics. These are biocompatible, tetra functional block copolymers of ethylene and propylene oxide. Four arms of PEO-PPO form X-shaped poloxamines, linked by an ethylenediamine group, and seem crucial for the osteoinductive capability of tetronics. It exploited until now for rendering temperature and pH-responsive micelles and gels dually. There is no other polymer reported to be osteoinductive itself. Hydrophilic one is more cytocompatible than hydrophobic and shows better compatibility as their molecular weight increases [91-94].

Poly (N-isopropyl acrylamide) or PNIPAAm

It is a thermosensitive polymer with a reversible phase transition at 32-35 °C; it is closer to the human body temperature reach therapeutic targets [95-98].

CONCLUSION

The use of biocompatible, biodegradable, and water-soluble polymers for the in situ gel formulation can make excellent and excellent drug delivery systems. In recent years, researchers have drawn interest, providing a lot of scope to advanced drug delivery techniques. A novel carrier can incorporate these systems to obtain sustained drug delivery in a much improved and extreme manner. Finally, in situ, gels are easy to apply and offer patient comfort and compliance.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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