IN SITU GEL DRUG DELIVERY SYSTEM – A REVIEW

ABSTRACT

In situ **gel forming polymeric formulations are drug delivery systems that are in sol form before being administered to the body, but gel *in situ* from which the medication is released in a sustained and controlled manner. Temperature modulation, pH alteration, ions present in the site and ultraviolet irradiation are factors that influence gel formation. Gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly(DL-lactic acid), poly(DL-lactide co glycolide), and poly caprolactone are some of the polymers used to make *in situ* gels. Solvents such as water, dimethyl sulphoxide, N-methylpyrrolidone, triacetin, and 2-pyrrolidone are utilized for these formulations, depending on the solubility of the polymer. Major routes of administration of In situ gels are oral, ocular, rectal, vaginal, injectable, and intraperitonial . In comparison to conventional drug delivery systems, *in situ* gel forming polymeric formulations provide various advantages, including sustained and prolonged action. From a manufacturing standpoint, such devices are less complex to produce, resulting in cheaper investment and manufacturing costs.**

Key words: *in-situ gel, gel forming polymers, sustained release,biocompatibility*

INTRODUCTION

Controlled and sustained medication administration has recently become the industry standard, and extensive research has been conducted in order to improve drug product effectiveness, reliability, and safety. *In situ* gel forming systems have been reported in the literature for a variety of biomedical applications in recent years, including medication administration, cell encapsulation, and tissue restoration. In situ gel forming polymeric delivery systems provide several advantages, including ease of use and reduced administration frequency, as well as better patient compliance and comfort.(1) Gellan gum, xyloglucan, chitosan, poly(DL-lactic acid), poly(DL-lactide-co-glycolide), and poly-caprolactone are among the biodegradable polymers used to make in situ gels.(2) Solvent exchange, UV irradiation, ionic cross-linkage, pH change, and temperature modulation are some of the mechanisms that might contribute to *in situ* gel formation.(2) Oral, ocular, rectal, vaginal, injectable, and intraperitoneal routes are used to give in situ gels.(1)

The potential advantages of *in situ* forming polymeric delivery systems;

- **Ease of administration.**

Comentado [SAGR1]:
This information is the same of that of following paragraphs.

- **Improved local bioavailability.**
- **Reduced dose**
- **Reduced dosing frequency.**
- **Improved patient compliance and comfort.**
- **Low investment and manufacturing cost. (1),(2).**

IN SITU GEL FORMING POLYMERS.

- **Pectin**
- **Xyloglucan**
- **Gellan gum**
- **Alginic acid.**
- **Xanthum gum.**
- **Chitosan.**
- **Carbopol.**
- **poly(DL- lactic acid)**
- **poly (DL- lactide co glycolide)**
- **poly caprolactone.(4),(5)**

Approaches of *in situ* gel drug delivery

There are certain broadly defined mechanisms used for triggering the *in situ* gel formation of biomaterials:

- **Physiological stimuli**
- **Physical mechanism**
- **Chemical reaction**

***IN SITU* FORMATION BASED ON PHYSIOLOGICAL STIMULI**

Thermally triggered systems

The most commonly investigated class of environment sensitive polymer systems in drug delivery research is temperature sensitive hydrogels, whose sol-gel transitions are induced by temperature changes. The ideal critical temperature range for such a system is ambient and physiologic temperature, as this allows for therapeutic modulation and

eliminates the need for an external source of heat to initiate gelation. (6) Thermally triggered systems are classified in to

- **Positively thermosensitive**
- **Negatively thermosensitive**
- **Thermally reversible gel.**

Positively thermosensitive

A positively temperature sensitive hydrogel is having upper critical solution temperature (UCST),such hydrogel contract upon cooling below this UCST

EX;poly(acrylicacid)(PAA),poly(acrylamide)(PAAm),poly(acrylamidecobutyl methacrylamide).(7),(8)

Negatively thermosensitive

It has lower critical solution temperature (LCST), contract upon heating above LCST. EX; poly (N-isopropylacrylamide)(PNPAAm, is a water soluble polymer at its low LCST,but hydrophobic above LCST, which result in precipitation from the solution at the LCST.(7),(8)

Comentado [SAGR2]: For instance,

Thermally reversible gels

Pluronics and tetronics are the most often utilized thermally reversible gels. Pluronics are poly (ethylene oxide)poly (propylene oxide)-poly (ethyelene oxide)(PEO-PPOPEO) triblock co-polymer that are fluid at low temperature ,but forms thermo responsible gel when heated as a consequence of a disorder- order transition in micelle packing which makes these polymers suitable for *in situ* gelation.(9)

p^H triggered systems

Comentado [SAGR3]: pH is the correct form

In reaction to variations in external p^H, all p^H sensitive polymers include pendant acidic or basic groups that receive or release protons. If the polymer contains weakly acidic (anionic) groups, swelling increases when the external pH rises, but decreases if the polymer contains weakly basic (cationic) groups. PAA, Carbopol –carbomers, or their derivatives are used in the majority of anionic pH sensitive polymers. Similarly, low viscosity polyvinylacetal diethylaminoacetate (AEA) solutions at pH 4 create hydrogel at

neutral PH. PMMA, PEG, CAP latex, pseudolatex, and other similar materials are examples. (10)

Comentado [SAGR4]: pH is the correct form

***IN SITU* GEL BASED ON PHYSICAL MECHANISM**

Swelling

Material absorbs water from the surrounding environment and expands to cover the desired space, leads gel formation. Myverol 18-99 (glycerol monooleate), a polar lipid that expands in water to produce hydropic lipid crystalline phase structures, is one typical example. It has some bioadhesive characteristics and undergo enzymatic degradation *in vivo*. (1)

Solvent exchange –Diffusion

The diffusion of solvent from the polymer solution into the surrounding tissue leads in the precipitation or solidification of polymer matrices. The solvent N-methyl pyrolidine (NMP) has been found to be effective in such systems. (11)

IN SITU GEL FORMATION BASED ON CHEMICAL REACTIONS

Following chemicals reaction cause gelation.

- **Ionic cross linking**
- **Enzymatic cross – linking**
- **Photo-polymerization**

Ionic cross linking

In the presence of various ions, ion sensitive polymers may go through phase transitions. Gellan gum, also known as Gelrite, is an anionic polysaccharide that gels in situ in the presence of monovalent and divalent cations such as Ca2+, Mg2+, K+, and Na+. i-carrageenan forms elastic gels in the presence of ca2+, whereas k-carrageenan forms dense, brittle gels in response to a tiny quantity of k+. Divalent cations, particularly Ca2+, can produce gellation of low methoxypectins. In the presence of divalent or polyvalent cations, such as Ca2+, alginic acid gels due to interaction with the galactoronic acid block in the alginate chain. (12)

Comentado [SAGR5]: Ca^{2+}

Comentado [SAGR6]: K^{+}

Enzymatic cross linking

Natural enzyme-catalyzed in situ gel formation has not received much attention, but it appears to have some advantages over chemicals and photochemical techniques. An enzymatic process, for example, can function effectively under physiological settings without the use of potentially dangerous substances like monomers and initiators. The use of hydrogel to administer intelligent stimuli-response delivery devices that can release insulin has been researched. Cationic pH-sensitive polymers with immobilised insulin and a high glucose level release the encapsulated insulin in a pulsatile manner. The ability to control the rate of gel formation by adjusting the amount of enzymes also allows the mixes to be injected prior to gel formation. (13)

Photo polymerization

For the *in situ* gel production of biomaterials, photopolymerization is extensively utilized. A solution of monomers or reactive macromeres, as well as an initiator, can be injected into a tissue location, and the gel can then be formed using electromagnetic radiation. Because they photopolymerize quickly in the presence of a suitable photo initiator, acylates or similar polymerizable functional groups are commonly utilised as polymerizable groups on individual monomers and macromers (2,2 dimethyl -2-phenylacetophenone,). (!4).

IN SITU FORMING POLYMERIC SYSTEMS FOR ORAL ADMINISTRATION

Natural polymers such as pectin, xyloglucan, and gellan gum are employed to build oral medication delivery systems *in situ*. Pectins are a type of polysaccharide with a backbone primarily made up of -(1-4)-D-galacturonic acid residues. Although pectin gels in the presence of H+ ions, a source of divalent ions, calcium ions are often required to generate gels that are appropriate as drug delivery vehicles. It has been observed that an orally administered in situ gelling pectin formulation can supply paracetamol for a long time. The fundamental benefit of employing pectin in these formulations is that it is water soluble, which eliminates the need for organic solvents. When pectin is taken orally, divalent cations found in the stomach help it transition to a gel state. Calcium ions in the complexed state may be incorporated in the formulation for the induction of pectin gelation.(15),(16),(17).

***IN SITU* FORMING POLYMERIC SYSTEMS FOR OCULAR DELIVERY**

Because high tear fluids flip over and dynamics produce fast medication removal from the eyes, traditional administration techniques generally result in poor bioavailability and therapeutic response. As a result, ophthalmic *in situ* gels were created to overcome bioavailability issues. The temperature and ionic condition (Ca++) in the tear fluid cause an aqueous solution of gellan to transition into the gel form when put into the eye. The application of gellan gum for ocular drug administration has sparked a lot of attention in the pharmaceutical community. Because the viscous gels have longer precorneal contact periods than typical eye drops, drug release from these in situ gels is delayed. Natural polymers such as gellan gum, alginic acid, and xyloglucan are the most often employed polymers for in situ gels based ocular administration. Antimicrobials, anti-inflammatory medicines, and autonomic medications used to alleviate intraocular tension in glaucoma have all been delivered via local ophthalmic drug delivery. (18),(19)

Using xyloglucan (1.5 percent w/w) as the natural polymer, Miyazaki et al. attempted to manufacture in situ gels for ocular administration. When administered into the lower cul-de-sac of the rabbit eye, these in situ forming polymeric systems showed a substantial mitotic response for a period of 4 hours. pH-induced in situ precipitating polymeric systems include a variety of water soluble polymers such as the carbopol system-hydroxypropylmethylcellulose system and poly (methacrylic acid)-poly (ethylene glycol). HPMC is used in conjunction with carbopol to give the carbopol solution viscosity while also lowering the acidity. (18)

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 utilisation 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. (20)

IN SITU FORMING INJECTABLE DRUG DELIVERY SYSTEMS

Over the last decade, there has been a lot of interest in the development of injectable in situ forming drug delivery devices. Chitosan is a thermosensitive, biodegradable polycationic polymer made from the alkaline deacetylation of chitin, a natural component of shrimp and crab shells. Chitosan is a biocompatible cationic polymer with a pH of 6.2 that remains dissolved in aqueous solutions. When a chitosan aqueous solution is neutralised to a pH greater than 6.2, a hydrated gel-like precipitate forms. Chenite et al. explored this type of thermosensitive gel formulation, in which the formulation was in the SOL form at room temperature and living cells and therapeutic proteins could be integrated. When this mixture is administered into the body, it transforms into gel implants. This technology was successfully employed to deliver physiologically active growth factors and an encapsulating matrix for living chondrocytes for tissue engineering applications in vivo.(21),(22).

For tumour treatment, a new injectable thermosensitive in situ gelling hydrogel was developed. Synthetic polymers are frequently used in parenteral formulations. The trend in drug delivery technology has been toward biodegradable polymers that don't need to be removed surgically once the drug supply has run out. The most recent investigations have focused on aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide-co-glycolide), poly (decalactone), and poly-caprolactone. Other polymers used include triblock polymer systems made up of poly(D,L-lactide)-block-poly(ethylene glycol)-block-poly(DL-lactide), blends of low molecular weight poly(D,L-lactide) and poly(-caprolactone), and blends of low molecular weight poly(D,L-lactide) and poly(-caprolactone). Injectable in situ formulations are mostly made with these polymers. Lactide/glycolide polymers have been shown to be effective as excipients for the regulated release of bioactive substances. These materials have undergone rigorous animal and human testing with no negative side effects found. When made properly under GMP conditions from pure monomers, the polymers show no signs of inflammatory reaction or other negative effects after being implanted. (23)

IN SITU FORMING NASAL DRUG DELIVERY SYSTEMS

The efficacy of an in situ gel system for nasal administration of mometasone furoate in the treatment of allergic rhinitis was investigated. In situ gel forming polymers included gellan gum and xanthan gum. The impact of in situ gel on antigen-induced nasal symptoms in sensitised rats was reported in animal research utilising an allergic rhinitis paradigm. When compared to the marketed formulation nasonex, in situ gel was demonstrated to limit the increase in nasal symptoms (mometasonefuroate suspension 0.05 percent). (24)

Comentado [SAGR7]: Sensitized?

Comentado [SAGR8]: Utilizing?

Wu et al. created a novel thermosensitive hydrogel for insulin administration in the nose by combining N-[(2-hydroxy-3-methyltrimethylammonium)propyl]chitosan chloride and poly (ethylene glycol) with a little amount of —glycerophosphate. At room temperature, the formulation was in solution form, but when held at 37°, it converted into a gel form. In animal studies, hydrogel formulation reduced blood glucose concentrations by 40-50 percent of original levels after 4-5 hours after treatment, with minimal cytotoxicity. As a result, these systems are appropriate for the administration of protein and peptide drugs via the nasal route.(25)

EVALUATION AND CHARACTERIZATION OF IN SITU GELS SYSTEMS

In situ gels may be evaluated and characterized for the following parameters;

Viscosity and rheology

This is a crucial parameter to consider when evaluating in situ gels. A Brookfield rheometer or another type of viscometer can be used to test the viscosity and rheological parameters of in situ forming drug delivery systems. These formulations' viscosity should be such that no issues are anticipated during patient administration, particularly parenteral and ocular administration

Sol-Gel transition temperature and gelling time:

The sol-gel transition temperature can be defined as the temperature at which the phase transition of the sol meniscus is first detected when retained in a sample tube at a certain temperature and then heated at a specified pace for in situ gel forming systems comprising thermoreversible polymers. The absence of movement of the meniscus when the tube is tilted indicates gel formation.

Gel Strength:

A rheometer can be used to test this parameter. A specific amount of gel is prepared in a beaker from the sol form, depending on the mechanism of the gelling of the gelling agent used. This gel-containing beaker is lifted at a set rate, allowing you to slowly push a probe into the gel. The load on the probe can be quantified as a function of the probe's depth of immersion below the gel surface.

Comentado [SAGR9]: It is repeated

In vitro drug release studies:

The plastic dialysis cell is used to conduct drug release experiments for in situ gel formulations that will be delivered by oral, ocular, or rectal routes. The formulation's sol form is deposited in the donor compartment. In an incubator, the constructed cell is shook horizontally. Analytical techniques are used to examine the receptor solution for drug release. The formulation is poured into vials containing receptor media and placed on a shaker water bath at the desired temperature and oscillations rate for injectable in situ gels. Periodically, samples are taken and evaluated.

Fourier transform infra-red spectroscopy and thermal analysis:

Using the potassium bromide pellet approach, the nature of interacting forces can be determined during the gelation process. The percentage of water in a hydrogel can be determined by thermo-gravimetric measurement for in situ forming polymeric systems. Differential scanning calorimetry is used to see if there are any thermogram changes when compared to the pure constituents, indicating interactions.

Texture analysis

The firmness, consistency, and cohesiveness of hydrogels are evaluated using a texture analyzer, which primarily shows the syringeability of the sol, allowing the formulation to be injected in vivo with ease. .(1),(26) (27)

CONCLUSION

In conclusion, increasing patient compliance is the key prerequisite of a successful controlled release product, which in situ gels provide. The use of polymeric in situ gels for controlled drug release offers a number of benefits over traditional dosage forms. The in situ gel dosage forms are particularly trustworthy due to the drug's sustained and prolonged release, as well as its good stability and biocompatibility.

In situ gel formulations that use biodegradable and water soluble polymers can be more acceptable and effective drug delivery strategies. In situ gel preparations have the potential to be more effective than a traditional liquid dosing form. When compared to traditional dosage forms, they have higher patient acceptance and compliance and may offer superior biopharmaceutical characteristics, improved efficacy, prolonged drug administration, and improved safety. Because of the availability of new technology, as well as high market acceptability and patient demand, the potential for such a dosage form is encouraging. With the continuing development of new pharmaceutical products, more novel in situ gel technologies are likely to emerge in the future.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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