

IN SITU GEL FOR DRUG DELIVERY SYSTEM: REVIEW

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Abstract: *In situ* gel was determined to ensure that the prepared preparation met the standard and it safe. This review describes every aspect of this novel application and characterization of *in situ* gel preparations, which present the readers an exhaustive detail and might contribute to research and development. In the chemical evaluation *in situ* gel determined the diffusion of the active substance of a compound by measuring its concentration. In physical evaluation of isotonic calculated by osmotic pressure, drug release was determined by melting point of the substance polymer, gel strength as measured by remoter, homogeneity test determined by under the light, and stability test with environmental conditions setting. In microbiology evaluation determine if the preparations were contaminated or not, also be effective and safe. Ocular irritation studies-Draize Test us an animal mice or rabbit and determination of visual appearance, clarity, and pH is required. *In situ* gels offer the primary requirement of a successful controlled release product that is increasing patient compliance.

Keywords: In situ gel, D, Drug delivery system, Application, preparation

Introduction

Over the past 30 years, greater attention has been focused on development of controlled and sustained drug delivery systems. The goal in designing these systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of the action, decreasing the dose required or providing uniform drug delivery. Polymers have historically been the keys to the great majority in drug delivery systems.

Gel

Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a three dimensional network of inter connected molecule or aggregates which immobilizes the liquid continuous phase. Gels may also be classified based on the nature of the bonds involved in the three-dimensional solid network. Chemical gels arise when strong covalent bonds hold the network together and physical gels when hydrogen bonds and electrostatic and van der Waals interaction maintain the gel network.¹

Hydrogels

Hydrogels are polymeric networks that can absorb and retain large amounts of water and biological fluids and swell, still maintaining their three-dimensional structure. These polymeric networks contain hydrophilic domains that are hydrated in an aqueous environment, thereby creating the hydrogel structure. The term *network* indicates the presence of cross-links, which helps avoid the dissolution of the hydrophilic polymer in an aqueous medium.

Hydrogels have many advantages over other drug delivery systems such as good mechanical and optical properties and biocompatibility. The degradation products of hydrogels are usually non-toxic or have lower toxicity. Lower interfacial tension between the surface of the hydrogel and the physiological fluid helps to minimize protein adsorption and cell adhesion on the hydrogel's surface. The soft rubbery nature of hydrogels also can minimize mechanical irritation when used as *in-vivo* implants. Hydrocolloids can be defined as polymers endowed with the ability to swell in water or aqueous solvent and induce a liquid to gel transition. Gels are at the upper limit of viscous preparations, and they are formed when high molecular weight polymers or high polymer concentrations are incorporated in the formulations. In addition, the ability of hydrogels to release an entrapped drug in an aqueous medium and to regulate the release of such drug by control of swelling and by cross linking makes them particularly suitable for controlled release applications. Hydrogels can be applied for the release of both hydrophilic and hydrophobic drugs and charged solutes.

Currently, two groups of hydro gels are distinguished, namely preformed and in situ forming gels. Preformed hydro gels can be defined as simple viscous solutions, which do not undergo any modifications after administration. *In-situ* gels can be defined as formulations, applied as solutions, sols or suspensions that undergo gelation after instillation due to physicochemical changes inherent to the stomach.^[2]

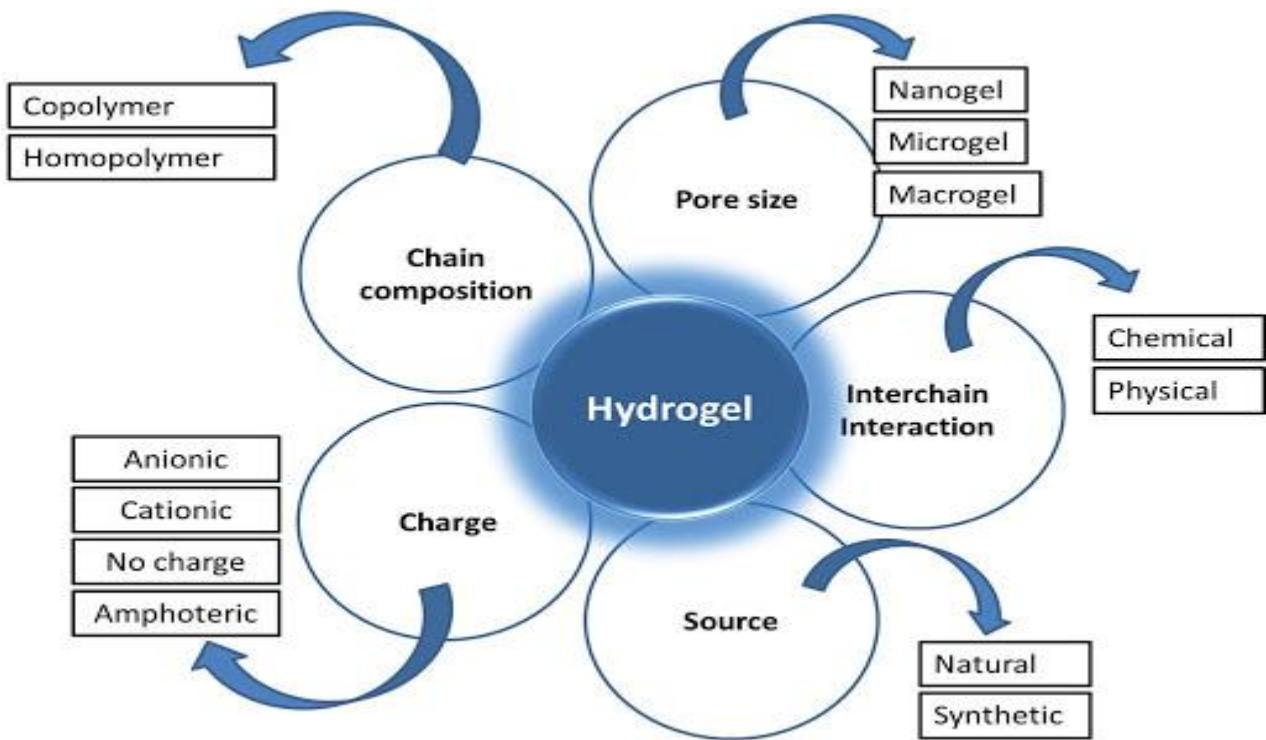


Fig. Classification of hydrogel

***In-Situ* Gel Delivery Systems**

In-situ gelation is a process of gel formation at the site of application after the composition or formulation has been applied to the site. In the field of human and animal medicine, the sites of application refer to various injection sites, topical application sites, surgical sites, and others where the agents are brought into contact with tissues or body fluids. As a drug delivery agent, the *in-situ* gel has an advantage related to the gel or polymer network being formed *in-situ* providing sustained release of the drug agent. At the same time, it permits the drug to be delivered in a liquid form. *In-situ* is a Latin phrase meaning *in the place*.

Distinguishing from preformed hydrogels, *in-situ* forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way, the polymers, which show sol-gel phase transition and thus trigger drug release in response to external stimuli, are the most investigated. *In-situ* hydrogels are providing such „sensor“ properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition. These “intelligent” or “smart” polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released [3].

Advantages of *in-situ* forming gel:

- Ease of administration
- Improved local bioavailability
- Reduced dose concentration Reduced dosing frequency
- Improved patient compliance and comfort
- Its production is less complex and thus lowers the investment and manufacturing cost.

Method for preparation of *in-situ* gel:

There are four broadly defined mechanisms used for triggering the *in-situ* gel formation of biomaterials: Physiological stimuli (e.g., temperature and pH), physical changes in biomaterials (e.g., solvent exchange and swelling), chemical reactions (e.g. enzymatic, chemical and photo-initiated polymerization).

In-situ formation based on physiological stimuli:

Thermally triggered system:

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach *in-situ* formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is facilitated and no external source of heat other than that of body is required for trigger gelation. A useful system should be tailor able to account for small differences in local temperatures, such as might be encountered in appendages at the surface of skin or in the oral cavity.

Three main strategies are exists in engineering of thermo-responsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermo-sensitive, positively thermo-sensitive, and thermally reversible gels^[4-6]. Negative temperature-sensitive hydrogels have lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. One of the most extensively investigated polymers that exhibit useful LCST transition is poly (N-isopropyl acrylamide) (PNIPAAm). PNIPAAm is a water soluble polymer at its low LCST, but hydrophobic above LCST, which results on precipitation of PNIPAAm from the solution at the LCST^[7,8] Pluronics are poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO) triblock copolymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequences of a disorder-order transition in micelle packing which makes these polymers suitable for *in-situ* gelation^[9].

In-situ formation based on physical mechanism:

Swelling

In-situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space^[17]. One such substance is myverol 18-99 (glycerol mono- oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bio-adhesive properties and can be degraded *in-vivo* by enzymatic action^[18].

Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system^[19].

In-situ formation based on chemical reactions

Chemical reactions that result *in-situ* gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

Ionic cross-linking

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones^[20]. While k-carrageenan forms rigid, brittle gels in reply of small amount of K⁺, i-carrageenan forms elastic gels mainly in the presence of Ca²⁺. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes *in-situ* gelling in the presence of mono- and divalent cations, including Ca²⁺, Mg²⁺, K⁺ and Na⁺. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca²⁺. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations.

e. g. Ca²⁺ due to the interaction with guluronic acid block in alginate chains^[21].

Enzymatic cross-linking

In-situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation^[22].

ENHANCEMENT OF MUCOSAL ABSORPTION

Unlike the most small drug molecules, some drugs and peptides do not cross the mucosal membrane efficiently. As a result, the systemic bioavailability in simple solution formulation is very low. The low mucosal absorption can be attributed to poor membrane permeability due to molecular size, lack of lipophilicity or enzymatic degradation. To overcome these problems of poor membrane permeability most frequently used approach is the use of absorption enhancers. It is possible to greatly improve the mucosal absorption of polar drugs by administrating in combination with an absorption enhancer that promotes transport of drug across the mucosal membranes (in case of oral or nasal or ocular or rectal or vaginal tissue).

EVALUATION AND CHARACTERIZATIONS OF *IN-SITU* GEL SYSTEM

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

Clarity

The clarity of formulated solutions determined by visual inspection under black and white background.

Texture analysis

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringe ability of sol so the formulation can be easily administered *in-vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surfaces like tissues^[23].

Sol-Gel transition temperature and gelling time

For *in-situ* gel forming systems incorporating thermoreversible polymers, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first detection of gelation as defined above.

Gel-Strength

This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

Viscosity and Rheology

This is an important parameter for the *in-situ* gels, to be evaluated. The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) instead of 5% mannitol, were determined with Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties are envisaged during their administration by the patient, especially during parenteral and ocular administration^[25].

CONCLUSION

In conclusion, the primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in-situ* gels offer. Exploitation of polymeric *in-situ* gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the *in-situ* gel dosage forms very reliable. Use of biodegradable and water soluble polymers for the *in-situ* gel formulations can make them more acceptable and excellent drug delivery systems.

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