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Review Article

PREFORMED GEL VS *IN SITU* GEL: A REVIEW

Insan Sunan Kurniawansyah *[1,2], Iyan Sopyan [2], Wahyu Ashri Aditya [3], Hani Nuraini [1], Fikri Dwi Alminda [1], Anggun Nurlatifah [1]
[1]Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia
[2]PUSDI Drug Delivery and Drug Disposition, Universitas Padjadjaran, Sumedang, Indonesia
*Corresponding Author Email: insan.sunan.kurniawansyah@unpad.ac.id

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ABSTRACT

In situ gel is a gelatinous solution when interacting with the eye due to changes in the physical properties of chemistry by the eye so as to not cause problems like the previous gel. Preformed gel usually consists of dried, crosslinked polyacrylamide powders. The objective of this study was to compare between preformed gel and in situ gel preparation. In this review is explained about comparing the advantages and disadvantages, mechanism of drug release, and polymers used in both these dosage forms. Currently there was a lot of progress in the field of dosage formulations. One of them was a hydrogel dosage form. Hydrogels were polymers that have the transition ability between the liquid-gel. There were two groups of preformed gels and in situ gel. Preformed gel and in situ gel which can increase the residence time and bioavailability.

Keywords: Preformed gel, *in situ* gel, polymer

INTRODUCTION

Gel is a substance containing liquid and solid components. Gel consists of three-dimensional solid tissue. One example of a gel used for treatment is hydrogel[1]. Hydrogels form polymeric chains of 3-D macromolecules so they can be easily formed in various shapes and sizes. Hydrogels have a good absorbing ability[2]. Hydrogels are polymers that have ability to transition between liquid-gel[3]. Hydrogel itself is a type of preparation that is hydrophilic because it has a network of physics and chemistry, commonly called "crosslink" serves to accommodate a very large amount of air. The rheology associated with the hydrogel preparation is based on the properties and concentrations of polymers which are the laws of Newton[4-6]. Hydrogel consists of two groups: preformed gel and *in situ* gel. Preformed gel and *in situ* gel that can improve residence time and bioavailability[7].

In situ gel

In situ gel is a gelatinous solution when interacting with the eye due to changes in the physical properties of chemistry by the eye so as to not cause problems like the previous gel[3]. Administration route for gel preparation *in situ* usually through oral, ocular, rectal, vaginal, injectable and intraperitoneal[8]. In the preparation of *in situ* gel required a trigger to form the gel when contacts with the target organ as in the eye. There are four mechanisms used to trigger *in situ* gel formation of biomaterials, physiological stimulation (temperature and pH), physical changes (exchange of solvents and swelling), chemical reactions, and photo-initiated polymerizations. There are three gel forming systems in the *in situ* gel preparation when in contact with target organs, ie thermo reversible *in situ* gels, pH sensitive *in situ* gels and ion sensitive *in situ* gels[9].

Preformed gel

Preformed particle gel (PPG) is a particled superabsorbent crosslinking polymer that can swell up to 200 times its original size in brine. The use of PPG as a fluid-diverting agent to control conformance is a novel process designed to overcome some distinct drawbacks inherent in *in situ* gelation systems[10]. Gel particles that are currently available consist of different sizes from µm (micrometer) to mm (millimeter) preformed gel[11], microgels[12-14], pH crosslinked polymers[15-16].

Advantages and Disadvantages

The advantages of *in situ* gel preparations are simple polymer delivery systems and reduce the frequency of administration, improve patient compliance and comfort, minimize the local or systemic side effects of a drug[8]. Other excess gel *in situ* such as showed increased gastric retention with slowed release, and showing less adverse effects than other dosage forms. In addition to the advantages, *in situ* gel also has disadvantages such as more susceptible to stability problems resulting in chemical degradation, requiring high levels of fluids and will lead to degradation caused by storage problems of preparations[1]. When compared with other preparations, *in situ* gel has the following advantages: these preparations will not provide blurred vision as in ointment, the decrease of nasolacrimal drainage which will cause a decrease in the occurrence of unwanted side effects, will be more convenient than insoluble insertion or soluble[17].

In preformed gel has the advantage of environmentally friendly, thermostable, insensitive to residual material. In addition, preformed gel on suspense preparations can use ordinary water in an environmentally friendly manner, preformed gel injection preparations have the advantage of uncomplicated processes that cut production costs[18]. Preformed gel have a drug-hydrogel

interaction can be modified in such a way based on the duration of the desired drug when entering the body. Drug-hydrogel interactions such as physics (ionic interactions between polymers and drugs) and chemicals (covalent bonds) have their own advantages particularly in the duration of the drug released in the body[19].

The use of preformed gel can overcome several weaknesses, such as lack of gelation time control, degradation, changes in gelant composition and dilution by water[20]. The use of preformed gel still has weakness in ophthalmic dosage form including less accurate dose, blurred vision, lacrimation[21].

Preformed gel is formed on the surface before it is injected through the reservoir so no gelation occurs. Need to be considered include pH, salinity, multivalent ions, hydrogen sulfide, temperature and shear rate[18].

In-situ gel was suggested in terms of developing the concept of production [22]. *In situ* gel can remain in eyes in longer time due to having a high viscosity and also have mucoadhesive. *In situ* gel is more comfortable for ophthalmic use because of it has liquid form when used but gradually changed into a gel.

Mechanism of drug release

The medicine used through the attention organs should have the tissue layer to be followed by non-corneal permeation. This non-corneal permeation can involve the diffusion of the drug throughout the mucosa and also the eye sclerotic coat. it's necessary to grasp that medications area unit less absorbed within the tissue layer[23]. There area unit 3 drug unleash mechanisms within the in place gel preparation for target organs[24] :

1. Diffusion

The drug are free unendingly into the watering liquid. If associate insertion is created from a solid body that may not be worn with pores and spread medicine. The drug unleash by this method happens through diffusion through the pores.

2. Osmosis

In this mechanism, there's associate water-resistant elastic membrane which is able to insert into 1st compartment and also the second compartment; within the first compartment is delimited by a semi-permeable membrane, and also the second compartment are restricted by associate water-resistant material. there's a drug unleash hole on the water-resistant wall of insertion. within the 1st compartment system containing solutes, that can't have the semi-permeable membrane otherwise on the second compartment provides a reservoir for the drug, once more in liquid or gel type. within the binary compound surroundings the attention are inserted, at which period the water can diffuse into the primary compartment and stretch the elastic membrane that has operate to expand the primary compartment and contract the second compartment so the drug is forced through the drug unleash hole.

3. Bio-erosion

In this mechanism, there's associate insertion body configuration fashioned from a matrix of bioerodible materials used as an area of medication to be spread. The teardrops can get contact with the inserts that may lead to the continual unleash of the drug by the bioerosion matrix then drug are equally spread, however if the drug is focused on the matrix it'll be obtained a additional controlled unleash.

Preformed gel incorporates a straightforward viscousness that may not modification when administration. Meanwhile, the in place gel undergoes gelation when administration supported chemistry properties. In preformed gel on repair of refined cell tissue then inserted into polymer then drug and biological signals area unit inserted at the same time then injected into the body as a result of the character of colloidal gel within the kind of "sustain release" the drug are issued bit by bit supported patient's vital sign[25].

Polymers

***In situ* gel**

The most important ingredients in the manufacture of *in situ* and prefomed gel is the polymer. The formulation of *in situ* gel using various polymers such as hydroxy ethyl cellulose, carbopol, sodium alginate, and gums such as guar hydroxypropyl, xanthum gum[26]. As for the properties that need to be present in the *in situ* gel formulation is first, the formulation must be a free flowing liquid which may facilitate the administration of a reproducible dose. Secondly, after gradual preparation of *in situ* gel must form sol-to-gel with the transition phase and thirdly, the *in situ* gel preparation may form a strong gel so sufficient to withstand shear forces in the cul-de-sac functioning to extend the residence time drug[27,28]. The polymer used for the preparation of *in situ* gel must be in accordance with the criteria, ie non-toxic and not absorbed from the gastrointestinal tract, does not cause irritation to the mucous membranes, and the cost used is not too high. The polymer used in each formulation is not the same because *in situ* gel has the type according to gel formation[29].

The preparation method is to mix the polymer with water. This solution is stirred periodically until the solution is homogeneous and cooled to 4°C. then added another polymer like HPMC to the solution. The sample was then transferred to the bottle and stored in the refrigerator overnight which was finally sterilized by autoclaving at 121°C at 15psi for 20 minutes[30]. The polymer used in the preparation of *in situ* gel differs by *in situ* gelling system.

Polymer used in thermo reversible *in situ* gelling system.

The system of this polymer consists of a central polypropylene oxide surrounded by polyethylene oxide. At room temperature (25^{o}C), this polymer is a viscous liquid and will then turn into a transparent gel when temperature increases (37^{o}C). At low temperatures, this polymer will form a small micellar subunit in solution that will lead to increased viscosity leading to swelling to form a large cross-crossed micellar tissue. Examples of polymers for this system are poloxamer[29].

Polymer used in pH sensitive *in situ* gelling system.

The mechanism is based on the mucoadhesive properties caused by electrostatic interactions or hydrophobic interactions, hydrogen bonding. This is an acidic molecule. When the polymer is dispersed into water, the carboxylic group of molecules will partially dissociate and form a coil. Because of the polymer sensitive pH, the increase of the pH of the solution results in polymer swelling. Polymer example with this system is carbopol[29].

Polymer used in ion sensitive *in situ* gelling system.

The mechanism of this system is a monomer of alginate β-D-Mannuronic acid and α-L glucuronic acid arranged as an M-M block with a block that will cause a sequence change (M-G). After block G the polymer interacts with calcium moieties will result in

homogeneous gel formation. Mechanical strength and hydrogel porosity depend on G: M ratio, cross linker type used and concentration of alginate solution. Examples of polymers used in this system are sodium alginate[29].

Preformed Gel

Preformed gel usually consists of dried, crosslinked polyacrylamide powders[10]. When it makes contact with water, it can swell from several to a few hundred times compared to its original size. Thus all PPG products belong to the family of superabsorbent polymers (SAP). Union Carbide first introduced superabsorbent polymers in the 1960s. In the 1970s, a superabsorbent starch for use as a soil conditioner to improve porosity and soil retention was developed and widely used. Research and development on SAPs started to become active since then[31].

In addition, polymers that can be used on preformed gel include:

1. Natural polymers

Hyaluronic acid

The properties of hyaluronic acids are biodegradable and biocompatible, forming gels when conforming to water is the reason for the use of this polymer[32]. In the use of tissue engineering HA itself will be easily degraded by the enzyme so that the immune system does not recognize it as antigen when injected into the tissue is often modified to be responsive to temperature because of its nature in unlike it[33].

Chitosan

Chitosan polymers are obtained from exoskeleton of aquatic animals and insects derivatized by the reaction of N-acetyl-D-glucosamine[34]. Insulin hydrogel injection using chitosan polymer base added glycerophosphate has 1 minute gelatization time so it becomes one of the reference of diabetes treatment[35]. But several studies have described chitosan-glycosphosphate hydrogel to have an undesirable immune response when administered to patients[36].

Hydrogel Cellulose Derivatives

One of the natural polymers synthesized from the cell wall of the plant has a repeated B- (1,4)-D-Glucose composition on its chain[37]. Hydrogels with cellulose polymer constituents are widely used in the provision of skin tissue and other tissue repair. The advantages of cellulose polymers include amphiphilic groups, and conjugate with other polymers so that in the administration of injection preparations will produce highly responsive medicinal properties, in addition to administering with a controlled release system it is easy to do.

Other natural polymer

Gelatin, collagen, and agarose are not recommended polymers made into hydrogels because they are easily formed when the temperature of the room and the phase changes to liquid when given high temperature. Matrigel, in contrast to the three previously mentioned polymers, is derived from the derivatization of "chondrosarcoma" or derived from the tumor but the study states that there is no carcinogenic reaction[38,39]. One study mentioned anticancer drugs incorporated into Matrogel-based hydrogels could inhibit tumor growth[40,41]. The properties of the liquid Matrigel below room temperature and turned into gel when body temperature becomes the basis of Matrigel are used as a base but there is a deficiency of Matrigel itself ie that high hydrogel affinity is usually combined with synthesis polymer.

2. Polymer synthesis

PDTR (Polyacrylamide Derived Thermo Responsive) Hydrogel

Polyacrylamide polymers that have been studied for a long time and are still frequently used, especially hydrogel polymers. Some types of polyacrylamide used include Poly (N-(-hydroxypropyl) methacrylamide lactate, poly (N-vinyl caprolactum), etc. have good potential in hydrogel injection preparation[42,43].

Poly (Oligo (ethylene Glycol) Methacrylate)

Derived Thermo-Sensitive Hydrogel

Polyphosphazene-Derived Thermo-Sensitive Hydrogel

Pluronic-Derived Thermo-Sensitive Hydrogels

PEG-Polyester-Derived Thermo-Sensitive Hydrogels

CONCLUSION

Currently, drug delivery systems are still under development. One of them is a hydrogel dosage form. The hydrogel dosage forms comprise preformed gel and *in situ* gel. *In situ* gel dosage forms are preferred because they have slight deficiencies with preformed gel because *in situ* gel have non-viscous eye drop properties, accurate and precision sustained release properties with little or no eye irritation is possible.

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