RESEARCH ARTICLE

Utilization of Poloxamer as Well as Combinations with Other Polymers as Base in Ophthalmic in Situ Gel Dosage Form

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ABSTRACT

The aim of this review was to find out which formulation were good for making in-situ gels using a combination of poloxamer and other bases. Formulation was characterized for appearance and homogeneity, pH and gelation studies, viscosity measurements, in vitro drug release, drug content, and stability studies. In vivo rabbit, eye irritation tests were conducted to evaluate the irritation of the in-situ gel delivery system; in addition, osmolality testing, sterility test, and isotonicity evaluation were also carried out. The results have shown that in-situ gel solution can increase residence time and also maintain the mechanism of drug release.

Keywords: Enzymatic cross-linking, In-situ gel, Ionic cross-linking, Photo-polymerization, Poloxamer, Residence time.

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INTRODUCTION

In the human body, the organ that plays the most vital role in the eye because it can see the whole world. Parts of the eye include the cornea, lens, sclera, optic nerve, pupils and others. The most important struggle through ocular routes contains non-productive absorption, drainage of tear fluid, making lacrimation, changing tears and impermeability of the drug to the cornea.[1]

One of the most challenging and most interesting ways to deal with pharmaceutical scientists is the administration of eye drugs, which makes the eyes very resistant to foreign substances, namely because of structural and functional aspects. The challenge of formulators in making eye preparations is to overcome eye barriers without causing permanent tissue damage. Topical administration can cause major problems, namely rapid pre-corneal loss caused by nasolacrimal drainage and high tear fluid turnover which causes only 10% of the drug concentration available at the site of action.[2]

Conventional ocular delivery systems such as solutions, suspensions, and performance have disadvantages such as increased precursor elimination, each with high variability inefficiency and blurred vision.[3] The in situ gelation approach combines the advantages of two conventional preparations namely solution and gel, such as the accuracy and ease of first administration and the retention of the old pre cornea from the latter.[4]

In the early 80's the concept of gel-forming in situ emerged, and the system was investigated using phase-transition polymers.[5] An in-situ gel is a simple transparent polymer solution which is a liquid under storage conditions but is converted into the viscoelastic gel after being inserted into the eye because of environmental changes, such as changes in temperature, changes in pH and changes induced by ions. The reason why gel in situ is preferred is that they are liquids that can easily fall in the eye and allow for repeated planting of accurate doses compared to implanting preformed gels.[6]

The gel formation process occurs because of the cross-linking between polymer chains through covalent bonds (chemical cross-linking) or non-covalent (physical cross-linking). An important factor in in-situ gel formation is the rate of gel formation because after the preparation and before a strong gel is formed, a solution or gel will form weak because of the mechanism of formation of lacrimal fluid by the eye.[7]

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In situ formation based on physical mechanism, there are:

- *Swelling*

In situ formation can also occur when the material absorbs water from the surrounding environment and extends to the desired space. Myverol (glycerol mono-oleate) is one of these substances, which is a polar lipid that swells in water with the aim of forming a lyotropic liquid crystal phase structure. It has several bioadhesive properties and can be degraded in vivo by enzymatic action.[8]

- *Diffusion*

Diffusion of solvents from polymer solutions into the surrounding tissue and results in precipitation or compaction of the polymer matrix. one of the substances that have been proven to be a useful solvent for the system is N-methyl pyrrolidone (NMP).[8]

In situ formation based on chemical reactions mechanism

Chemical reactions that produce situ gelation can involve precipitation of inorganic solids from saturated ionic solutions, photo-initiated processes, and enzymatic processes.[8]

Ionic Cross-linking

Certain ion-sensitive polysaccharides such as carrageenan, Gellan gum (Gelrite), Pectin, Sodium Alginate undergo a phase transition in the presence of various ions such as K +, Ca2 +, Mg2 +, Na +. This polysaccharide belongs to the ion-sensitive class. For example, alginic acid is gelated in the presence of divalent/polyvalent cations, e. g. Ca2 + because of interactions with guluronic acid blocks in the alginate chain.[9,10]

Enzymatic Crosslinking

In-situ formations catalyzed by natural enzymes haven't been extensively studied but appear to have several advantages over chemical and photochemical approaches. For example, enzymatic processes run efficiently under physiological conditions without the need for dangerous chemicals such as monomers and initiators. The intelligent stimulus-responsive delivery system using hydrogels that can release insulin has been studied. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to insulin-releasing blood glucose levels that are trapped pulsatile. Adjusting the amount of enzyme also provides a good mechanism for controlling the rate of gel formation, which allows the mixture to be injected before gel formation occurs.[9]

Photo-polymerization

A monomer or macromer solution and a reactive initiator can be injected into a tissue site and the gelling agent used is the application of electromagnetic radiation. Acrylate or similar polymerizable functional groups are usually used as polymerizable groups in each monomer and macromers because they rapidly undergo photopolymerization in the presence of a suitable photoinitiator. Photopolymerizable systems when contacted to the desired site via injection get photocured in situ with the support of fiber optic cables and then release the drug for a prolonged period of time.[9]

The ideal in-situ gel system must have a low viscosity so that it is easily transferred to the eye as a reproductive droplet and becomes a gel in contact with eye compilation.[7] Some of the polymers used as in situ gelling agents are Gellan gum, Alginic acid, Poloxamer 407, Xyloglucan, Pectin, Xanthum gum, Chitosan, and Carbomer.[10-12] The most commonly used polymers in in-situ gel formulations are poloxamer, carbopol, and polymeric alginate. These polymers are for systems that are temperature, pH and ionic.[10,13,14]

In the pharmaceutical industry, poloxamer is widely used as a dispersing agent, emulsifier, solvent, tablet lubricant, wetting agent, and as a surfactant, but is most often used as an emulsifier or solvent. Poloxamer is a polyoxyethylene-poloxypropylene non-ion copolymer that generally appears as white granules, waxes, free-flowing or as solid objects. Poloxamer is practical, odorless and tasteless.[15] In making an in-situ gel, a surfactant is needed. Surfactants that are often used are a poloxamer. Poloxamer itself has several types, namely Poloxamer 124, Poloxamer 188, Poloxamer 237, Poloxamer 338, and Poloxamer 407. Which is often used in the pharmaceutical industry namely Poloxomer 407 because it provides clear and colorless solutions.[16] However, Poloxamer 407 has a limitation that is its weak mechanical strength which causes rapid polymer erosion. In several studies, it was reported that Poloxamer 407 at a concentration of 18% (b / v) or higher, has the ability to convert a low viscosity solution to gel under ambient temperature.[17]

Advantages of in-situ ocular drug delivery systems are:

- Can increase the dose accurately. To overcome the side effects of pulsating doses produced by conventional systems.
- To provide continuous and controlled drug delivery.
- To improve the ocular bioavailability of the drug by increasing contact time with the cornea. This can be achieved by effective adherence to the surface of the cornea.
- Targeting in the eyeball to prevent loss of other eye tissue.
- To avoid protective barriers such as drainage, lacrimation, and absorption of the conjunctiva.
- To provide comfort, increase better compliance with patients and to improve the performance of drug therapy.
- Better housing delivery systems[18]

Drugs that may be used in In situ technology for ocular delivery:[18]

- Naphazoline HCl
- Ofloxacin
- Chloramphenicol
- Gentamycin
- Dexamethasone
- Prednisolone
- Tobramycin
- Brimonidine Tartrate
- Pilocarpine
- Pilocarpine nitrate ophthalmic solution 2% w/v 5ml
- Timolol
- Ketorolac tromethamine

- Clotrimazole
- Econazole
- Lignocaine HCl
- Proparacaine HCl
- Atropine sulfate
- Cyclopentolate
- Phenylephrine HCl
- Tropicamidel
- Triamcinolone Acetonide[18]

REPORTED OPHTHALMIC IN SITU GEL FORMULATION WITH POLOXAMER AS WELL AS COMBINATIONS WITH OTHER POLYMERS

Nagaich *et al*., conducted a study of in-situ gel with the following method: In-situ gel formulation of Poloxamer and HPMC started with dispersing them in distilled water with constant stirring. Active ingredients were dissolved in glacial acetic acid and added to HPMC solution. To make a clear solution, HPMC solution poured into Poloxamer solution with constant agitation and was allowed to stand at 4°C for 24 hours.[19] Whereas Saxena and Singh used this method to make the gel in situ too. First, dispersed gelrite deionized water by heating up to 90°C for 20 minutes to prepare the solution followed by cooling to room temperature. Then, dissolved levofloxacin hemihydrates in a mixture of propylene glycol and water (1: 0.08) as the drug solution. After that, the polymer solution that has been made is mixed with the drug solution using a magnetic stirrer and the preservative benzalkonium chloride is added to the mixture. The finished in situ gel is put into a glass bottle that is covered with a rubber cover and covered with an aluminum cap and sterilized by autoclave at 121°C for 20 minutes.[12,20]

While El-Laithya *et al*., used this method to make Carbopol in situ gel. Initially, disperse the required amount of carbopol into distilled water while stirring continuously until it dissolves completely. Then, add methylcellulose to the carbopol solution while stirring until thoroughly mixed. To give a final drug concentration of 0.5% b/v, a certain amount of Moxifloxacin is dissolved in distilled water. After that, the polymer solution is mixed with the drug solution. To prevent the deposition of the drug, propylene glycol is added while stirring until homogeneous. Then add distilled water until the total volume is obtained. The pH of the formulation is adjusted to 4.0 ± 0.1 by using NaOH 0.1 N.[21]

Pawar *et al*., make in situ gel that was prepared using Pluronic F-68 and sodium alginate concentrations which were different with a fixed pluronic concentration of F-127. Voriconazole was separately weighed and dissolved in distilled water with (1.5% b / v) HP-β CD. A solution of sodium alginate with different concentrations (0.5%, 1%, and 1.5%) was prepared by dispersing the amount needed in distilled water with continuous stirring until dissolved completely. The solution was added to the alginate solution, while constant stirring was carried out until a clear solution was obtained. Furthermore, in this mixture, Pluronic F-127 (15% b/v) and pluronic F-68 with different concentrations (14%, 15%, and 16%) were added. Preservative added, Benzalkonium chloride (0.01% b/v) to the previous solution. In the mixture, a sufficient amount of sodium chloride is added to maintain isotonicity. Finally, the volume is adjusted by adding distilled water to 100 mL. Some of the dissolved pluronic solutions were stored in the refrigerator at 4°C. This storage is for hydration. Then stirred regularly until a clear homogeneous solution was obtained. Nine batches of formulations were made using different concentrations of sodium alginate and PF-68.[22]

A certain amount of each polymer was dispersed in 45 mL phosphate saline buffer (PBS) containing 0.01% benzalkonium chloride (BKC) as a preservative and stirred until the solutions completely dissolve. FLZ (0.3% b/v) was dissolved in PBS 45 mL and added HPMC. The two solutions were mixed using a magnetic stirrer. The volume was adjusted to 100 mL and after that, transferred to a dry, clean, and sterile glass bottle. In-situ P407 gel was made by following the same method except that the polymer was added to PBS which was previously cooled to 4oC. FLZ was not added for simple formulations used for assessment of the gelling capacity prepared by the same method.[23]

Based on several journals that have been reviewed, it can be concluded that the method of making in-situ gel is dissolving each substance, such as an active substance, polymer, and preservative in a suitable solvent and then mixing each into one. After the mixture is formed, the sterilized preparation uses an autoclave at 121°C for 20 minutes.

CHARACTERIZATION OF IN-SITU GEL FORMING

Appearance and Homogeneity

Appearance and homogeneity can be examined visually by looking at the color and background of the presence of particles. This visual test with color is seen by the way the product is seen under a black and white background with content driven by swirling actions. Also, the formation of turbidity or unwanted particles in the solution is observed.[24]

pH and Gelation Studies

pH is determined using a digital pH meter at 25°C. To identify the appropriate gel in situ formulations, the gelation capacity was evaluated. Mixing the formulation with tear fluid simulated in a proportion of 25: 7 visually examined was used for gel formation.[25]

Viscosity Measurement

Viscosity evaluation was carried out using a river-field viscometer with S-04 spindles. From various journals that we have read, it is evident that the formulation in the form of soles has a viscosity value of 5–1,500 cps while the formulation in the form of a gel has a viscosity value of around 50–50,000 cps. The viscosity of the sol is measured at room temperature of 25°C and viscosity of the gel (after addition of artificial tear fluid [ATF]) at body temperature 37°C ± 0.5°C with a thermostatic water bath connected to the adapter. Gel viscosity is measured in the ratio of 1 : 3 formulation and ATF. The

spindle angular velocity was increased to 0.3, 0.5, 0.6, 1, 1.5, 2, 2.5, 3.4, 5, 6, 10, and the viscosity of the formulation was recorded.[26]

In-Vitro Drug Release

The modified USP-1 dissolution device was used for *In-vitro* release studies from in-situ gels. Whatman filter No. 41 is taken and moistened by dipping into the lacrimal liquid to ensure the contact of the release media with a simulated formulation for a minimum period of one minute. A total of 100µl of the formulation was applied to Whatman filter paper and 50 mL of lacrimal liquid was put into a beaker and the basket was rotated over the surface. A total of 3 mL of the sample was withdrawn at a certain time interval and replaced with the same amount as the new lacrimal liquid. The samples were analyzed using a UV-visible spectrophotometer at a wavelength of 286 nm.[27]

Drug Content

Take 1 ml of the formulation and put it in a 10 mL volumetric flask then dilute it with distilled water to the limit mark. After that, 1 mL of this solution is taken and diluted with distilled water up to 10 ml. Then the solution obtained is filtered through a 0.45-micron filter membrane and measures its absorbance at the wavelength of certain drugs using UV visible spectroscopy.[28]

Stability Study

There are several factors that influence the stability of pharmaceutical products, including the stability of active ingredients and the potential for interactions between active and inactive ingredients. The International Conference on Harmonization guidelines is used as a reference to calculate the shelf life of formulations. The overall degradation is 5%, tentative 2-year shelf life can be established for optimized formulations. The stability study was carried out by means of preparations packed in a collapsible aluminum tube (5 g) and subjected to stability studies at 40°C / 75% RH, for a period of 3 months. Samples were evaluated for physical appearance, rheological properties, and drug content at 45-day intervals.[29]

EVALUATION PARAMETERS

Osmolarity Testing

Osmolarity was tested using Model-5520 Wescor Vapor Pressure Osmometer. Before use, the instrument needs to be calibrated first using a standard solution of 290, 1000, and, 100 mOsm /kg. Measurements were made three times and the average value for each formulation was calculated.[30]

Sterility Test

To check for bacterial or fungal growth, a sterility test is performed. The media used to detect fungal organisms are aerobic, anaerobic, and digestive media for soy casein. For 14 days the In-situ Gel was incubated in an incubator at 37^0C ± 1°C using thioglycollate media fluid and media digestion soybean casein.[12,31,32]

Ocular irritancy test

The potential for eye irritation in eye products before marketing is tested first with the Draize irritation test. According to the Draize test, the amount of the substance dropped on the eye is usually as much as 100µl placed into the lower cul-de-sac. Observations were made with various criteria made at intervals of 1 hour, 24, 48, 72 hours, and 1 week after administration. In this test, three rabbits (males) were used, weighing 1.5 to 2 kg. Sterile formulations were induced twice a day for 7 days, and cross-over studies were conducted (a 3-day wash period with saline was carried out before the cross-over study). redness, swelling, watery eyes in rabbits are observed regularly.[33,34]

Isotonicity Evaluation

One important characteristic of ophthalmic preparations are isotonicity. Isotonic conditions must be maintained to prevent tissue damage or eye irritation. This test is carried out for all eye preparations because they show good release characteristics and the gelling capacity and viscosity needed. The method of carrying out this test is by mixing the formulation with a few drops of blood and then observing it under a microscope at 45X magnification and comparing it with a standard ophthalmic formulation marketed.[15]

CONCLUSION

From the results of the review above, it can be concluded that the in-situ gel can be given in a controlled manner for a long period of time in the form of eye insertion. Different formulations can change the pattern of drug release from this insertion. Formulations that promise to be able to provide benefits such as increasing residence time, prolonged drug release, reducing the frequency of administration and thus proven to improve patient compliance. Several journals stated that gel solution in-situ can increase residence time and maintain the mechanism of drug release.

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