ABSTRACT

Poor bioavailability is one of the most significant problems in the delivery of the ocular drug system. Ophthalmic ointments, solutions and suspensions are the most frequently used dosage forms to treat ocular disease, and their effectiveness as a drug are compromised by several limitations that lead to poor ocular bioavailability. In situ gel is one of the most promising strategies and solutions to improve the ocular bioavailability of drugs. The purpose of this review is to discuss the formulation and characterization of in situ gel. This review is written based on the data obtained by using several search engines and several scientific journals, focused on Poloxamer 407 and Hydroxy Propyl Methyl Cellulose (HPMC) bases combination.

Active ingredients to treat ocular disease such as Ciprofloxacin, Fluconazole and Ofloxacin can be formulated with the combination of Poloxamer 407 as polymer gelling agent and HPMC as viscosity enhancer to produce good quality in situ gel dosage forms. The in situ gel dosage forms can be a promising alternate solution for the ophthalmic delivery system.

Keywords: In situ gel, Ocular disease, Bioavailability, Poloxamer 407, HPMC, Ciprofloxacin, Fluconazole, Ofloxacin

INTRODUCTION

Topical application of drugs is the most common route of administration for the treatment of many eye conditions. The eyes is special because of the structural and functional aspect of this organ makes it highly impervious to foreign substances and material. Protective mechanisms of the eye such as blinking, baseline and reflex lacrimation and drainage prevent foreign ingredients including drugs from the eye’s surface. Because of it, targeting of drugs to eye tissues is one of the hardest challenge in drug delivery [1, 2].

Conventional and frequently used ophthalmic dosage forms such as solutions and suspensions have several drawbacks, for example-rapid preconosal elimination of drugs because of the nasolacrimal drainage, the need for frequent application and pulse release. Other dosage forms, which is ophthalmic ointments, provide prolonged contact with the eye surface. But it may trigger some side effects such as foreign body sensation, blurred vision and inconvenience to the patient [2, 3].

Physiological constraints imposed by the eye’s protective mechanism lead to low absorption of drugs and short duration of therapeutic effect. Drug absorption is also influenced by the chemical nature of the drugs, since the permeability of cornea depends on molecular size and hydrophobicity of drugs. In order to increase drug effectiveness, a dosage form that increases the contact time of the drug in the eye should be selected. This can lead into increased bioavailability, reduced systemic absorption and reduce the need for frequent drug administration, leading to the improvement of patient compliance. One of the solution to increase precorneal residence time is by increasing the viscosity of drug [4].

This condition can be achieved by gelling systems or in this case in situ gel dosage form [5]. The purpose of this journal review are to discuss the formulation and characterization of in situ gel drug made using a combination of poloxamer 407 and HPMC bases.

Methods

The source of data for this journal review about in situ gel formulation and characterization are summarized and cited from several international journals, obtained from the internet using internet browser software and search engine. 50 international journals are used as a reference, obtained from various sources. The keywords used include in situ gel, formulation, characterization, poloxamer, Hydroxy Propyl Methyl Cellulose/HPMC.

DISCUSSION

In situ gelling systems can be defined as viscous liquids, which undergo a phase transition from solution to gel when applied to the human body [1]. In situ-forming hydrogels can also be described as liquid form upon instillation and undergo phase transition in the ocular cul-de-sac to form a viscoelastic gel and this provides a response to environmental changes [5]. The triggers to phase change are either temperature, pH or ionic strength.

In the temperature-based method, gelling of the solution is triggered by change in the temperature. Sustained drug delivery can be achieved by the use of a polymer that changes from solution to gel at the eyes temperature. But the disadvantage of this method is characterized by very high polymer concentration. The examples of temperature-based in situ gel is methylcellulose and smart hydrogels. In pH based method, gelling of the solution is triggered by a change in the pH. CAP latex cross linked polyacrylic acid and its derivatives such as carbomers are used. They are low viscosity polymeric dispersion in water, which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-de-sac. In ionic strength-based method, of the solution, instilled is triggered by change in the ionic strength [6].

Gels that undergo sol-gel phase transition caused by a temperature change are called thermoresponsive in situ gels. Such gels have been extensively investigated as temperature-responsive materials for invertible thermoresponsive gelation under certain temperatures and concentrations [7].

The efficacy of ophthalmic hydrogels is mostly based on an increase of ocular residence time by enhancing the viscosity and mucoadhesive properties. Since resulted swollen hydrogel is aqueous-based, it is very comfortable in the patient’s eye. Because of this, in situ gels are preferred since they are conveniently dropped in the eye as a solution, where undergo transition into a gel [8].
Temperature-sensitive systems are the most commonly studied formulation of in situ, which prolongs the residence time of the drug [18]. In situ systems are attractive ways to achieve site-specificity, be a non-irritant to the mucous membranes, and possess some optical clarity, influences the tear behavior and the polymer should be capable of decreasing the viscosity with increasing shear rate [15].

According to this journal written by Chand et al., the polymers used in in situ gel should be non-toxic and non-absorbable from the gastrointestinal tract. It should adhere quickly to moist tissue and should possess some site-specificity, be a non-irritant to the mucous membranes, and possess a wide margin of safety both locally and systematically. Another important thing, the cost of the polymer should be not too high so that prepared dosage form remains competitive [14].

Another journal written by Saini et al., describe the ideal characteristics of polymers for the preparation of in situ ophthalmic gel. It should be biocompatible, capable of adhering to any eye also membrane, have pseudoplastic behavior, has good tolerance and optical clarity, influences the tear behavior and the polymer should be capable of decreasing the viscosity with increasing shear rate [15].

Laddha and Mahajan also describe three ideal properties for in situ formulations: physical state, phase transition and strength of gel [16]. First, the formulation should be a free-flowing liquid which follow: Gelation of cellulose solutions is caused by the hydrophobic interactions between molecules containing methoxy substitution. At low temperatures, the macromolecules are hydrated and polymer-polymer interaction is minimal. As the temperature is raised, the polymer will gradually lose their water of hydration. This condition is reflected by a decline in relative viscosity [32]. For the main discussion, we will compare three journals about Poloxamer 407 and HPMC combination as reference.

A. Controlled ocular drug delivery of ofloxacin using temperature modulated in situ gelling systems. Authors: Upendra Nagai, Nidhi Jain, Divya Kumar and Neha Gulati. Published in Journal of the Scientific Society, Vol 40/Issue 2/May-August 2013 [32].

B. In situ Gelling Ophthalmic Formulations for Sustained Release and Enhanced Ocular Delivery of Flunisolide. Authors: Nabil Abdullah Ali Khater, Osama A. Soliman and Elham A. Mohamed. Published in IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) Volume 11, Issue 2 Ver. I (Mar-Apr.2016), PP 43-51 [33].

C. Ophthalmic In situ Sustained Gel of Ciprofloxacin. Preparation and Evaluation Study. Authors: Fadia Yasser Al-Bazaa and Myasar Al-Kotaji. Published in International Journal of Applied Pharmaceutics Vol 10, Issue 4, 2018 [1].

| Formulation          | FI   | F2   | F3   | F4   | F5   |
|----------------------|------|------|------|------|------|
| Ofloxacin (% w/v)    | 0.3  | 0.3  | 0.3  | 0.3  | 0.3  |
| Pluronic F 127 (% w/v)| 16   | 18   | 20   | 22   | 24   |
| HPMC 50 cps (% w/v)  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  |
| NaCl (% w/v)         | 0.51 | 0.51 | 0.51 | 0.51 | 0.51 |
| Benzalkonium chloride (% w/v) | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Disodium hydrogen phosphate | 1.125 | 1.125 | 1.125 | 1.125 | 1.125 |
| Distilled water (ml) | 100  | 100  | 100  | 100  | 100  |

One of the journals claims that among all in situ gel-forming systems, activation by change in ionic strength is most effective. The advantage is based on the fact that fluctuations in pH and temperature, which could cause changes in the gelation process, are not associated with the ion-activated system. These fluctuations in pH could cause ocular irritation, and storage conditions could lead to changes in temperature [9]. There are several mechanisms of in situ gels based on its physical mechanism: swelling, diffusion and formation based on the chemical reaction. In the swelling mechanism, in situ forming gel occurs when a material absorbs water from the surrounding environment and expand to the desired space. One such substance is myverol (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures [10].

In the diffusion mechanism, it 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. And in the chemical reaction mechanism, chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes [11-13].

HPCM is a semisynthetic, inert, viscoelastic polymer which is non-ionic nontoxic, a good carrier for application of pharmaceutical drug which shows high swelling capacity [29, 30]. Methylcellulose solutions transform into opaque gel between 40-50 °C, whereas HPMC shows a phase transition between 75-90 °C. These phase transition temperatures can be lowered by chemical or physical modifications [31]. The mechanism of HPMC gelation process is as follows: Gelation of cellulose solutions is caused by the hydrophobic interactions between molecules containing methoxy substitution. At low temperatures, the macromolecules are hydrated and polymer-polymer interaction is minimal. As the temperature is raised, the polymers will gradually lose their water of hydration. This condition is reflected by a decline in relative viscosity [32]. For the main discussion, we will compare three journals about Poloxamer 407 and HPMC combination as reference.

Formulation

**Formulation of in situ gel from journal A**

**Table 1: Formula of developed in situ gel systems**
A clear solution [32].

Characterization and evaluation of in situ gelling system from the three journal

**Table 2: Composition of fluconazole selected in situ gel formulations**

| Formulation code | Temperature triggered in situ gelling system | Ion activated in situ gelling system |
|------------------|---------------------------------------------|-------------------------------------|
|                  | F1  | F2  | F3  | F4  |
| Fluconazole      | 0.3 | 0.3 | 0.3 | 0.3 |
| P407             | 15  | 15  | -   | -   |
| HPMC             | 2   | 3   | 2   | 3   |
| ALG              | -   | -   | 0.4 | 0.3 |
| BKC              | 0.01| 0.01| 0.01| 0.01|
| Water q. s.      | 100 | 100 | 100 | 100 |

The differences between all three formulations from each journal is the active ingredients used. Ofloxacin for the first, Fluconazole for the second and Ciprofloxacin for the third. Ofloxacin and Ciprofloxacin acts as an antibiotic, whereas Fluconazole on the other hand acts as an antifungal. The concentration of the excipients such as Poloxamer 407, HPMC, and Benzalkonium Chloride as preservative ingredients is different too. Another differences between the three of them is the amount of formulations variant. The third journals use 12 formula, different too. Another differences between the three of them is the gelling capacity results, optimal concentration(s) of each polymer (P407, ALG, and CP934) with viscosity enhancing agent, HPMC, was dissolved in hot acetate buffer and then sodium chloride and benzalkonium chloride were added to the solution. After that, the drug solution was added to the polymer solution and mixed.

**Formulation of in situ gel from journal B**

**Table 2: Composition of fluconazole selected in situ gel formulations**

| Composition of ophthalmic in situ gels of ciprofloxacin hydrochloride % (w/w) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Formula                        | Ciprofloxacin HCl | P407 | HPMC | Benzalkonium chloride | Sodium chloride equivalent to |
| F1                             | 0.3             | 13   | 0.2  | 0.02                      | 0.9                     |
| F2                             | 0.3             | 13   | 0.4  | 0.02                      | 0.9                     |
| F3                             | 0.3             | 15   | 0.6  | 0.02                      | 0.9                     |
| F4                             | 0.3             | 16.25| 0.2  | 0.02                      | 0.9                     |
| F5                             | 0.3             | 16.25| 0.4  | 0.02                      | 0.9                     |
| F6                             | 0.3             | 16.25| 0.6  | 0.02                      | 0.9                     |
| F7                             | 0.3             | 17.5 | 0.2  | 0.02                      | 0.9                     |
| F8                             | 0.3             | 17.5 | 0.4  | 0.02                      | 0.9                     |
| F9                             | 0.3             | 17.5 | 0.6  | 0.02                      | 0.9                     |
| F10                            | 0.3             | 20   | 0.4  | 0.02                      | 0.9                     |
| F11                            | 0.3             | 16.25| 0   | 0.02                      | 0.9                     |
| F12                            | 0.3             | 17.5 | 0   | 0.02                      | 0.9                     |

1. **Preparation methods**
   
a. **Journal A** (Controlled ocular drug delivery of ofloxacin using temperature modulated in situ gelling system)
   
   Aqueous solutions of Pluronic F127 and HPMC were prepared by dispersing them in distilled water with constant stirring. Ofloxacin was dissolved in glacial acetic acid and added to HPMC solution. HPMC drug solution was then poured into Pluronic solution with constant agitation and was allowed to stand at 4 °C for 24 h to make a clear solution [32].

   b. **Journal B** (In situ gelling ophthalmic formulations for sustained release and enhanced ocular delivery of fluconazole)
   
   Different in situ gelling preparations of FLZ (Fluconazole) were prepared under aseptic conditions to ensure the sterility of the final products. Based on the gelling capacity results, optimal concentration(s) of each polymer (P407, ALG, and CP934) with HPMC were determined. The required amount of each polymer was dispersed in 45 ml phosphate buffer saline (PBS) containing 0.01% benzalkonium chloride (BKC) as a preservative and stirred till complete dissolution. FLZ (0.3% w/v) was dissolved in 45 ml PBS and HPMC was added. The two resultant solutions were mixed using a magnetic stirrer. The volume was adjusted to 100 ml and transferred to a dry, clean, and sterile glass bottle.

   In situ gel of P407 was prepared by following the same method except that the polymer was added to previously cooled PBS to 4 °C.

   c. **Journal C** (Ophthalmic in situ sustained gel of ciprofloxacin, preparation and evaluation study)
   
   Twelve different formulas of ciprofloxacin HCl in situ gel were prepared by using different concentrations of (P407) with different concentrations of HPMC.

   An in situ gel of ciprofloxacin was prepared by using the cold method [10, 34]. The required amount of (P407) was added to acetate buffer (pH 4.5) at 4 °C with gentle mixing and then allowed to hydrate overnight at the same temperature. The required amount of viscosity enhancing agent, HPMC, was dissolved in hot acetate buffer and cooled to 4 °C and then added to polymer solutions. Ciprofloxacin HCl was dissolved in the required amount of acetate buffer and then sodium chloride and benzalkonium chloride were added to the solution. After that, the drug solution was added to the polymer solution and mixed.

   The samples were then transferred to vials and stored in a refrigerator overnight. Finally, the vials were sterilized by autoclave at 121 °C at 15 psi for 20 min [1, 35].

   The differences between the three preparation methods above is the sterilization process. Method from Journal B and C explains the aseptic and sterilization process to ensure that the product is in a sterile condition.

**Characterization**

Characterization and evaluation of in situ gel from the three journal is similar.

a. **Visual appearance and clarity**

   The appearance of the prepared in situ gel systems was determined visually. Clarity of the in situ gel was observed against a white and black background for presence of any particulate matter [1, 36, 37].

b. **Drug content**

   In situ gel forming systems were also characterized for the drug content. 1 ml of the preparation was left for 24 h in simulated artificial tear fluid (pH 7.4) and the sample was analyzed in ultraviolet spectrophotometer (UV 1601, Shimadzu, Japan) at 288 nm [1, 37, 38].
c. Viscosity and pH

The viscosity was measured using a Brookfield viscometer (LV-DVE model, Brookfield, USA). pH of the formulation was measured using a digital pH meter [1, 37-39].

d. Gelling capacity

The gelling capacity was determined by placing one drop of the formulation in a vial containing 2 ml of freshly prepared artificial tear fluid and visually assessing time for gelation and the time taken for the gel to redissolve. The composition of artificial tear fluid used was NaCl 0.670 g, sodium bicarbonate 0.200 g, calcium chloride 2H2O 0.008 g, in 100.0 ml of purified water [1, 40].

e. Ocular irritancy test

 Draize irritancy test was performed on male albino rabbit (or female rabbit in Journal C) in order to demonstrate the safety potential of prepared formulation in animal model. A total of 100 µl of the optimized batch formula was placed in the lower cul-de-sac and was observed at various time intervals. Rabbits were visually examined for any redness, swelling or excessive tear production [1, 41].

f. In vitro studies

Dissolution studies of samples were performed using Franz diffusion apparatus and phosphate buffer (pH 7.4) as a dissolution medium. Phosphate buffer with pH 7.4 will simulate the lachrymal fluid. The temperature was maintained at 37±0.5 °C with the speed of rotation maintained at 100 rpm. The samples were withdrawn at various time intervals and analysed spectrophotometrically for the drug content [1, 42-46].

 g. In vivo studies

In vivo therapeutic efficacy of developed optimized formulation and marketed eye drop formulation was investigated by using normotensive New Zealand albino rabbits. Intra ocular pressure of normotensive rabbits decreased within 1 h administration of single dose of developed in situ gel system and showed 10.8±4.33 % reduction which continued up to 8 h with 31.22±3.65 % reduction (p<0.01). It is worthy to note that marketed eye drop formulation immediately reduced intraocular pressure with 18.22±4.42 % up to 2 to 3 h. From the in vivo study, it was concluded that the after administration of developed in situ gel in the rabbit eye, it turned out in gel form. During gel formulation, formulation got converted into the gel and thus drug release become slowly. Developed formulation confirmed gelling ability of poloxamer-407 at physiological conditions where as HPMC K15M enhances viscosity and sustained release profile of developed formulation. It was also observed that initial reduction in intraocular pressure was very rapid, this may be due to slow conversion of solution to gel formation, but the reduction in intraocular pressure became slow in latter period after gel formation. It was observed after administration of marketed eye drop formulation, the rapid reduction in intraocular pressure up to 3 h, but due to liquid nature of formulation it had no ability to retain in cul de sac region. The results showed that after 3 h % decrease in IOP again decrease in case of marketed formulation due to its liquid nature [47, 48-50].

Evaluation result from all three journals and formulations shows that the developed formulation of in situ gel using combination of Poloxamer 407 (Pluronic F127) as gelling agent and HPMC as viscosity modifying agent is successfully formulated. The optimized formula from each of the three journals represent a promising alternative solution to the conventional ophthalmic dosage forms because of its ability to enhance bioavailability.

CONCLUSION

Ophthalmic in situ gel is able to change into gel when applied to the eye. An in situ gel drug delivery system provides several benefits, such as prolonged pharmacological duration of action, simpler production techniques, and low cost of manufacture, as compared to conventional drug delivery systems. Poloxamer 407 is a well-known stimuli-responsive polymer type with thermostresponsive behaviour. It is commonly used as an eye drug delivery system as it could prolong drug release for eye tissue. The addition of hydroxypropyl methylcellulose (HPMC) can reduce the concentration of poloxamer 407 needed to form in situ gel gelation. Active ingredients to treat ocular disease such as Ciprofloxacin, Fluconazole and Ofloxacin can be formulated with the combination of Poloxamer 407 as polymer gelling agent and HPMC as viscosity enhancer to produce a good quality in situ gel dosage forms. Compared to the conventional ophthalmic dosage, the in situ gel dosage forms can be a promising alternative solution for ophthalmic delivery system.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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