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FORMULATION AND EVALUATION OF PH TRIGERRED IN-SITU GELLING OPHTHALMIC DRUG DELIVERY SYSTEM OF OFLOXACIN

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ABSTRACT

The body's most sensitive and important organs, the eyes' defense system prevents outside substances from entering. Since the medication is rapidly eliminated from the eye due to high tear fluid turnover and dynamics, conventional drug delivery techniques often result in low bioavailability and therapeutic responses. The in-situ gelling ophthalmic drug delivery system is one of the novel approaches created to address the issues with bioavailability. Viscose polymer-based liquids known as "in-situ gelling systems" display a sol-to-gel phase transition on the ocular surface as a result of a change in a particular physicochemical parameter, such as pH, ionic strength, or temperature. This formulation of pH-triggered in-situ gel systems allows for longer-lasting, therapeutically more effective, non-irritating, and stable drug release compared to traditional eye drops.

Keywords: sol-to-gel phase transition, pH-triggered, in-situ gel, ophthalmic medication administration.

1. INTRODUCTION

Eyes are important sensory organs in the human body, which convert light to an electric signal that later will be interpreted by brain1. It can restrict the entry of any exogenous substance because of its anatomical- physiological structure and defence mechanisms2. But, as eyes are unique organs, they also can be infected by various diseases like conjunctivitis, dry eye syndrome, glaucoma, keratitis, trachoma and so on3. Therefore, to target the drug at a required ocular site in therapeutic dose has been one of the most challenging tasks until now4. Various factors like nasolacrimal drainage of drug, binding of drug to lachrymal protein, induced lachrymation, availability of limited corneal area create a barrier for absorption of drug through ocular routes3,5.

There are two types of ophthalmic drug delivery systems, classified as conventional and newer drug delivery systems. The conventional ophthalmic drug delivery system in the form of eye drops, has a dynamic effect and high tear fluid turnover that causes rapid pre-corneal elimination of the drug and also only 1-10% of topically applied drug get absorbed that often results in poor bioavailability and therapeutic response6. Consequently, to achieve the desired therapeutic effect, frequent instillation of concentrated solutions is needed. Due to tear drainage, more than 75% of the administered dose of the drug goes through the nasolacrimal duct and goes into the Gastrointestinal tract, leading to systemic side effects2,7. In order to enhance the ophthalmic bioavailability and lengthen the residence time of instilled dose, many ophthalmic vehicles have been developed, such as aqueous gels, inserts, ointments and suspensions. However, because of low patient compliance in using the inserts and the side effect of using an ointment such as blurred vision, these ocular drug delivery systems have not been used extensively until now.

For the past few years, this new drug delivery systems that have been developed received

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significant interest by ophthalmologists is in-situ gel systems. In-situ gel forming system has showed their potential in increasing the residential time because of bio-adhesiveness of formed gel that has been produced. Additionally, polymers used to achieve in-situ gelling may result in sustained release of drug molecules8,9,10.

In-situ gelling systems are described as low viscosity solution that phase transition in cul-de-sac to form viscoelastic gel. This sol-to-gel phase transition happens due to conformational changes of polymer in response to a physiological environment. In-situ formulations are more acceptable for patient because they are administered as solution or suspension which immediately undergoes to gelation as coming in contact with the eye11.

Depending on the method chosen to cause sol-to-gel phase transition on the surface of the eyes, three types of in situ gelling systems are widely accepted namely ion activated systems, pH triggered systems and temperature sensitive systems4. The ideal properties for in-situ gel formulation can be divided into three categories involving a physical state – the formulation should be free flowing liquid which allows ease of administration with reproducible dose delivery to the eyes:

Phase transition – as drug has been instilled, it should undergo sol-to-gel formation by phase transition12.

Strength of gel – to withstand the shear force in cul-de-sac phase so it can prolong residence time of the drug, and the gel formed should be strong enough5.

Table 1: Example of pH triggered mechanism in-situ gelling system.

Mechanism	Drug	Polymers	Release extension	Reference
pH	Simvastatine HCl (SDX)	Carbopol 940 and HEPMC E4M	Up to 8 h	25
pH	Baicalin	Carbopol 971P and HEPMC E4M	Up to 8 h	31
pH	Timolol Maleate	Carbopol Cationic	Up to 24 h	32
pH	Ciprofloxacin	Carbopol 940 and Methocel E50LV	Up to 8 h	34

Use of in-situ gel forming polymeric formulations may increase patient compliance by a decrease in frequency of administration and overall cost of treatment13,14.

In this article, a summarised concept of approaches used in stimuli responsive systems, which is pH by triggered in- situ gelling systems specifically, along with information on different polymers that can be used in this approach, an example list of FDA approved-based on the concept of ocular pH triggered in-situ gel, review in the field of pH triggered in-situ gelling system, and a basic method of preparation for pH triggered in-situ gelling system.

2. MATERIALS AND METHODS

Approaches used on the in-situ gelling system

Various techniques or approaches can be applied for in- situ gelling systems as follows:

Stimuli-responsive in-situ gelling system that can be divided into two methods:

Temperature induced in-situ gelling system pH triggered (induced) in-situ gelling system

Chemically induced in-situ gelling system can be divided into two methods:

Ionic cross linking (Ion-activated systems)
Enzymatic cross linking

However, in this article we will focus on stimuli-responsive in situ gel system using the method of pH triggered in-situ gelling systems.

Stimuli-responsive in-situ gelling systems

Smart polymers used in stimuli responsive systems are also known as stimuli-sensitive and responsive polymers, intelligent and environmentally sensitive polymer. This new development of drug administration technology

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happens because the smart polymers have shown an active response to small signs and changes in the surrounding environment, which lead to significant changes in their microstructure, physiological and also their chemical proprieties15,16. For example, smart polymers can carry and deliver the drug by itself because of its ability to respond to a stimulus by showing physical or chemical changes to the surrounding area17.

By changing the electrical charge of the polymer molecule, this group of smart polymers can change its solubility depending on the surrounding environment18. Thus, by decreasing its pH, for example, by reducing the hydrophilicity or increasing the hydrophobicity and also neutralizing the electric charge of the polymeric macromolecules, the polymer's electric charge will also decrease, so that the phase transition from a soluble state to an insoluble state can happen19.

pH triggered in-situ gelling systems

Phase transition from sol-to-gel is achieved by changing in the pH area. The ionic pH sensitive of smart polymers are also called as polyelectrolytes that can respond to pH changes, by accepting or releasing a protons in their structure15,16. This smart polymers structure contains acid groups for example carboxylic or sulphonic or basic groups which are ammonium salts that will respond to pH changes in the surrounding environment20.

Swelling of in-situ gel happens by increasing the external pH in case of weakly acid which is anionic groups, but if polymer contains weak basic which is cationic groups, the pH will decrease. Most of anionic pH-sensitive polymers available nowadays are based on PAA (Carbopol, carbomer) or its derivatives. When pH rises from 4.2 to 7.4, sol-to-gel phase transition occurs because at higher pH, polymer with addition of mucin will form hydrogen bonds that lead to the formation of in-situ gel system3. The advantages of formulation using pH-triggered in-situ gel systems are the release of the drug that can be sustained for longer periods of time, therapeutically efficacious, stable, and non-irritant rather than conventional eye drops2.

Examples of this kind of polymers already available in the market are: polyacrylamide (PAAm), poly (acrylic acid) (PAA)(Carbopol®) and derivatives, poly(methacrylicacid)(PMAA), poly(2-diethyl-amino- ethyl-methacrylate) (PDEAEMA), poly(ethyleneimine), poly(L-lysine) and poly(N,N-dimethyl-amino-ethyl- methacrylate) (PDMAEMA).21

Polymer used in pH triggered in-situ gelling system Carbomer is a chemical bond poly (acrylic acid), available commercially as Carbopol and has been widely used in ophthalmic formulation in order to enhance pre-corneal retention of a drug. Carbomer is a white colour hygroscopic powder with characteristics of slight odour, soft and acidic form. It has a glass transition temperature in range of 100-105 oC22,23.

The advantage of using Carbopol is it can display an excellent mucoadhesive properties compared to other polymers. Interaction between mucin and poly (acrylic acid) occurrs in four types of mechanism namely electrostatic interaction, hydrogen bonding, and hydrophobic interaction and inter diffusion process. When pH is raised above 5.5, this pH sensitive polymer will undergo sol-to-gel phase transition in aqueous solution required in high concentration to form stiff gel3. At higher concentration it forms highly acidic solution which is not easily neutralized by buffer action of tear fluid and results in ocular irritation. To reduce the concentration without affecting the viscosity and gelling capacity of the solution can be achieved

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by addition of HPMC, which is one of the viscosity increasing polymers24,25,26.

Another example of polymer used in pH triggered in-situ gelling system is chitosan, which is poly-cationic polymer

Table 2: Example list of FDA approved ocular pH triggered in-situ gel.

No	Product Name	API	Polymer	Type of in situ gel	Indication
1.	Pilogene HS	Pilocarpine HCl	Carbopol 940	pH (sensitive) triggered	Glaucoma
2.	Timolol	Timolol Maleate	Carbopol Chitosan	pH triggered	Glaucoma

obtained from alkaline deacetylation of chitin. The characteristic of this polymer is biodegradable and thermosensitive27.

Furthermore, chitosan is a biocompatible pHdependent cationic polymer, that can remain dissolved in aqueous solutions up to a pH of 6.2 but if neutralization happens above pH 6.2, it will lead to the formation of a hydrated-gel like precipitation. Without any modification of chemical process or cross linking by addition of polyol salts bearing a single anionic head such as fructose, glycerol, sorbitol, or glucose phosphate salts to chitosan aqueous solution, the pH of gelling cationic polysaccharides solution is transformed into thermally sensitive pH-dependent gel and eventually forms an aqueous solutions28.

Cellulose acetate phthalate (CAP) is another type of smart polymer going through coagulation process when the pH is being raised by the tear fluid of eye from the original pH of the solution which is pH 4.5 to pH 7.4. It is also registered in the USA-FDA as an inactive ingredient guidelines and licensing as non-parental medicines in the Europe as one of the smart polymers being used in gelling system24,29,30.

3. RESULTS AND DISCUSSION

Some examples of the stimuli responsive polymers of in- situ gelling systems using pH triggered mechanism can be seen in Table 1, while Table 2 contains FDA approved marketed in-situ gel system products. This clearly indicates that formulation of ophthalmic in-situ gel is possible to be made on lab-scale as well as on large scale products. It also has an ability to sustain release of the drug.

Worked review in the field of pH triggered in-situ gelling system

Gupta and Vyas, (2010) described the formulation and evaluation of an ophthalmic delivery system of an anti- glaucoma drug that uses Timolol Maleate (TM) as an active pharmaceutical ingredient based on the concept of pH-triggered in-situ gelation systems. Polyacrylic acid (carbopol) was used as the gelling agent in combination with chitosan (amine polysaccharide), which was acted as a viscosity-enhancing agent. Formulations were evaluated for pH, viscosity, gelling capacity and drug content. The

0.4 % w/v carbopol / 0.5 % w/v chitosanbased in-situ gelling system was in liquid state at room temperature at the pH formulated (pH 6.0) and underwent rapid transition into the viscous gel phase at the pH of the tear fluid (lacrimal fluid) (pH 7.4). The in-vitro drug release and in- vivo effects of the developed in-situ gelling system were compared to those of Glucomol® (0.25 % TM ophthalmic solution), 0.4 % w/v carbopol solution as well as liposomal formulation. The results clearly demonstrated that developed carbopol-chitosan based formulation was therapeutically efficacious and showed a diffusion controlled type of release behaviour over 24-hour periods32.

Srividya et al., (2001), described the formulation and evaluation of ophthalmic delivery system of an antibacterial agent, namely Ofloxacin as an active pharmaceutical ingredient, based on the concept of pH- triggered in-situ gelation systems. Polyacrylic acid (Carbopol 940) was used as the gelling agent in combination with hydroxypropylmethyl cellulose (Methocel

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E50LV) which acted as a viscosity enhancing agent. The developed formulation was therapeutically efficacious, stable, and non-irritant; it also provided sustained release of the drug over an 8 hours period. The developed system is one of the alternatives to conventional eye drops24.

Parthiban et al., (2010), studied the characteristics of pH triggered in-situ gel-based ophthalmic drug delivery system of non-steroidal anti-inflammatory drug (NSAID), namely ketorolac as an active pharmaceutical ingredient. Polyacrylic acid (carbopol 940) was used as a gelling agent in combination with hydroxyl-propyl methyl cellulose (HPMC-K15M, K4M) as a viscosity enhancer. Benzalkonium chlorides at a suitable concentration were used as a preservative. The formulations were sterilized by moist heat sterilization. The prepared formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, and in-vitro diffusion study. Under rheological investigation both solution and gel were found to be in pseudo-plastic behaviour. The selected formulations showed sustained release over a period of 8 hours with increased resident time. Eye irritation tests using the Draize test protocol with cross over studies were performed on selected formulations. All studies shown showed favourable results, thus in-situ gelling system is a valuable alternative to counter the pre-corneal loss a major drawback in the ophthalmic preparation33.

Wu et al., (2011), investigate the correlation between the stability of baicalin and pH-triggered in-situ gelling system. Carbopol®974P (0.3 %, w/v) was used as the gelling agent combined with hydroxyl-propyl methyl cellulose E4M (0.6 %, w/v) which acted as a viscosity enhancing agent. In-vitro and in-vivo evaluations were performed using several techniques, namely confocal scanning light microscopy analysis, rheometry, Gamma scintigraphic technique and microdialysis method. The rheological behavior showed a significant enhancement in gel strength under physiological conditions, and the formulation provided sustained release of the drug over an 8-hour period. The results demonstrated that pH-triggered in-situ gelling system have better ability to keep baicalin stable and retain drug release than marketed baicalin eye drops to enhance the ocular bioavailability in treatment of anti-inflammatory and anti-cataract effects on eye tissue31. The basic method preparation for formulation using pH triggered (induced) in-situ gelling systems can be seen in Figure 1.

Basic method of preparation for pH triggered (induced) in-situ gelling systems

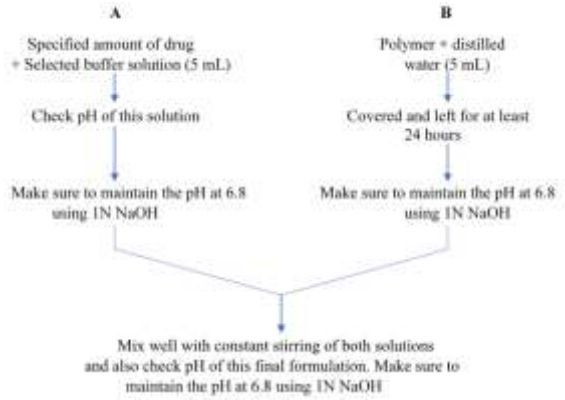

Figure 1: Basic method preparation of in-situ gelling systems using pH triggered mechanism34

4. CONCLUSION

There are many benefits to using stimuli-responsive polymers as a modified release pharmaceutical dosage form. These benefits include the avoidance of systemic side effects from the conventional ophthalmic formulation, which drains the drug from the eye and then enters the systemic circulation through the oesophageal route. Additionally, the use of pH-sensitive gels, which do a great job of instantly changing from sol-to-gel form when in contact

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with ocular fluid and exhibiting better therapeutic level, helps to reduce side effects or adverse systemic reactions. Furthermore, this selective kind of pharmaceutical drug delivery systems has shown both patient compliance and a decrease in therapeutic dosages. Although there are many different kinds of sensitive polymers, pH-sensitive polymers are the ones that have shown encouraging outcomes.

A pH shift in the surrounding environment may cause a pH-sensitive polymer, which is a smart polymer with acidic or alkaline functional groups in its structure, to go through the sol-to-gel transformation process. The formulation is a free-running solution at a lower pH of 4.4, which is acidic. When the pH is raised to pH 7.4 by the tear fluid, the polymer will establish hydrogen bonds with the addition of mucin, resulting in the creation of in-situ gelation. After the formulation, which has a pH of 4.4, is infused into the tear film, there is a pH shift of around 2.8 units, which results in an the very fluid latex changed almost instantly into a thick gel. The hydrogel's swelling process rises with an increase in the external pH when weakly acidic (anionic) polymers are employed; nevertheless, the hydrogel's swelling process decreases when weakly basic (cationic) polymers are utilized. Polyethylene glycol (PEG), carbomer and polymethacrilic acid (PMMA), and cellulose acetate phthalate (CAP) latex are examples of polymers that exhibit pH-induced or triggered gelation systems.

Using in situ gelling systems as new ocular drug delivery systems can solve a number of issues that arise from the formulation using conventional drug delivery systems, such as low response in therapeutic effects, poor bioavailability due to the drug's rapid elimination from the eyes due to high tear fluid turnover, which can have detrimental effects on the body as a whole, and poor patient adherence to prescribed therapy. The latest advancements in ophthalmic drug delivery technology aim to facilitate an amalgamation process. This involves the use of build-up systems that have the capacity to prolong the vehicle's contact time at the ocular surface and decelerate the drug's evacuation from the eyes.

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