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Research Article

pH Triggered *In-situ* Gelling Ophthalmic Drug Delivery System

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ABSTRACT
Eyes are delicate and most vital organs of the body whose defence mechanism restricts entry of exogenous substance. Conventional drug delivery systems get washed off within a short period of time that usually cause poor bioavailability and therapeutic responses because high tear fluid turnover and dynamics cause rapid elimination of the drug from the eye. *In-situ* gelling ophthalmic drug delivery system is one of the new methods that is developed to overcome this bioavailability problems. *In-situ* gelling systems are viscous polymerbased liquids that exhibit *sol-to-gel* phase transition on the ocular surface due to a change in a specific physicochemical parameter like temperature, ionic strength, or pH triggered *in-situ* systems. Using this formulation of pH triggered *in-situ* gel systems, the release of drug can be sustained for longer periods of time, therapeutically more efficacious, non-irritant and stable than conventional eye drops.

Keywords: *in-situ* gel, ophthalmic drug delivery, pH triggered, *sol-to-gel* phase transition.

INTRODUCTION

Eyes are important sensory organs in the human body, which convert light to an electric signal that later will be interpreted by brain[1]. It can restrict the entry of any exogenous substance because of its anatomical-physiological structure and defence mechanisms[2]. But, as eyes are unique organs, they also can be infected by various diseases like conjunctivitis, dry eye syndrome, glaucoma, keratitis, trachoma and so on[3]. Therefore, to target the drug at a required ocular site in therapeutic dose has been one of the most challenging tasks until now[4]. 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 routes[3,5].

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 response[6]. 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 effects[2,7].

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 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 molecules[8,9,10].

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 eye[11].

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 systems[4]. 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 transition[12].

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 enough[5].

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

Mechanism	Drug	Polymers	Release extension	Reference
pH	Sinomenine HCl (SIN)	Carbopol 940 and HPMC K4M	Up to 8 h	25
pH	Baicalin	Carbopol 974P and HPMC E4M	Up to 8 h	31
pH	Timolol Maleate	Carbopol/Chitosan	Up to 24 h	32
pH	Ciprofloxacin	Carbopol 940 and Methocel E50LV	Up to 8 h	24

Use of *in-situ* gel forming polymeric formulations may increase patient compliance by a decrease in frequency of administration and overall cost of treatment[13,14].

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.

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 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 proprieties[15,16]. 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 area[17].

By changing the electrical charge of the polymer molecule, this group of smart polymers can change its solubility depending on the surrounding environment[18]. 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 happen[19].

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 structure[15,16]. 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 environment[20].

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 system[3]. 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 drops[2].

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 ^{o}C[22,23].

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 gel[3]. 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 by addition of HPMC, which is one of the viscosity increasing polymers[24,25,26].

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.	Pilopine 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 thermosensitive[27]. 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 solutions[28].

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 system[24,29,30].

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 periods[32].

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 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 drops[24].

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 preparation[33].

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 tissue[31].

The basic method preparation for formulation using pH

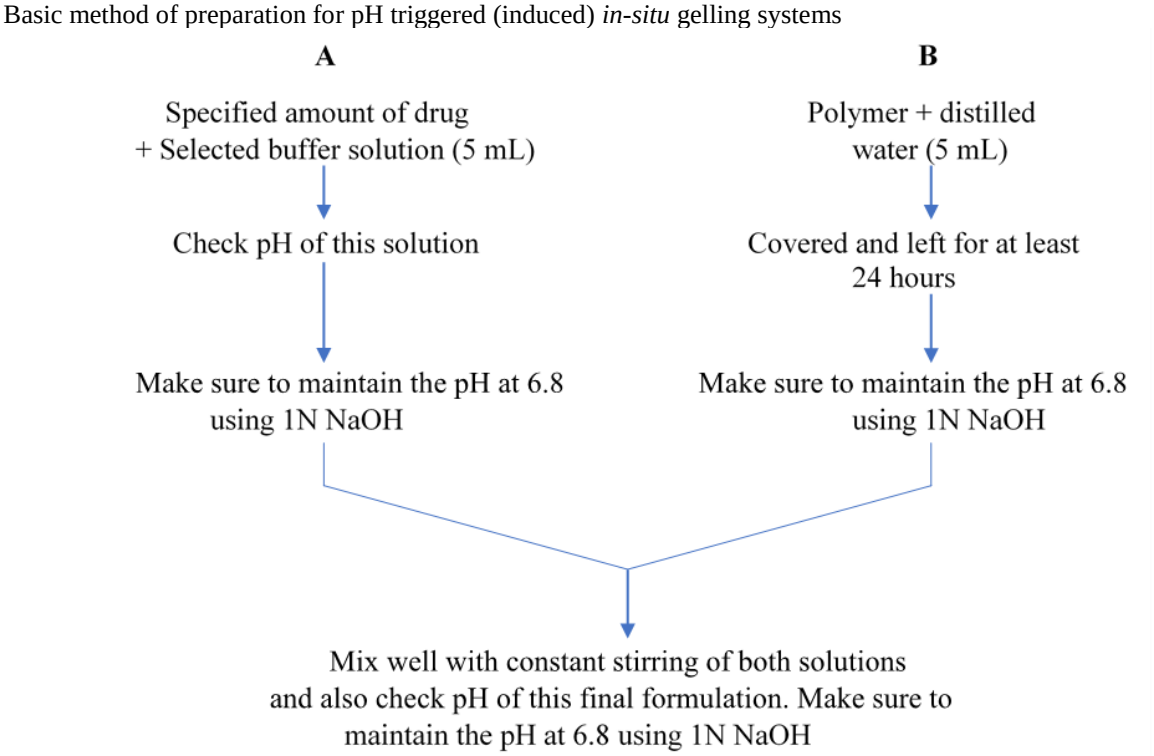

Figure 1: Basic method preparation of *in-situ* gelling systems using pH triggered mechanism[34]

triggered (induced) *in-situ* gelling systems can be seen in Figure 1.

CONCLUSION

Many advantages from using this method which is stimuli-responsive polymers as a modified release pharmaceutical dosage forms, including the systemic side effects that caused from the conventional ophthalmic formulation which is drained out from the eye and then goes to systemic circulation through oesophageal route can be avoid using stimuli-responsive polymers because this method will release and distribute the drug in a specific target, and also pH sensitive gels that has excellent job in transforming from *sol-to-gel* form instantly when coming in contact to ocular fluid and exhibiting better therapeutic level, thus reducing the side effects or adverse systemic reactions. Furthermore, patient compliance and reduction in therapeutic doses have also been shown by this selectivity type of pharmaceutical drug delivery systems. There are several types of sensitive-polymers; however, pH-sensitive polymers are those that have provided promising results.

pH sensitive polymer is a smart polymer that contains acidic or alkaline functional groups in its structure and can be triggered to undergo *sol-to-gel* transformation by a change in the pH of the surrounding area. At a lower pH of 4.4 which is acidic, the formulation is a free-running solution which can undergo coagulation when the pH is raised by the tear fluid to pH 7.4, because at a higher pH, the polymer with addition of mucin will form hydrogen bonds which lead to the formation of *in-situ* gelation. The pH change of about 2.8 units after instillation of the formulation, which is pH 4.4, into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel. As the external pH increases in the case of weak- acid which is anionic groups, the swelling process of the hydrogel also increases but it will decrease if the polymer contains weakly basic which is cationic groups is being used. Examples of polymers that show pH induced or triggered gelation systems are cellulose acetate phthalate (CAP) latex, carbomer and polymethacrilic acid (PMMA), and polyethylene glycol (PEG).

Many problems that occur because of the formulation using conventional drug delivery systems can be solved by using *in situ* gelling system as new ocular drug delivery systems, including low response in therapeutic effects, poor bioavailability because of the rapid elimination of the drug from the eyes that happen because of high tear fluids turn over the dynamics, that leads to systemic side effects or adverse effects and also poor patient adherence to the therapy given. This newer technology in ophthalmic drug delivery systems is directed towards an amalgamation process, which includes build-up systems which can not only extend the contact time of the vehicle at the ocular surface but also slow down the removal of the drug from the eyes.

CONFLICT OF INTEREST

The authors declare no conflict of interest with the data contained in the paper.

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