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Comparison of polymer types on physical evaluation of in situ ophthalmic gel preparations: A Review

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Abstract: The development of temperature, pH, and ion-responsive *in situ* ophthalmic gels aims to enhance drug retention and release efficacy in the eye. Polymers such as Poloxamer (thermosensitive), Gellan Gum (ion-sensitive), and Carbopol (pH-sensitive) exhibit adaptive gelation mechanisms suited to ocular physiological conditions. Poloxamer forms a gel at body temperature, prolonging drug contact duration, while Gellan Gum creates a stable gel network through ionic interactions with lacrimal fluid, increasing viscosity and extending drug release. Carbopol, which transitions into a gel at neutral pH, provides optimal viscosity stability in the ocular environment. This study employs a literature review method, gathering data from indexed journals and scientific publications over the past 10 years. Evaluation results indicate that a combination of Gellan Gum and Methacrylated Gellan Gum at a concentration of 0.6% w/v yields the highest viscosity and encapsulation rate, with a contact time of up to 8 hours, making it an excellent formulation for long-term ophthalmic applications. This paper highlights the significant potential of in situ gels as drug delivery systems, optimizing ophthalmic therapy by enhancing drug viscosity and encapsulation stability.

Keywords: *in situ*; Ion-sensitive; Ophthalmic; pH-sensitive; Temperature-sensitive.

Introduction

Ophthalmic treatment usually treats the anterior part of the eye, such as the cornea, conjunctiva and sclera [1] which requires passing through the tear film, mucus layer, conjunctiva and cornea [2]. In the tear layer, drug elimination will occur because ophthalmic preparations can be dissolved in tears. This can affect the contact time of the drug in the eye, especially if there are cases of excess lacrimal fluid production, eye medication can only last 1 - 2 minutes. One of the elimination mechanisms that affect the speed of drug elimination in the eye is drainage, protein binding, tear turnover, induced tear production, and non-productive absorption in the conjunctiva [3].

Recent advancements in in situ ophthalmic gel formulations have significantly improved drug retention and bioavailability in ocular therapy. Unlike conventional eye drops, which suffer from rapid elimination due to blinking and tear turnover, in situ gels offer prolonged contact time, reducing the need for frequent administration.

Ophthalmic *in situ* preparations are preparations that are given to the eye in liquid form and will become a gel when they come into direct contact with the eye. these changes occur due to pH, ion, and eye temperature factors [4]. In - situ preparations can change the drug preparation from liquid to gel form when in direct contact with the eye, providing benefits such as making it easier to use *in situ* preparations because they are still in liquid preparation if they have not been in contact with the eye surface, and extending the time the drug is with the eye surface [5]. Gel formation in ophthalmic *in situ* preparations occurs through crosslinking of polymer chains, forming covalent bonds and non-covalent bonds [6].

The choice of polymer types in the *in situ* manufacture of ophthalmic gels is important to increase the contact time at the ocular surface for a longer duration. The types of polymers commonly used in *in situ* ophthalmic manufacturing are pH-sensitive polymers such as carbopol, temperature-sensitive polymers such as poloxamer, Poly (N-isopropylacrylamide), and ion-sensitive polymers such as gellan gum, sodium alginate, etc [7].

Encapsulation, as one of the evaluation parameters of ophthalmic in situ preparations, has an important role in extending the release time of the active substance (slow release) so that it can be absorbed optimally. With encapsulation, the active substance is protected in a polymer matrix, which helps to increase the therapeutic effectiveness over a longer period [8]. It also promotes controlled degradation of the biopolymer in the body tissues, which enables sustained and therapeutically appropriate drug release [9]. The purpose of this review article is to determine the best polymers for *in situ* formulation and the factors that influence physical evaluation.

This review aims to highlight the latest developments in in situ ophthalmic gel formulations, focusing on polymer selection, gelation mechanisms, and their impact on drug retention and encapsulation. The discussion will also cover the challenges faced in ophthalmic gel development and potential solutions, including novel polymer modifications and integration with emerging drug delivery technologies.

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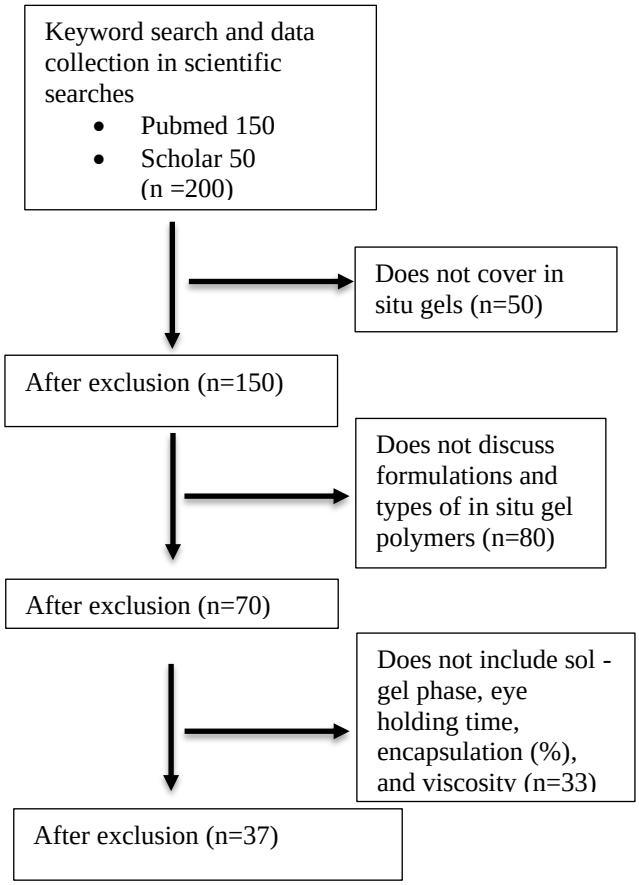
Research Methods

The method used for the preparation of this review article is the literature review method. Using reference data searched through online databases such as Google Scholar, NCBI, and PubMed. The keywords used in searching for journals are *in situ*, ophthalmic, pH-sensitive, ion-sensitive, and temperature-sensitive.



Results and Discussion

The development of *in situ* forming ophthalmic gel systems has garnered considerable attention in recent years due to their potential to enhance ocular drug delivery by improving precorneal retention time and enabling sustained drug release. Conventional eye drops often suffer from poor bioavailability, primarily caused by rapid nasolacrimal drainage and limited corneal permeability, resulting in less than 5% of the instilled dose being absorbed. In situ gels offer a promising alternative by undergoing a sol-to-gel transition upon contact with ocular stimuli such as temperature, pH, or ionic strength, thereby prolonging the drug's residence time and enhancing therapeutic efficacy. The selection of an appropriate polymer is critical in the formulation of such systems, as it dictates the gelation mechanism, mechanical properties, biocompatibility, and drug release kinetics.

A variety of natural and synthetic polymers have been employed in the design of in situ gels, with chitosan, poloxamer 407, and hydroxypropyl methylcellulose (HPMC) being among the most extensively studied. Chitosan, a natural polysaccharide, offers mucoadhesive properties and pH-sensitive gelation, making it suitable for ocular application. Poloxamer 407, a synthetic triblock copolymer, exhibits thermo-reversible gelation, transitioning to a gel at physiological temperatures. HPMC, a semi-synthetic cellulose derivative, contributes to viscosity modulation and film formation, and can enhance the mechanical strength of the gel matrix. The comparative evaluation of these polymers focuses on key physical characteristics such as clarity, pH, viscosity, gelation temperature or time, and rheological behavior, all of which are essential for ensuring formulation stability, ocular tolerability, and patient compliance.

Despite significant advancements, the literature reveals a lack of systematic studies comparing the physical performance of different polymers under standardized conditions within ophthalmic in situ gel systems. Understanding these comparative properties not only informs formulation science but also bridges gaps in optimizing patient-centered ocular therapies. Therefore, this study seeks to provide a comprehensive comparison of selected polymers in terms of their physicochemical behavior within in situ ophthalmic gel preparations, ultimately contributing to the development of more effective and patient-friendly ocular drug delivery systems.

Table 1. Physical evaluation data results from various literatures

Type of polymer	Name of polymer	Sol-gel phase	Lasting time on the eyes	Encapsulations (%)	Viscosity
pH Sensitive polymer	0.5% carbopol 934, with 1.5% HPMC 15 [10]	Gels at pH 6.6	Lasts for a long time	-	Post-gelation: 1263 cps
	Carbopol 934 (0.6%), with HPMC K15 M (0.1%) [11]	Gels at a dosage pH of 7.4	Lasts up to 8 hours	98.18%,	Pre-gelation: Viscosity 700 cps. Post-gelation: 4323 cps.
	Carbopol®974P (0.3 %, w/v), with hydroxyl-propyl methyl cellulose	Gels at a dosage pH of 4.5 to 7.4	Lasts up to 8 hours	-	increased viscosity

	E4M (0.6 %, w/v) [12]				
	Carbopol 934 (0.3 w/v), with HMMC K100 (0,8 w/v) [13]	Gels at a dosage pH of 7.4	Lasts up to 8 hours	97.67± 0.113 %	Pre-gelation: 0.001 viscosity 400 cps Post-gelation: 1000 cps
	0,5% carbopol 934, with 0,5% HPMC 5 [14]	Gels at a dosage pH of 6.9	gelation instantly within 60 seconds and remains stable for a long time	-	Post-gelation: 1200 cps
Ion Sensitive Polymer	0,4 % Deacetylated gellan gum (DGG) [15]	Contact with cation ions in the eye in the lacrimal fluid	Lasts up to 30 minutes	47%.	Post-gelation: 9,97 cps
	gellan gum 0,8%, with carbopol 940 1,5% [16]	Contact with cation ions in the eye in lacrimal fluid with an eye pH of 7.4	Lasts up to 10-12 hours	90%	Post-gelation: 471 to 6500 cPs
	Gellan Gum (GG), with Methacrylated Gellan Gum (MeGG): 0,6% w/v (30 mg GG or MeGG in 5 ml of solution).[17]	Contact with cation ions in the eye in lacrimal fluid with a pH of 7.4. When in contact with Ca ions in lacrimal fluid	Lasts up to 8 hours	90-99%	Post-gelation: 6500 cPs
	Gellan gum (0,15% w/v), with hydroxyethylcellulose (HEC) [18]	Contact with cation ions in the eye in the lacrimal fluid	Lasts up to 3 hours	85%	Post-gelation: 80 cps
	0,4% sodium alginate [19]	Contact with cation ions in the eye in the lacrimal fluid	Lasts more than 2 hours	70,5%	Post-gelation: 204 cps
	0,8% w/v sodium alginate, with 1,5% w/v HPMC [20]	Contact with cation ions in the eye in the lacrimal fluid	Lasts up to 6-8 hours	98.63% to 99.63%	Post-gelation: 64,8 cps to 1857 cPs
	Sodium alginate 2%, with HPMC 0,2% [21]	Contact with cation ions in the eye in the lacrimal fluid	Bertahan hingga 10 jam,	70-90%	Peningkatan viskositas
Temperature Sensitive Polymers	Pluronic F127 14% w/w, with Carbopol 0.3% w/w [22]	At 31°C to 37°C	Lasts up to 6 hours	79,35%,	Post-gelation: 20,917 cps
	Poloxamer 188: 20%, HPMC K200M: 0,75%, with HPMC Low Viscous: 1% [23]	At 37.87°C	Lasts up to 7 hours	90,89%	Post-gelation: 2331,6 cPs
	Poloxamer 407: 10% w/v, with Hydroxypropyl Methylcellulose	At 37°C	Gels in 30 seconds, and lasts up to 5 minutes	-	Post-gelation: 10 cps

	(HPMC): 0.725% w/v[24]				
	Poloxamer 10% w/v, with HPMC 1% [25]	The physiological temperature of the eye is 37°C	Extend the contact time with the eyes	90,89%.	Post-gelation: 4139,3 cPs
	Pluronic F127 14% w/w, with Carbopol 0.3% w/w [26]	At 31°C to 37°C	-	79,35%	Post-gelation: 18.340 cps

Thermosensitive Gel

Temperature-sensitive *in situ* gel systems utilize thermosensitive polymers that can change from liquid to gel form at a certain critical temperature, known as the Lower Critical Solution Temperature (LCST). Below the LCST, the polymer remains in liquid form, but will gelate at physiological body temperature, thereby improving drug retention in the eye [27]. One thermosensitive polymer often used in ophthalmic applications is Poloxamer, which has amphiphilic properties- the PEO (Polyethene Oxide) block is hydrophilic and water-soluble, while the PPO (Polypropylene Oxide) block is hydrophobic. This structure allows Poloxamer to form micelles as the temperature increases, until it reaches a stable gel consistency [28].

In ophthalmic applications, Poloxamer has the advantage of having a PEO-PPO copolymer block structure. The hydrophilic PEO block improves the stability of the preparation while it is still in liquid form, while the PPO block facilitates the transition to gel form when it reaches physiological temperatures, particularly when in contact with the eye [5]. This gelation process starts with micellization, when the hydrophobic PPO blocks form micelles as the core of the structured network, and the interaction between micelles then increases the viscosity and partial rigidity of the gel. This slows down the dissolution rate of the drug, prolongs its release, and facilitates more efficient distribution and extended contact time with the ocular surface, thus significantly optimizing ocular treatment [28].

pH-sensitive gel

pH-sensitive *in situ* formulation should ideally have a pH range between 5 and 7.4 10. One method that can be used to induce a sol-gel phase transition on the ocular surface is to use the pH of the eye. Phase gelation can occur when the pH increases by 2.8 from the initial condition of the eye drop solution. When the pH increases from 4.2 to 7.4, a transition from sol to gel phase occurs. At higher pH, mucins in the eye bind by hydrogen bonding, leading to the formation of an *in situ* gel system [12].

Ophthalmic products containing *polyacrylic acid* (PAA) are formulated at low pH and form a gel when placed in a higher pH environment, such as tear fluid. PAA polymers with molecular weights above 16.5 kDa show the ability to undergo a sol-gel phase transition, while polymers with lower molecular weights do not. Gelation can also occur at pH above 5 [29].

Ion-activated system

Ionic polymers can be used as the main ingredient in the preparation of *in situ* gels, which can gel when in direct contact with the tear fluid in the eye. Lacrimal fluid contains ions such as Na^+, Ca^{2+}, and Mg^{2+} [30]. The transition from tear fluid to gel is known as the sol-gel transition, which can occur when ionic polysaccharides crosslink with divalent cations such as Mg^{2+} and Ca^{2+} and monovalent cations such as Na^+. These interactions increase the cation concentration, which in turn increases the viscosity of the polymer and leads to gel formation [31].

One polymer classified as ion-sensitive is gellan gum and sodium alginate. Gellan gum, which is an anionic heteropolysaccharide, can form a gel when it comes into contact with cations in the aqueous humor, such as Na^+, Ca^{2+}, and Mg^{2+}. Meanwhile, sodium alginate can gel by ionic cross-linking between the alginate chain and Ca^{2+} ions present in tears [32]. Gellan gum forms a double helical structure linked by weak van der Waals forces, and when it comes into contact with cationic electrolytes in the tear fluid, these helices come together to form polymeric cross-links. On the other hand, alginic acid, an anionic polysaccharide, can increase the residence time of ocular medications due to its mucoadhesive properties as well as its ability to form a gel upon interaction of guluronic acid residues with Ca^{2+} ions from the lacrimal film [33].

Effect of polymer type on viscosity and encapsulation

According to the results in the table above, the addition of polymers to the *in situ* formulation of ophthalmic gels has an effect mainly on increasing viscosity and encapsulation. Poloxamer (Pluronic) has thermoresponsive properties, increasing viscosity at body temperature (37°C). In combination with gelling agents, the mechanical strength of the gel can be increased, thereby extending the contact time with the eye. Although effective for applications requiring rapid drug release, this polymer's thermoreversibility makes it less than ideal for long-term retention times [34]. Gellan gum can form stable gels through ion interaction with the ocular fluid, forming a three-dimensional network that increases viscosity and drug retention. This allows for strong encapsulation and sustained drug release, making it an excellent choice for long-term ophthalmic applications where good efficacy and low dosing frequency are required5. Gellan Gum, forms gels by reacting with ions (mainly calcium) in an efficient "egg box" structure. It increases viscosity and allows optimal encapsulation at low polymer concentrations. However, its viscosity stability is lower than gellan gum under varying

physiological conditions, although it remains superior in drug release control [35]. Carbopol, this pH-sensitive polymer increases viscosity at neutral pH, resulting in a stable gel under physiological ocular conditions. Carbomer is effective in encapsulation and consistent release, but is dependent on one stimulus (pH), making it less flexible and more susceptible to pH variations [34].

Poloxamers, when combined with a natural polymer derivative such as *hydroxypropyl methylcellulose* (HPMC), enhance gel stability and facilitate ocular drug delivery by increasing viscosity and prolonging contact time with the ocular surface. Recent research highlights the effectiveness of thermosensitive poloxamers, particularly triblock copolymers, in ocular drug delivery systems (DDS), demonstrating superior therapeutic efficacy compared to existing commercial treatments. Additionally, ion-sensitive polymeric DDSs incorporating gellan gum have shown promise in extending precorneal retention time and improving drug bioavailability. Notably, studies on *gellan gum*, a linear anionic polysaccharide, indicate its potential to enhance drug retention and absorption, further optimizing ocular drug delivery [36].

In the table data, the results obtained show different physical evaluation results. The difference in results is due to differences in the polymers used, the combination with gelling agents and the concentration used in the formulation. The best formulation results are gellan gum (GG) and methacrylated gellan gum (MeGG): 0.6% w/v (30 mg GG or MeGG in 5 ml solution) with a post-gelation viscosity of 6500 cps, encapsulation of 90-99% and eye contact time of up to 8 hours. The worst result was deacetylated gellan gum (DGG) 0.4% with a viscosity of 9.97 cps, encapsulation of 47% and an eye contact time of only 30 minutes. A good viscosity for *in situ* ophthalmic gel is 5-1000 cps before gelation and 50-50,000 mPas after gelation [37] . Viscosity can be influenced by the polymer and the gelling agent. Formulations that use additional gelling agents have higher viscosity results than those that do not, so the higher the viscosity, the better and longer the drug can stay in the eye.

Conclusion

Temperature, pH and ion sensitive *in situ* ophthalmic gel systems use polymers such as *poloxamer*, *gellan gum* and *carbopol* to improve drug retention and release in the eye. *Poloxamer*, a thermoresponsive polymer, forms a gel at physiological temperatures, increasing viscosity and contact time. *Gellan Gum*, which is ion-sensitive, interacts with cations in the tear fluid to form a stable gel, enabling effective encapsulation and sustained drug release. *Carbopol*, which is pH sensitive, forms a gel at neutral pH, maintaining viscosity stability and prolonging contact with the eye. The combination of this polymer with thickeners improves mechanical strength and prolongs drug residence time. Formulations using *gellan gum* (GG) and *methacrylated gellan gum* (MeGG) provide superior viscosity, encapsulation and contact time of up to 8 hours due to the three-dimensional network structure of ionically crosslinked GG.

Author Contribution

H.E. Putra contributed mainly to the preparation of the article with the guidance of A.A. Zahra and was assisted by coauthors K.N. Aini, M. Rafifa, V.S. Maulida, and L.M. Sabrina.

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