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A Comparative Study on The Therapeutic Effect of pH, Temperature Triggered, and Ion Activated In Situ Gelling System For Ocular Delivery

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ABSTRACT

One of the most popular pharmaceutical preparations for the eyes today is in situ gel. The in situ gel system is a system that is liquid at room temperature but will form a gel when it comes into contact with the body or undergoes a change in pH. The form of the drug delivery system is in-situ is a type of mucoadhesive drug delivery system. Gel formation depends on several factors such as temperature modulation, pH changes, the presence of ions, ultra-violet irradiation, electrical sensitivity, and the enzyme by which the active substance is released. The purpose of this study is to compare the therapeutic efficacy of in situ gel medicines on pH, temperature triggered, and ion activated gelling systems. A drug in situ gel is a drug delivery device that transforms into a gel after being applied to the body. The findings revealed that the pH, temperature triggered, and ion activated gelling system factors had a substantial influence on the extended release medicines that affect the therapeutic effect of in situ gel medications. This comparative investigation demonstrates that the pH, temperature triggered, and ion activated gelling system factors have significant implications on the therapeutic benefits of in situ gelled medicines. A deeper knowledge of the relationships between these variables and in situ gel drug delivery methods can lead to the development of more effective and dependable medication compositions. These findings could aid in the development of improved gel in situ drug delivery systems to improve therapeutic benefits in the treatment of a variety of medical disorders.

Keywords: in situ gel, pH triggered, temperature triggered, ion activated, therapeutic effect.

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1. Introduction

The eye is a peripheral organ of the visual system, hence its protection is very important. To create a structural state that protects the eye from injury that does not diminish or even optimize its function, the eyeball is located in a skeletal cavity called the orbita.

Ocular drug absorption is the process by which a topically administered drug (directly applied to the eye) is absorbed into the tissues of the eye to reach its therapeutic target. The eye has a unique drug absorption mechanism that allows the active substance in the drug to reach the parts of the eye that need it. Some of the factors that influence drug absorption in the eye include:

1. Physicochemical properties of the drug: Drug properties such as molecular size, water solubility, lipophilicity, and chemical stability can affect drug absorption in the eye. Drugs that are more water-soluble tend to be absorbed more easily by the eye.
2. Drug formulation: The dosage form of the drug used can also affect the absorption of the drug in the eye. Some common dosage forms used for eye treatment include eye drops, eye ointment, eye gel, or therapeutic contact lenses. Each dosage form has different formulation characteristics, which may affect the speed and rate of drug absorption.
3. Corneal permeability: The cornea, the transparent outer layer of the eye, is the main part responsible for drug absorption in the eye. Corneal permeability may be affected by pathological conditions, such as keratitis or inflammation, which may interfere with drug absorption.
4. Drug contact time: The duration of drug contact with the eye surface can also affect drug absorption. Usually, it is recommended to keep the eyes closed after drug administration for a few minutes to allow the drug sufficient time to be absorbed.
5. Eye drainage system: The eye has a drainage system that allows eye fluid to be excreted. This can also affect drug absorption in the eye, as eye fluid that is excreted too quickly can reduce the contact time of the drug with the eye tissue.

One of the most popular pharmaceutical preparations for the eyes today is in situ gel. The in situ gel system is a system that is liquid at room temperature but will form a gel when it comes into contact with the body or undergoes a change in pH. The form of the drug delivery system is in-situ is a type of mucoadhesive drug delivery system. Gel formation depends on several factors such as temperature modulation, pH changes, the presence of ions, ultra-violet irradiation, electrical sensitivity, and the enzyme by which the active substance is released.

This preparation is specifically designed for application to the eye and has several advantages over other formulations, such as eye drops or eye ointments. Some of the advantages of in situ gel for eyes are as follows:

1. Adhesion Ability: In situ gels have the ability to adhere to the surface of the eye once applied. This allows the medication to stay in the desired

place and prevents it from being wasted or rubbed off when the eye blinks.

2. Controlled Release: In situ gels are designed to release the drug substance gradually over a longer period of time. This allows continuous delivery of the drug to the eye over a longer period of time, thereby minimising the frequency of drug application.

3. Stability and Bioavailability: In situ eye gels can improve the stability and bioavailability of the drug, thereby maximising its absorption and effectiveness in eye treatment. In gel form, the drug can also remain on the surface of the eye longer than other dosage forms.

4. Moisture and Protection: In situ eye gels usually contain moisturising ingredients that help keep the eye moist and protect it from external irritants. This can provide a sense of comfort and reduce dry eye symptoms.

5. Ease of Use: In situ eye gels are often easier to use than other eye medications, such as ointments or eye creams. They usually come in the form of drops or sprays that are easy to apply to the eyes.

2. Method

MECHANISM OF IN SITU GEL FORMATION

The mechanism of in situ gel formation can be divided into chemical and physical mechanisms. Physical mechanisms are stimulated by temperature, electric field, light.

Chemical mechanism is stimulated by pH change and ion activation. The mechanism of in situ gel formation by pH, temperature, and ions may vary depending on the type of in situ gel system used. Here are some common mechanisms associated with these factors:

1. pH Triggered In Situ Gel

a. pH sensitive polymers: Some polymers have pH sensitive properties, where they change from liquid to gel form when a change in pH occurs. For example, polymers such as polyacrylate, alginate, or methyl cellulose can form a gel when the pH of the solution reaches a certain threshold. Changes in pH can cause changes in the bonds between polymers, leading to gel formation.

b. Changes in environmental pH: Some in situ gels can form gels in response to changes in environmental pH. For example, in the acidic environment of the stomach, in situ drug gels containing acidic polymers will experience a decrease in pH and form a gel, which allows the release of the drugs contained in them.

2. Temperature Triggered In Situ Gel

a. Sol-gel transition: Some polymers can undergo sol-gel transition when temperature changes occur. At a certain temperature, polymers in liquid solution form a stable gel network. For example, poly(N-isopropyl acrylamide acid) (PNIPAAm) is one of the most commonly used polymers in temperature-sensitive in situ gel systems. PNIPAAm can form a gel at temperatures above a certain "gelling temperature" called the Critical Point of Solution (LCST).

b. Gel formation by changes in ambient temperature: Some in situ gels can form when subjected to environmental temperature changes. For example, in injection applications, in situ gels may form when the polymer solution injected into the body experiences a temperature drop due to the lower body temperature, thus forming a stable gel.

3. Ion Activated In Situ Gel

a. Formation of ionic bonds: Some polymers can form gels through the formation of ionic bonds with certain ions. For example, gelatin is a polymer often used in in situ gel systems, in which calcium ions are used to form stable cross-links between gelatin chains, thereby forming a strong gel.

b. Control of viscosity by ions: The addition of certain ions to a polymer solution can affect the viscosity of the solution and aid in gel formation. For example, the addition of sodium or calcium ions to an alginate solution can increase the viscosity and form a stable alginate.

3. Result and Discussion

1.pH

Ingredients %w/v	F1	F2	F3	F4	F5	F6	F7
Moxifloxacin Hcl	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC (K15 M)	0.1	0.2	0.3	0.3	0.3	0.3	0.3
Carbopol 934	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Sodium chloride	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Benzalkonium chloride	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled water (ml)	100	100	100	100	100	100	100

Formulations	Appearance	Clarity	pH	Gelling capacity
F1	Light yellow	Clear	4.41	-
F2	Light yellow	Clear	4.41	-
F3	Light yellow	Clear	4.44	+
F4	Light yellow	Clear	4.40	+
F5	Light yellow	Clear	4.40	++
F6	Light yellow	Clear	4.41	+++
F7	Light yellow	Clear	4.43	+++

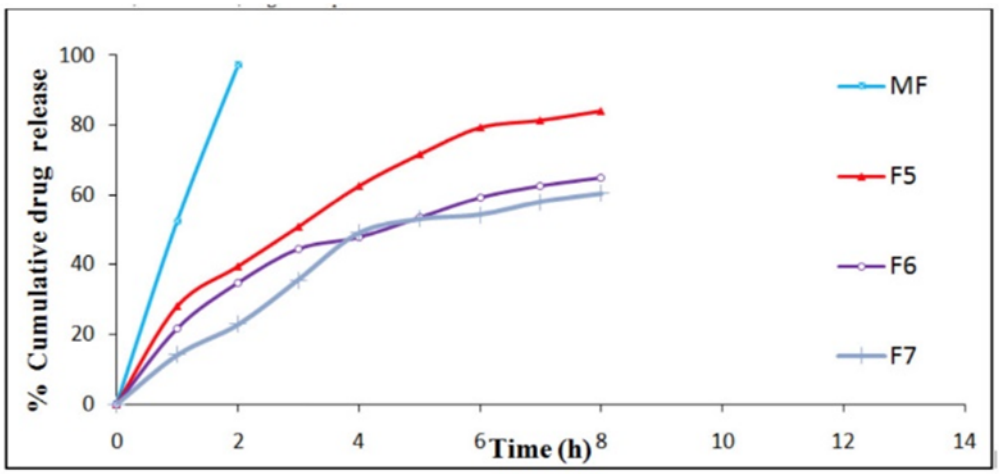

Table and **Figure 1.** The result of formulation and evaluation of thermosensitive ocular in situ gels for sustained release of balofloxacin research by Sundari et.al., 2015

The formulations were in solution state at pH 4.4, but when inserted into the eye (pH 7.4), it underwent sol-gel transformation, which indicates an increase in precorneal residence duration of medication, enhancing ocular bioavailability, reducing dose frequency, and improving patient compliance. The three formulations demonstrated sustained release during an 8-hour period.

2. **Temperature Triggered In Situ Gel**

Ingredients(%w/v)	G1	G2	G3	G4	G5	G6	G7	G8
Balofloxacin (mg)	100	100	100	100	100	100	100	100
Poloxamer	12	12	12	12	14	14	14	14
Chitosan	0.05	0.1	0.15	0.25	0.05	0.1	0.15	0.25
Benzalkonium chloride	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Sodium chloride	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Distilled water(upto 100ml)	qs	qs	qs	qs	qs	qs	qs	qs

Formulation code	Appearance	Clarity	pH	Drug content	Gelling capacity
G1	Yellow	Clear	7.4	76.8	+
G2	Yellow	Clear	7.4	78.2	++
G3	Yellow	Clear	7.4	80.4	++
G4	Yellow	Clear	7.4	83.80	+++
G5	Yellow	Clear	7.4	75.2	+
G6	Yellow	Clear	7.4	82.3	++
G7	Yellow	Clear	7.4	89.82	+++
G8	Yellow	Clear	7.4	81.34	++++

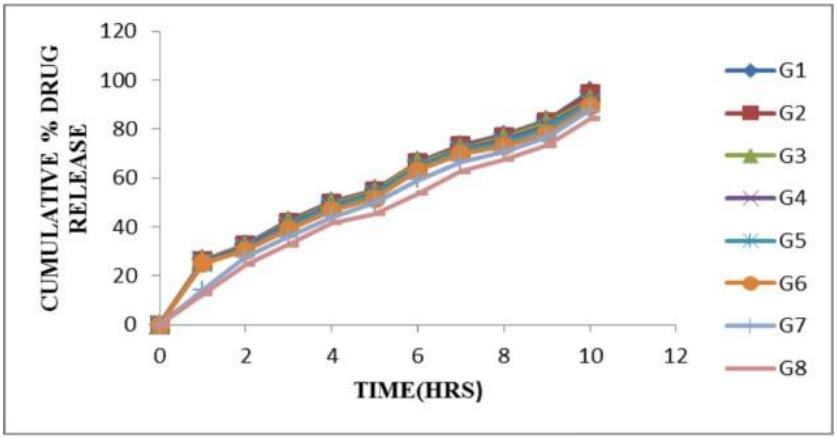

Table and **Figure 2.** The result of formulation and evaluation of pH triggered in situ ophthalmic gel of moxifloxacin hydrochloride research by Shashank et.al., 2012

The experiments demonstrated that the cumulative percentage drug release of all formulations ranged from 84 to 95%. Slow drug release from the polymeric solution comprising in situ gel was caused by an increase in polymer concentration, which resulted in an increase in viscosity, resulting in sustained drug release.

3. **Ion Activated In Situ Gel**

Gelrite concentration (% w/v)	Physical properties	Gelling capacity
0.1	Clear and transparent solution	+
0.2	Clear and transparent solution	+
0.3	Clear and transparent solution	++
0.4	Clear, transparent, and viscous solution	+++
0.5	Clear, transparent, and viscous solution	+++
0.6	Clear, transparent, and viscous solution	+++
0.7	Clear, viscous, easily pourable solution of gel-like consistency	+++
0.8	Clear, more viscous solution of gel-like consistency	++++
0.9	Slightly turbid formed gel	++++

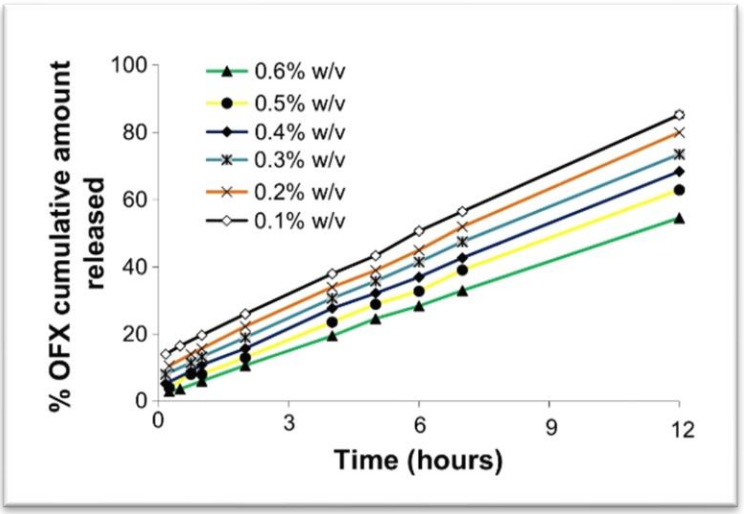

Table and **Figure 3.** The result of Improved corneal bioavailability of ofloxacin: biodegradable microsphere-loaded ion-activated in situ gel delivery system research by Sayed et.al., 2015

After 12 hours, the release of OFX from Gelrite in situ gel formulation reduced as Gelrite concentration increased. After 12 hours, the in situ gel formula with Gelrite concentration of 0.1% w/v released more than 80% of the medication, whereas the in situ gel formula with 0.6% w/v Gelrite released roughly 54% cumulative OFX. The decrease in OFX release from in situ gel formulations is related to an increase in polymer concentration, as increasing polymer concentration results in a denser polymeric chain structure. As a result, OFX diffusion through denser formulations is reduced. Furthermore, the amount of water introduced into these formulations was lowered, resulting in lower dissolution rates.

Sustained release is a drug formulation approach that allows a medication or therapeutic agent to be delivered over time while maintaining a steady and therapeutic level of the substance in the body. It entails creating drug delivery systems that gradually release the active component over time, often resulting in increased patient compliance and decreased dose frequency. Sustained release formulations can improve therapeutic efficacy by keeping drug concentrations within the therapeutic range for an extended length of time. This can result in improved disease control, management of symptoms and medical efficacy.

From these research studies, it can be seen that the effect of pH, temperature triggered, and ion activation changes the time at which the drug release is longer, which indicates that the drug is a sustained release drug. From these studies, it can be seen that the best sustained release effect is the ion activated gelling system, due to the prolonged release time of the drug and the longer contact time of the drug with the target.

The drug contact time of sustained-release formulations is generally longer than that of immediate-release formulations. One of the main objectives of sustained release drugs is to provide a gradual and sustained release of the drug over a longer period of time. As such, sustained-release drugs are designed to maintain therapeutic drug levels in the body over a longer period of time than immediate-release drugs.

The structures and materials used in sustained release formulations are intended to slow the release of the drug from the formulation, thereby prolonging the contact time with the desired tissue or target.

4. Conclusion

From these studies, it can be seen that the best sustained release effect is the ion activated gelling system, due to the prolonged release time of the drug and the longer contact time of the drug with the target. The gradual and sustained release of the drugs in sustained release formulations can maintain drug levels over a longer period of time, optimize therapeutic effects, and reduce fluctuations in drug levels that can affect disease control.

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