In situ ophthalmic gel is a type of eye drug preparation that has a higher bioavailability value and has a longer contact time with maximum therapeutic effect and with minimal side effects compared to conventional eye preparations. The preparation of ophthalmic in situ gel is required to make sure that the prepared preparations meet the standards and are safe when used. This journal review aims to look at the methods used in characterizing physical properties in in situ ophthalmic gel formulations with different active substances such as rheology studies, organoleptic tests, pH, clarity, and gelling capacity. In order to get the best formulation of in situ ophthalmic gel preparations so as to provide maximum therapeutic effect.

Keywords: Rheology, Organoleptic, pH, Clarity, Gelling capacity, In situ gel, Ophthalmic

INTRODUCTION

The eyes are a sensory organ with a unique anatomical and physiological structure that cannot be penetrated by foreign particles. There are various preparation forms for the introduction of eye medications but because the eye has a strong mechanism and barrier protection, the absorption and penetration of eye medications, especially to the posterior part of the eye obstructed. The presence of lacrimal fluid and the eye-to-blink reflex movement can prevent the eye from drying and can remove all foreign substances present in the conjunctival sac. Thus a small portion of the drug applied to the eye will get to the anterior segment of the eye while the majority are lost in lacrimal fluid. Only 5% intraocular bioavailability can be achieved by topical ophthalmic preparation form [3, 4].

The most commonly used form of eye preparation is a solution and suspension, but this preparation form has poor ocular bioavailability. It is developed an in situ hydrogel eye preparation form that has a higher bioavailability value by increasing the contact time with the corneal tissue so the delivery frequency can be reduced [5, 6].

The main problem in liquid ophthalmic preparation formulations is the loss of the drug in the area of precorneal by the presence of lacrimal fluid. Nasolacrimal drainage and short contact time on the preparation of the solution. To increase contact time and ocular bioavailability used different opthalmic delivery system such as ointment, gel, suspense or polymer. An ointment may cause blurred vision to lower patient adherence. In addressing this problem can be used in situ opthalmic gel preparations made of polymers with a form of solid changes to the gel caused by the presence of changes in certain physical chemical parameters such as pH, temperature, and ion-sensitive. The main advantages of gel in situ are easily administered with accurate preparations and can increase contact time [7].

In situ Drug Delivery system is a new drug delivery system that uses natural or synthetic polymer. Changed from solution to gel after insertion into the inner part of the eyelid caused by the response of the physicochemical properties of liquids ophthalmic. The process of gelation is triggered by several parameters such as pH, temperature, solvent exchange and ions that form a chemical cross bond or physics between the polymer materials used to form the gel. The formed Gel should be able to withstand the sliding force on the inside of the eyelid and should withstand the drainage of the cornea. The gel-forming polymer acts as a polymer controlling the rate of discharge so as to increase the biological availability or bioavailability of the ocular preparations [8].

The advantage of in situ drug delivery system compared with other ocular preparation forms is to increase biological availability, slightly influenced by nasolacrimal drainage compared with conventional eye preparations so that can reduce absorption into the eye tissues, preventing systemic adverse effects, easily applied to the eye so as to improve patient adherence. Other benefits are able to reduce the frequency of delivery because the gel in situ can maintain the contact time of the drug in the eyes so as to provide maximum therapeutic effect [9]. The classification of In situ gel are [10].

1. Based on physical stimulation
   a. Thermally Triggered System: formulation is liquid at room temperature (20-25 °C) which undergoes gelation in contact with body fluid (35-37 °C)
   b. pH Triggered System: phase transition occur due to rise in pH from 4.2 to 7.4

2. Based on a physical mechanism
   a. Swelling: the polar lipid or polymer swells from inside to outside and slowly releases the drug
   b. Diffusion: this process solvent diffuses from the polymer solution into surrounding tissue and results in precipitation or solidification of the polymer matrix

3. Based on a chemical reaction
   a. Ion Cross Linking: formulation undergoes liquid-gel transition under influence of an increase in ionic strength
   b. Enzymatic Cross Linking: the gel was formed by cross-linking with the enzymes that are present in the body fluids
   c. Photo-polymerization: monomers or reactive micromere solutions and the initiators injected into a tissue site, and the application of electromagnetic radiation used to form a gel.
Evaluation in the preparations to ensure the formulation of the in situ ophthalmic gel made is the most excellent and stable formulation. The evaluations can be evaluated as physics, chemistry, or biology. For the physics evaluation, it is as follows as Rheology test, organoleptic test, clarity, pH, and gelling capacity. Appearance and homogeneity of the samples examined visually both color and clarity. Viscosity and rheology tests in situ ophthalmic gels are important parameters to be evaluated. The viscosity and rheological properties of the in situ drug delivery system can be assessed using the Brookfield or other types of viscometers such as the Ostwald viscometer. The viscosity value of the preparation formulation should be in a stable and optimal state will not cause problems for the patient, easy to apply, and quickly undergo transient from the Sol to the gel. The clarity test was observed with the help of visual inspection under good light rays, observations using black and white backgrounds, seen in various directions. It is also observed whether or not the turbidity or unwanted particles are spread at the preparation. The pH was measured using a pH meter that was previously librated using a standard buffer of pH 4 and 7 in accordance with the prescribed procedure [11].

**METHOD**

This article review contains review and research of several published articles. The process of finding sources from this review carried out through Pubmed, Google scholar, Scopus using the subject of the title associated with "Physical characterization of in situ ophthalmic gel". The search for keywords in detail is as follows: "in situ ophthalmic gel" [All Sectors] AND "Physical characterization" [All Fields] AND "in situ drug delivery system" [All Fields] by sorting [Year of Publication] in the last 10 y, and included "Reviewing articles". From 50 journals after sorted by inclusion and exclusion criteria, 30 journal references used in this journal review.

**RESULTS AND DISCUSSION**

Some of the characteristics of physical properties performed in situ ophthalmic gel preparations

| No | Active substance           | Physical characterization | Visual appearance | Clarity | pH    | Gelling capacity |
|----|---------------------------|---------------------------|--------------------|---------|-------|-----------------|
| 1  | Levofloxacin mesylate      | Pseudoplastic viscosity   | Clear              | n/a     | 4.8   | -               |
| 2  | Dexamethasone sodium       | Pseudoplastic viscosity   | Pale yellow        | Clear   | 4-4.8 | ++              |
| 3  | Moxifloxacin hydrochloride | Pseudoplastic viscosity   | Clear              | n/a     | 4.8   | ++              |
| 4  | Levofloxacin hydrate       | Pseudoplastic viscosity   | Pale yellow        | Clear   | 7.36  | -               |
| 5  | Levofloxacin               | Pseudoplastic viscosity   | Pale yellow        | Clear   | 7.2   | ++              |
| 6  | Levofloxacin               | Pseudoplastic viscosity   | Clear              | n/a     | 4.8   | ++              |
| 7  | Levofloxacin               | Pseudoplastic viscosity   | Clear              | n/a     | 4.8   | ++              |
| 8  | Levofloxacin               | Pseudoplastic viscosity   | Clear              | n/a     | 4.8   | ++              |
| 9  | Levofloxacin               | Pseudoplastic viscosity   | Clear              | n/a     | 4.8   | ++              |
| 10 | Levofloxacin               | Pseudoplastic viscosity   | Clear              | n/a     | 4.8   | ++              |

**Characterization methods of physical properties**

**Rheology**

The main requirements of an in situ gel forming system are the viscosity and gel forming capacity. To evaluate the viscosity of the preparation formulation before and after the addition of STF was tested using Brookfield rheometer or Ostwald viscometer. All sample formulations selected must show pseudoplastic viscosity [22-24].

In the test sample preparations in situ ophthalmic gels levofloxacin mesylate rheological studies using the Brookfield viscometer (RV model). Simulated tear fluid (STF) with a pH of 7.4 was added by 25 ml slowly to 200 ml, then the viscosity was recorded where the gelation occurred. The STF contains 1.34 g of sodium chloride, 0.40 g of sodium bicarbonate, 0.016 g of calcium chloride, and water up to a volume of 200 ml. The pH of the solution was adjusted to 7.4 and also the solution must remain stable at room temperature [12].

In the active substance moxifloxacin hydrochloride, viscosity measurements were also carried out using Brookfield viscometer. Samples are placed in a sampler tube and analyzed at 37 °C±0.5 °C with a circulating bath connected to a viscometer adapter then angular velocity on the spindle will increase 1 to 4 and viscosity measurements [13].

For preparations containing the active ingredient brimonidine tartrate, rheological evaluation was tested with a Brookfield viscometer. Temperature was maintained with water circulating at 37 °C while crossing the sampler. Viscosity increases gradually from 10 to 100 rpm with the same time for each rpm. Viscosity was measured in both conditions [16].

In preparations with the active substance dexamethasone sodium phosphate formulation has optimal viscosity under non-physiological conditions (50-160 cps) which can be easier when applied to the eye and an increase in viscosity under physiological conditions (471-6500 cps) which indicates the sol-gel transition occurs with fast at lacrimal pH [16].

**Gelling capacity**

| Parameter | Information                      | Ref. |
|-----------|----------------------------------|------|
| -         | No gelation                      | 14, 25 |
| ++        | Gelation occurs for several hours| 14, 25 |
| +++       | Direct gelation, and last for a long time | 14, 25 |

The gel forming capacity of the prepared formulation is determined by placing a drop of the formulation in a vial containing 2 ml of simulated tear fluid that has just been prepared and visually observed. The time taken to form the gel is recorded [12].

In the ciprofloxacin hydrochloride preparation gelling capacity testing was carried out by inserting a drop of the sample preparation into a beaker glass containing 50 ml of concentrated calcium hydroxide solution, then visually observed when the gel formation occurs [13, 14, 26].

In situ ophthalmic gel preparation with the active substance levovoxin, gel formation capacity was evaluated to be used to identify an appropriate formulation as in situ gelling system. Gel formation was determined by mixing the formulation with STF liquid in the proportion of 25:7 and visually examined. With gelling capacity '++' it shows that the gelation is immediate and permanent for several hours [21].
For the evaluation of preparations with active substance brimonidine tartrate the gelation test was carried out by adding a sample solution with STF in a ratio of 25 μl: 7 μl [16].

Testing the capacity of the gel in the preparation with the active ingredient fluconazole was determined as follows: 20 ml of sample was put into a test tube containing 2 ml of STF solution consisting of NaHCO₃, NaCl, CaCl₂, 2H₂O and water. The test temperature was 35 °C. The visual assessment time of gel formation was carried out with three tests [18].

The gel forming capacity for in situ gels with the active substance levofloxacin hemihydrat was determined by adding 1 ml of sample to the vial containing 3 ml of STF with (pH 7.4), shaken for 30 seconds and visually assessing the strength of the gel formed [18].

Clarity

The Clarity Test was observed with the help of visual inspection under good light, observations using a black and white background, evaluation to do is the rheological, organoleptic test, clarity, pH, and Gelling capacity. This test is carried out to ensure that the drug preparation is in a completely mixed state and that no foreign particles are present in the preparation [14, 17].

Measurement of pH

The pH is measured using a pH meter that has previously been calibrated using a standard buffer of pH 4 and 7 in accordance with the selected drug preparation formulation must be with a perfect visual appearance that looks as this may affect the therapeutic effect.

Visual appearance

The appearance and homogeneity of the sample is visually examined both in color and clarity. When testing the visual appearance tests of in situ ophthalmic gel formulations, should be thoroughly considered how the visual appearance that looks as this may affect the interests of patients in using medicinal preparations. Therefore the selected drug preparation formulation must be with a perfect visual appearance and does not have a pungent smell [21].

CONCLUSION

Preparations of in situ ophthalmic gel formulation must be evaluated in order to assured the quality of medicines. Physical evaluation to do is the rheological, organoleptic test, clarity, pH, and Gelling capacity. This test is useful in determining the best formulation of in situ ophthalmic gel to get a higher bioavailibility values, longer contact times and minimize side effect and can increase the therapeutic effect.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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