A COMPREHENSIVE CHEMICAL CHARACTERIZATION OF IN SITU OPHTHALMIC GEL

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Received: 17 Jun 2021, Revised and Accepted: 03 Sep 2021

ABSTRACT

In situ ophthalmic gel is a gel preparation that is initially in the form of ophthalmic solution that dripped into the eye and then the solution turns into a gel after contact with the surface of the eye. In situ gel will undergo phase change to gel due to pH, electrolyte and temperature conditions. So that the preparation of ophthalmic in situ gel is required characterization to make sure that the prepared preparations meet the standards and are safe when used. Chemical evaluation includes pH, concentration, chemical bonds, crystallization and drug and polymer interactions. The purpose of this review is to discuss the evaluation methods used in preparations, and to see whether the pH of in situ ophthalmic gel formulation that provided can meet the ideal pH requirements of the eye, so that the ophthalmic in situ gel preparation would not causing irritation and liquid tear production.

Keywords: Chemical characteristics, In situ gel, Ophthalmic, Irritation

INTRODUCTION

One of the most process limitations in eye delivery is approve and the retention of optimum drug concentrations at work sites within the eye. Ophthalmic dose forms, like solutions, ointments, gels, and compound inserts have supported the efforts to increase the ocular duration of the drug for topical application to the eye [1].

An unchanged gel could be a clear compound resolution that liquid in storage, however reborn to elastic gel that is insert into the attention because of the transition section of the compound. The advantages given by the gel increase in ocular duration and area unit bioavailable; enable delivery of doses which will be reproduced befittingly and increase patient delivery. This conversion happen as result of the compound incorporated within the system will modified because of changes in temperature, pH or solution composition of the liquid lacrimal [1, 2].

The gel forming system in situ provides the advantage of straightforward administration and prolonged retention on the surface of the attention, thus overcoming the disadvantages of standard dose forms, which might improve patient safety and increase ocular improvement, which might improve treatments and_aspect effects [3, 4].

The ideal ophthalmic drug delivery should be able to maintain drug unleash and to stay round the eyes for long delivery [5].

The completion-to-gel activity will occur because:

a. Physical stimulus: these embrace changes in temperature, electrical fields, and light.

b. Chemical stimuli: enable changes in pH and activated ions from biological fluids.

c. Organic chemistry stimuli: these embrace changes in atomic number 20 levels [6, 7].

The gel will divided into 3 varieties supported their section change: sensitive to temperature, sensitive to pH, and sensitive to strength. Temperature-sensitive materials largely embrace block copolymers and poloxamer [8], pH sensitive materials embrace cellulose ester and carboxylic acid polymers, which, by dynamic the pH worth of the setting, will accessed via section [9].

Gels in places that area unit sensitive to a larger pH use carbohydrates and alternative additional acidic polymers, and their low pH will cause irritation to the surface of the attention [10].

The formation of gels elsewhere created supported physiological stimulation shape by gels created with changes in pH. During this system, the model resolution triggered by a amendment in pH. At pH 4.4 the formulation could be a flow resolution that will increase the action pH is raised by tear fluid to pH7.4. The pH changes around 2.8 units once step by step from the pH 4.4 formulation into the tear film resulting in a really speedy transformation from liquid latex to thick gel. Nucleon in response to changes in environmental pH. Polymers with giant amounts of ionising teams referred to as polyelectrolytes. Swelling of the colloidal gel will increase the compilation of pH on the far side increasing the weak (anionic) acid cluster. Medicine developed in liquid solutions have many limitations as well as bioavailability and alignments to distill by tear fluid. To approve these factors and exploit the delivery of this drug by creating poly (acrylic acid) (PAA) resolution that can gel at pH 7.4 we have a tendency to found that at high concentrations it causes gelation on the surface of the attention before being neutral by lacrimal fluid. This drawback is solve largely by transferring PAA with consistency enhancing compound HPMCs that turn out a pH responsive compound mixture containing an answer at pH four and a gel at pH 7.4 [11].

METHOD

Article review contains a review of several published articles. The process of finding sources from this review article in May 2020 carried out through Pubmed using the keyword "Chemical characterization of In situ ophthalmic gel". The search for keywords in detail is as follows: “In situ ophthalmic gel [All Sectors] AND” Chemical characterization [“All Fields”] AND “Evaluation” [“All Fields” AND “Drugs”] [All Fields] by sorting [Year of Publication] in the last 5 y, and NOT “Reviewing articles”. From 50 journals after sorted by inclusion and exclusion criteria, 30 journal references used in this journal review.

Chemical characterization

The chemical characterization of a preparation needs to known in order to guarantee that a drug or preparation meets the requirements and can used safely. Chemical characteristics include: crystallization, concentration, pH, drug interactions with polymers, and others related to other chemical bonds.
RESULTS AND DISCUSSION

Table 1: Chemical characterization of \textit{in situ} ophthalmic gel preparations in the past 5 y

| No | Active substance        | Method                        | Evaluation of chemical | Chemical evaluation results                                                                 | References |
|----|-------------------------|-------------------------------|------------------------|------------------------------------------------------------------------------------------------|------------|
| 1  | Ketorolac Tromethamine  | HPLC, Differential Scanning Calorimetry (DSC), FTIR | pH and concentration | The pH is neutral, ranging from 6.43±0.1 to 7.06±0.01 and the concentration of P407 increases in concentration P407: P188 (23:10 w/v%) and (23:15 w/v%) | [13]       |
| 2  | Ciprofloxacin           | HPLC, FTIR                   | pH                     | 7                                                                                                | [14]       |
| 3  | Vancomycin              | UV Spectroscopy, Differential Scanning Calorimetry (DSC), FTIR | pH                     | 4.8±5                                                                                            | [15]       |
| 4  | Levofloxacin Hemihydrate| UV Spectroscopy, FTIR        | pH                     | 7.05–7.24                                                                                        | [16]       |
| 5  | Brinzolamide            | HPLC                          | Concentration dan pH   | 6.06–6.54                                                                                        | [17]       |
| 6  | Betaxolol hydrochloride | HPLC                          |                        | Concentration poloxamer 407 (P407) (22% (b/v)) and poloxamer 188 (P188) (3.5% (b/v)) and pH = 6.51–6.52 | [18]       |
| 7  | Celecoxib               | HPLC, UV Spectroscopy        | pH                     | 7.6–7.8                                                                                          | [19]       |
| 8  | Ketoconazole            | HPLC, Differential Scanning Calorimetry (DSC), FTIR, XPRD | pH                     | Crystallization, interactions between drugs and polymers, pH                                     | [20]       |
| 9  | Itraconazole            | Spectrophotometry            | pH                     | 6.60–6.84                                                                                        | [21]       |
| 10 | Moxifloxacin            | UV Spectroscopy and FTIR     | pH                     | 6.5–6.9                                                                                          | [22]       |
| 11 | Acyclovir               | HPLC                          | pH                     | 7                                                                                                | [23]       |
| 12 | Triamcinolone Acetonide| HPLC, Differential Scanning Calorimetry (DSC), FTIR | pH                     | 6.8±0.5                                                                                          | [24]       |
| 13 | Gatifloxime             | HPLC, Differential Scanning Calorimetry (DSC), FTIR | pH                     | 7.2                                                                                              | [25]       |
| 14 | Tobramycin Sulfate      | HPLC, FTIR, Differential Scanning Calorimetry (DSC) | pH, pKa, concentration | pH = 4.5–5, pKa = 6.5, Concentration = 1.25–1.5% b/v                                              | [26]       |
| 15 | Ganciclovir             | HPLC, Differential Scanning Calorimetry (DSC) | pH                     | 7.4                                                                                              | [27]       |
| 16 | Azelastine Hydrochloride| UV Spectroscopy, Differential scanning calorimetry (DSC) | pH                     | 6.9–7.1                                                                                          | [28]       |
| 17 | Levofloxacin            | UV Spectroscopy, Differential Scanning Calorimetry (DSC) | pH                     | 4.7–7.4                                                                                          | [29]       |
| 18 | Nepafenac               | HPLC                          | pH                     | 5.62–5.73                                                                                        | [30]       |
| 19 | Voriconazole            | UV and FTIR Spectroscopy     | pH                     | 4.9–7.1                                                                                          | [31]       |
| 20 | Dexamethasone           | HPLC, Differential Scanning Calorimetry (DSC), and FTIR reversed-phase HPLC | pH                     | 6.56±0.15                                                                                        | [32]       |
| 21 | Brimonidine tartrate    | HPLC                          | pH                     | 7                                                                                                | [33]       |
| 22 | Ketotifen               | HPLC                          | pH                     | 6–8                                                                                              | [34]       |
| 23 | Brinzolamide Dimethyl Sulfoxide | FTIR and Raman Spectroscopy, UV Spectroscopy | pH                     | 6.8–7.2                                                                                          | [35]       |
| 24 | Bimatoprost             | HPLC, Differential Scanning Calorimetry (DSC), FTIR | pH                     | 7.2                                                                                              | [36]       |
| 25 | Besifloxacin            | HPLC, UV Vis Spectroscopy    | pH                     | 4.7–5.2                                                                                          | [37]       |
| 26 | Dorzolamide Hydrochloride| UV Spectroscopy              | pH                     | 5.16±0.01                                                                                         | [38]       |
| 27 | Giprofloxacin Hydrochloride| Spectrophotometry and FTIR | pH                     | 6.49–6.58                                                                                        | [39]       |
| 28 | Tetrahydrozoline        | HPLC, FTIR                   | pH                     | 6.8–7.4                                                                                          | [40]       |
| 29 | Acetazolamide           | UV Vis Spectrophotometry     | pH                     | 5.4–5.7                                                                                          | [41]       |
| 30 | Loteprednol             | HPLC                          | pH                     | 7.40–7.55                                                                                        | [42]       |

Evaluation method of drug content

HPLC

HPLC method is the most method widely used to characterize a preparation, one of which is evaluation of drug content. Active substances that use the HPLC method, namely Ketorolac tromethamine, Ciprofloxacin, Levofloxacin Hemihydrate, Brinzolamide, Betaxolol Hydrochloride, Celecoxib, Ketoconazole, Acyclovir, Triamcinolone Acetonide, Gatifloxime, Tobramycin Sulfate, Ganciclovir, Nepafenac, Dexamethasone, Ketotifen, Bimatoprost, Besifloxacin, Tetrahydrozine, Loteprednol and Brimonidine tartrate used reversed-phase HPLC method.

Determination of drug content was done by dissolving 0.125 ml of gel \textit{in situ} in a 25 ml mobile phase. The HPLC analysis followed by an estimated percentage of the drug [12].

Examples of procedures for evaluating drug content using the HPLC method:
Brinzolamide
A total of 1 ml of the formulation was dissolved in 100 ml phosphate buffer (pH = 7.4) before using HPLC to determine drug concentration. BLZ concentrations determined by HPLC. Separation was carried out at 30 °C using a reverse phase C18 column (5 μm, 4.6 mm). The mobile phase consist of methanol and water (60:40, v/v). The detection wavelength was 257 nm, and a flow rate of 1.0 ml/min was used.

Ganciclovir
High performance liquid chromatography system (Waters 600 pumps, Waters, Milford, MA), equipped with fluorescence detectors (HP1100, Hewlett Packard, Waldbronn, Germany) and reverse phase C8 columns (4 mm, 250 mm 4.6 mm, Phenomenex, Torrance, CA) was used for analysis. The detector used at 16 pm, at excitation and emission wavelengths of 265 and 390 nm, respectively. The mobile phase consists of a mixture of 15 mmol phosphate buffer (pH 2.5) and acetonitrile 25% pumped at a flow rate of 1 ml/min.

Napafenac
Photodiode Array Detector use to measure napafenac in formulation, release, permeation, and tissue retention studies. Kinnetex C18 reverse phase HPLC column (5 mm particles, 150 mm 4.6 mm) used for napafenac analysis. The mobile phase consists of 40:60 acetonitrile: water; the flow rate is set at 1 ml/min. The absorbance wavelength is set at 254 nm, with an injection volume of 10 ml.

Brimonidin tartrate
The reverse phase HPLC method was developed and validated for brimonidine tartrate analysis. HPLC (Shimadzu LC-20 AD) equipped with a photodiode array detector (PDA), rhodamine injector with a 20 μl loop and C18 column (chromasil, 250 mm × 4.6 mm, 50 μm particle size) were used. Optimized separation was achieved using a mobile phase consisting of a buffer of citric acid monohydrate pH 3, methanol and water (30:20:50) at 1.0 ml/min and the flow rate was detected at 246 nm.

UV-VIS spectrophotometry
The method used in the evaluation of drug content that is most widely used after HPLC is UV-Vis Spectrophotometry. In this review the method used in the evaluation of drug-polymer interactions is UV-VIS Spectrophotometry method. The active substance uses the UV-Vis Spectrophotometry method is Vancocycin, Levofloxacin Hemihydrate, Itraconazole, Metofloxacin, Azelastine HCl, Levofloxacin, Voriconazole, Brinzolamide Dimethyl Sulfoxide, Dorzolamide Hydrochloride, Ciprofloxacin Hydrochloride, and Acetazolamide.

Examples of procedures for evaluating drug content with the UV-Vis Spectrophotometry method:

Levofloxacin
Spectrophotometric method (Variant Cary 60) developed using pure water as a solvent system. For the formulation test analysis, an accurate amount of weighing in situ gel solution (1 ml) is equivalent to 15 mg of levofloxacin transferred into a 100 ml volumetric flask, and the volume adjusted to pure water. The prepared sample solution is dilute by transferring 3 ml of the solution in a 100 ml volumetric flask, and the volume was adjusted using purified water. The drug content of the prepared sample solution measured by a UV spectrophotometer at 289 nm. The method validated for linearity, precision, specificity, and resistance testing.

Azelastine HCl
For drug content, the weighed amount (100 mg) of Azelastine HCl loaded with ocular polymer in situ gel formulations was diluted using 5 ml of methanol. The dispersion produced by vortex uses Vortex shaker (Hicon®, New Delhi, India) and shaken for 10 min.

Bimatofloxacin
The drug content determined by diluting 1 ml of the infloxacin in situ gel formulation with 10 ml with the newly simulated tear fluid having a pH of 7.4. BSF concentrations were determined use to UV-Visible spectrophotometer at 290 nm (Shimadzu 1700, Japan) using simulated tear fluid as a blank.

Evaluation method of drug-polymer interactions
FT/IR
FTIR method is the method most widely used to characterize a preparation, one of which is evaluation of drug-polymer interactions. Active substances that use the FTIR method is Ketorolac tromethamine, Ciprofloxacin, Vancocycin, Levofloxacin Hemihydrate, Ketocnoazole, Moxifloxacin, Triamcinolone Acetonide, Tobramycin Sulfate, Voriconazole, Dexamethasone, Brinzolamide Dimethyl Sulfoxide, Bimatoproprost, Ciprofloxacin Hydrochloride, Tetrahydrozoline.

Examples of procedures for evaluating drug-polymer interactions with the FTIR method:

Ciprofloxacin
Fourier transforms infrared spectroscopy the chemical structure of a blank and loaded poly CIP (NIPAAm-MAA-VP) was studied by Fourier infrared spectroscopy (FTIR) transformation. FTIR spectra were obtained at 4 cm-1 resolution with a minimum scan of 256 per spectrum. All measurements carried out at room temperature. The spectrum of water, CO2 and KBr were reduced from the spectrum of the sample and the procedure is carried out under nitrogen gas to prevent interference with humidity.

Tetrahydrozoline
ATR FT-IR Spectrometry used to examine the spectrum of polymers, drugs, and formulations of drugs and ideal drugs, to show that the substances are compatible with each other. The substance analyzed at spectral resolution of 4 cm-1 in the frequency range of 4,000–400 cm-1 using the ATR-FTIR Spectrometer (Perkin Elmer, Spectrum 100 FT-IR Spectrometer). The peak position was determined using Perkin Elmer Spectra Version 6.0.2 Software.

Differential scanning calorimetry (DSC)
The method used in the evaluation of drug-polymer interactions that is widely used is Differential Scanning Calorimetry (DSC). In this review the active substances using the Differential Scanning Calorimetry (DSC) method is Ketorolac Tromethamine, Vancocycin, Ketocnoazole, Triamcinolone Acetonide, Cefuroxime, Tobramycin Sulfate, Ganciclovir, Azelastine Hydrochloride, Levofloxacin, Dexamethasone, Bimatoprost.

Examples of procedures for evaluating drug-polymer interactions with the DSC method:

Ketorolac tromethamine
The DSC study conducted at Mettler Toledo DSC 822e0, Switzerland. Medicines, polymers (P407 and P188) as well as their physical mixture (PM) with KT were weight separately in an aluminum pan, covered with an aluminum lid and tightly sealed using a pan press (Thermal Science, USA). Once on the calorimeter, the temperature of the pan gradually rises from 25 °C to 300 °C at a speed of 10 °C/min. Nitrogen is clean at a flow rate of 45 ml/min.

Trimcinolone acetoinde
Differential scanning calorimeters (DSC 25, TA instruments, New Castle, DE, USA) are used to observe the fusion and recrystallization behavior of drugs with excipients. Samples for DSC analyze include TA and the physical mixture of the lipid phase (in the same ratio as for the formulation) were melted and compacted. Estimate. 5 mg of sample, each sealed in an aluminum pan, placed on the sample platform. Reference pan, aluminum pan sealed empty, placed on the reference platform. The pan is heat from 25 to 32 °C at a rate of 20 °C/min under a nitrogen purifier (20 ml/min).

Levofloxacin
The thermal behavior of levofloxacin, physical mixture of levofloxacin and polymers and lyophilized preparations studied by differential scanning calorimetry (DSC) using Perkin Elmer 7 DSC (Waltham, MA). Samples were analyze by scanning at 4–40 °C at a rate of 5 °C/min in a nitrogen gas environment (20 ml/min).
XPRD
The XPRD method used in the ketoconazole formulation. The crystalline state of the NPs of the prepared drug compared to that of the pure ketoconazole powder was studied using XRPD (D/2θ, 2500; Rigaku, Tokyo, Japan). The diffraction patterns of the samples recorded at a scan speed of 0.5000 degree/min.

pH determination method
The method of checking pH with a device called a pH meter. Each formulation examined by dispersing 25 g of the formulation in 25 ml of pure water. The pH meter must calibrated before use with buffer solutions at pH 4 and 7 [13].

However, the discussion this time explains more about the pH of a preparation. Because every piece of literature is list, all the formulations characterize the pH of the preparation.

Chemical characteristics of some active substances in situ gel opthalmic preparations over the past 5 y:

**Ketorolac tromethamine**
The resulting preparations are clear and transparent both in a liquid and gel state. Concentration of P407 increased concentration of the pH of the preparation. Concentration formulations of P407 and P188 are set to 22% (w/v) and 3.5%. Formulations containing 22% (w/v) P407 and 3.5% (w/v) P188 meet the requirements. The pH value of the solution in situ found to be between 6.5-6.52 for all formulations [16].

**Ciprofl oxacin**
Ciprofl oxacin (NIPAAm-MAA-VP) poly nanoformulation used as an eye delivery system represents both temperature and gelation properties that are triggered by in situ pH. PNIPAAm (thermosensitive polymer) combined with MAA (pH-sensitive polymer) was used as a gelling agent. The formulation developed is a clear solution, which converted into a gel at temperatures above 36°C and pH 7 [14].

**Vancomycin**
The pH of the in situ gel forming system ranges from 4.8 to 5.1 for all formulations, which are suitable for ophthalmic applications [15].

**Levofl oxacin hemihydrate**
Gellan-based processed compositions prepared in situ ophthalmic solution forming levofloxacin gel. All formulations designed found to have test, pH, and osmolality in an acceptable range. For the pH test it produces a range of 7.5-7.74 which is within the acceptable range [16].

**Brinzolam ide**
For each batch formulated, the pH value was measured using a pH meter that was previously calibrated using a standard buffer of pH = 4.0 and pH = 7.0 according to established procedures. The pH value of solution in situ found to range between 6.06 and 6.54 for all formulations [17].

**Betaxolol hydrochloride**
Concentration formulations of P407 and P188 are set to 22% (w/v) and 3.5%. Formulations containing 22% (w/v) P407 and 3.5% (w/v) P188 meet the requirements. The pH value of the gel solution in situ found to be between 6.5-6.52 for all formulations [18].

**Celecoxib**
Initial pH values for Celecoxib formulations were in the range of 7.6-7.8. After 6 mo, there was little or no change in the pH value of the formulations stored at 30 °C and 35 °C, because their pH values maintained in the range 6.8-7.8 at 30°C and 6.4-7.8 at 35°C. This pH value was still in the range pH that easily tolerated by natural buffering of the eye system without irritation or discomfort [19].

**Ketoconazole**
No peak drug characteristics observed in the formulations that contained NP PLGA drugs, which is evidence that there were no crystalline medicinal ingredients in optimized drug formulations. This is an indication of changes in drug crystallinity and homogeneous drug dispersion in the PLGA matrix. The results of ketoconazole crystallization are amorphous and there is no interaction between the drug and its polymer and pH 7.4 for all formulations [20].

**Itraconazole**
The pH of all formulations before gelation that found towards acidic side (2.8±0.50-3.20±0.40) and after gelation, it shifted to 6.60±0.15-6.84±0.34. This explains the ability of the sol-to-gel transition in eye instillation. In addition, formulations with a pH range of 6.8-7.4 considered safe and acceptable for ocular delivery [21].

**Moxifloxacin**
Gel formed in situ shows the release of the drug with a pH free time for more than 10 h due to the presence of nanoparticles containing moxifloxacin. pH is between 6.5-6.9 for all Moxifloxacin formulations [22].

**Acyclovir**
In situ gel matrix formulations based on KC and HPMC were carried out in 500 ml of simulated tears prepared at pH 7.0 using the dialysis method [23].

**Triamcinolone acetonide**
The pH of the Triamcinolone formulation is 6.8±0.5, which is close to the pH of the lacrimal liquid. Therefore, Triamcinolone with 0.3% (F13) of gellan gum was considered optimal and used for further learning [24].

**Cefuroxime**
A weighted PF127 (14% w/v) was added to E1 to obtain M-TNH. SLN-based nanocomposite thermo-sensitive (S-TNH) hydrogels were prepared as follows: SLN made from E2 by the method reported above; after precipitation, a weighted amount of PF127 (20% w/v) added to the SLN aqueous dispersion to obtain S-NTH. In both cases, 7.2 was the pH produced [25].

**Tobramycin sulfate**
The level of chitosan protonation basically depends on pH, because it is a weak polycationic polymer with pKa 6.5. The pH of the TPP 5.0 solution and the chitosan solution between 4.5 and 5.0 with an increase in chitosan concentration from 0.5 to 1.5% w/v [26].

**Ganciclovir**
pH of the preparation = 7.4 on the ganciclovir preparation produced [27].

**Azelastine HCI**
The pH of Azelastine Hydrochloride the previous formulations gelated more towards the acid side (3.20±0.60 to 3.80±0.30) and after the gelation shifted to 6.90±0.11 to 7.1±0.54. Explain that the ability of the sol to transition gel in ocular gradually. In addition, formulations in the pH range of 6.8 to 7.4 considered safe and acceptable for eye delivery [28].

**Levofloxacin**
The selected gel in situ prepared turns out to be clear and light yellow in color. The formulation remains in a liquid state at pH 4.7 but is immediately convert into a gel at pH 7.4, when applied to the eye [29].

**Nepafenac**
The pH of the nepafenac formulation is 5.73, 5.62, 5.63, respectively. pH is still safe and can accepted by the eyes [30].

**Voriconazole**
The Voriconazole in situ gel formulation characterized, which showed a pH of 4.9-7.1 that was still eligible [31].
Dexamethasone
The Voriconazole in situ formulation gel formulation was characterized, which showed a pH of 6.56±0.15 which was still eligible [32].

Brimonidine tartrate
All formulations found to be transparent above pH 7 (physiological conditions). The pH of the formulation adjusted to 4.0±0.1 with the addition of a 0.5 M sodium hydroxide solution. The pH of the therapeutic agent applied to the eye can vary from 3.5 to 8.5. The capacity of gel formation observed in tear fluid. Gel capacity indicates that the formulation will get the gel under physiological conditions [33].

Ketotifen
The pH of the formulation is between 6.0 and 8.0 which indicates the Ketotifen formulation meets the requirements [34].

Brinzolamide dimethyl sulfoxide
In the aqueous phase, thromethamine (Tris buffer) add to pure water and the pH is adjusted between 6.8 and 7.2 using 1 M orthophosphoric acid using an Orion Star A211 pH meter, India [35].

Bimatoprost
The pH of the Bimatoprost formulation is 7.2 which indicates the Bimatoprost formulation meets the requirements [36].

Besifloxacin
Besifloxacin formulations are liquid at room temperature with a pH range of 4.7-5.2 and were converted to a gel phase at pH 7.4, that is, tears with isotonic for physiological (tear) tears [37].

Dorzolamide hydrochloride
The Dorzolamide HCl formulation has a pH value of 5.1±0.01. pH is an important parameter in the reception and tolerance of the formulation by the eye. The tear pH is around 7.4 with a buffering capacity that tolerates a pH of around 4-8. pH values outside this range, due to stimulate flushing and tearing, reduce the bioavailability of the drug. In this study, all formulations were prepared using phosphate buffer pH 5.8 as a solvent. It should noted that DRZ has a pH of 4-6 that is the highest stability [38].

Ciprofloxacin hydrochloride
The pH of the gel solution in situ found to be around 6.49-6.58 for all formulations. The Ig3 formulation has a pH of 6.53 which is an acceptable range for eye preparation [39].

Tetrahydrozoline
The pH of the Tetrahydrozoline formulation produces a range 6.87 to 7.4. After 3 mo, the stability of the gel in situ was re-evaluated resulting in successful pH of 6.76; 6.98; 7.1 [40].

Acetazolamide
The pH value of the prepared AZA NE is in the range of 5.4 to 5.7. Therefore, it is sufficient for their application to the eye because the NE prepared is not buffer and can adjusted to physiological values with tears. The value obtained is also able to maintain the stability of the drug, because AZA is very unstable at the base pH value and has a pH value of 4.5 at maximum stability [41].

Loteprednol
The ophthalmic dosage form must be clear enough and the pH must be close to the pH of the tear. All NE-ISG (NE-ISG1-NEISG5) formulations are clear and transparent with pH in the range 7.40-7.55 that meets the standards and is safe [42].

pH of in situ ophthalmic gel preparations
One of the most significant parameters is the pH of the ocular formulation. Eye pH must be maintained at normal levels (4-8), because a change from acidic to alkaline pH can cause eye injury [43, 44]. Thus, the ocular formulation that has just been prepared should not change the neutral ocular pH [45]. The pH recorded from the gel in situ meets requirements can be assumed that the gel in situ will not cause irritation and immediate tear fluid production [46].

Tears have a average pH of 7.4 and do not have a strong buffering system. Therefore, the pH of the eye drops given will determine the eye’s current pH. If the eye drops are acidic, they can cause the formation of insoluble complexes from denatured proteins. Strong alkaline eye drops will also damage the eye cell membrane integrity. Therefore, the ideal eye drug must have a pH between 6.8 and 7.4 [47]. However, pH values from 3.5 to 8.5 can be tolerated if they are not made or only very little buffered because in this case the buffer capacity of the tears is able to adjust the pH physiologically to the administrative level [48, 49].

pH affects the solubility and stability of the drug in an ophthalmic formulation. It must be such that the formulation will remain stable at that pH. The pH of the in situ gel system prepared after addition of all ingredients will measure using a pH meter [50].

CONCLUSION
In situ ophthalmic gel is a gel preparation that is initially in the form of ophthalmic solution that dripped into the eye and then the solution turns into a gel after contact with the surface of the eye. Evaluation methods in making in situ gel are drug content evaluations using HPLC and UV-Vis Spectroscopy methods. Then the method of evaluating drug-polymer interactions such as FTIR, DSC, and XRPD. The results of testing the pH of the preparations in this literature are still relatively safe and meet the ideal pH standard of eye fluid, 4-8. However, in general formulas the average dosage of normal dosage is 7.4 as in accordance with the pH of the tear fluid.

FUNDING
Nil

AUTHORS CONTRIBUTIONS
All authors have contributed equally.

CONFLICTS OF INTERESTS
Declared none

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