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Original Research Article

FORMULATION AND EVALUATION OF ACECLOFENAC IN-SITU GEL FOR THE TREATMENT OCULAR INFLAMMATORY DISEASES

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ABSTRACT

In situ gels are solutions or suspensions that can undergo rapid sol-to-gel transformation when stimulated by external stimuli such as temperature and pH during instillation. The primary disadvantage of eye drops is that the drug is rapidly eliminated from the precorneal region, resulting in poor bioavailability and therapeutic efficacy. To overcome these constraints, an ion-triggered in situ gel for sustained aceclofenac delivery was developed. Aceclofenac is a medication used to treat eye inflammation. The in situ gel was made up of two polymers: hydroxypropyl methylcellulose (HPMC) and sodium alginate. Formulations were chosen and further characterised for viscosity, in vitro release studies based on various physicochemical evaluation parameters such as pH, clarity, and gelling capacity. The optimised in situ gel (A5) achieved 90.14 percent drug release in 12 hours, demonstrating the in situ gel's sustained release nature. Thus, when compared to conventional systems, in situ gel-based systems containing gums can be a valuable approach for ophthalmic drug delivery.

Key words: Stimuli, Instillation, Ion-triggered, Bioavailability, Efficacy, Conventional.

INTRODUCTION:

Topically applied ophthalmic medications are frequently used to treat ocular inflammatory diseases. Ophthalmic in-situ gel formulations are frequently used to treat ocular inflammatory diseases such as uveitis, scleritis, and episcleritis (Rajesh et al., 2017). Topical medication application in the eyes results in a larger concentration at the local location with fewer overall adverse effects. Eye drops are the most often utilised medication type for the treatment of ocular disorders (Wadhwa et al., 2019). They are a safe, uncomplicated, and patient-friendly composition that accounts for about 90% of the current marketed eye products. Conventional eye drops have limited bioavailability due to the unavoidable pre-corneal evacuation of drugs, however this problem can be solved with the in situ gel formulation (Jain, 2016). Due to

environmental changes, in situ liquid rapidly converts into viscoelastic gels when delivered into the cul de sac of the eyes (Wu et al., 2019; Mohanty et al., 2018; Majeed and Khan, 2019).

Aceclofenac is a great nonsteroidal anti-inflammatory, analgesic, and antipyretic medication. NSAIDs are recommended for the treatment of a variety of pains and inflammatory eye conditions. Aceclofenac works by blocking the cyclooxygenase enzyme pathway (Iolascon et al., 2021; Raza et al., 2014). Due to the lipophilic nature of the drug it will be better absorbed by the cornea and tissue and will show better action (Dave et al., 2013). Rathapon Asasutjarit et al. successfully created an ophthalmic thermoresponsive in-situ diclofenac gel with increased ocular bioavailability when compared to conventional ophthalmic preparations (Asasutjarit et al., 2011).

The polymer sodium alginate, which forms an instantaneous gel due to calcium alginate formation as a result of its interaction with the divalent cation (Ca+2) present in lachrymal fluid (pH 7.4). When divalent cations are present, alginate can be ionically crosslinked. Hydroxy Propyl Methyl Cellulose (HPMC) is used as a viscosity enhancer to help achieve sustained drug delivery (Makwana et al., 2016; Liu 2006).

The current study aimed to prepare and characterise an aceclofenac ion activated in situ ophthalmic gel for the treatment of ocular inflammatory diseases. As a result, the novelty of the current work lies in the design and development of an in situ gel system to increase the precorneal residence time of the aceclofenac.

MATERIAL AND METHOD

Materials:

Aceclofenac was obtained from S.P. Pharmaceuticals in Jalgaon, as was sodium alginate, HPMC E5 and all other chemicals and reagents from LOBA Chemie.

Method:

UV Spectrophotometric Study:

Determination of λ max:

The absorption maximum of the standard solution was scanned between 200-400 nm regions on UV-visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

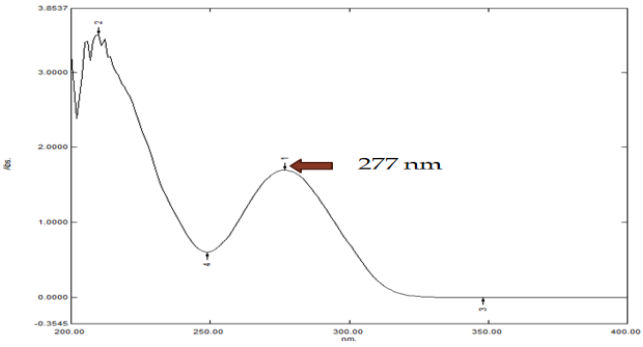

Fig. 1: λmax of aceclofenac

Development of Standard Calibration Curve of Aceclofenac in Ethanol:

Preparation of stock solution: Accurately weighed 10 mg of Aceclofenac was dissolved in 100 mL of distilled water to get the concentration of 100 µg/mL. Aliquots of 0.1 mL up to 0.6 mL from the stock solution representing 1 up to 6µg/mL of drug were transferred to 10 mL volumetric flask and the volume was adjusted to mark with same blank solution (Ethanol). Absorbance of the above solutions were taken at 277 nm against the blank solution prepared in the same manner without adding the drug. A graph of concentration vs. absorbance was plotted (Makwana et al., 2016).

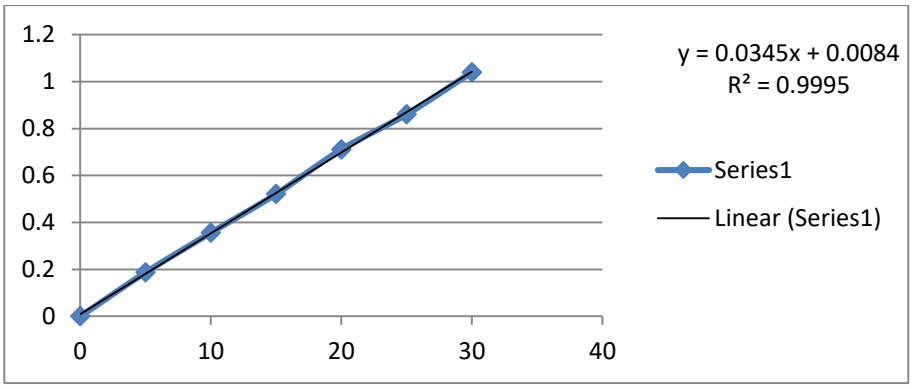

Fig. 2: Calibration curve of aceclofenac

FTIR spectroscopy:

The infrared spectrum was generally used as an Identification parameter to know the chemical structure of drugs. For the FTIR spectrum of Aceclofenac FTIR spectrophotometer was used. A small quantity of sample was mixed with sufficient potassium bromide and compressed into a pellet by applying a 10 tons pressure with help of a hand operated press. This pellet was kept in a sample holder and scanned from 4000 to 400 cm-1. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum (Skoog and Holler, 2017).

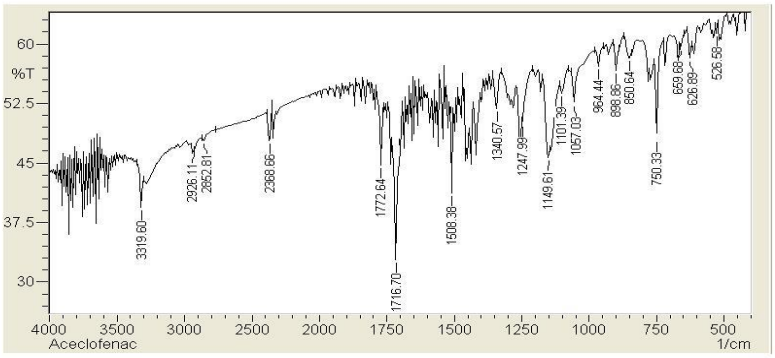

Fig. 3: FTIR Spectra of aceclofenac

FT-IR Spectrum of drug shows characteristics peaks at 3319.60cm^{-1} indicates the presence of Amines, 2926.11 & 2852.81cm^{-1} exhibits Alkanes, 2368.66cm^{-1} exhibits Alkynes, 1716.70cm^{-1} exhibits Carboxylic acid, 1508.38cm^{-1} exhibits Aromatic rings, 1149.61 & 1067.03cm^{-1} exhibits Alcohol & Ethers, 898.86 & 750.03cm^{-1} exhibits Alkanes. These functional groups confirms the structure of aceclofenac.

Formulation of aceclofenac in-situ gel:

Two polymers were separately, dissolved in 25 mL of water, and left to hydrate for 2 hours. After stirring for 1 hour, the two polymer solutions were combined. A 100 mg of aceclofenac was dissolved in 25 ml of phosphate buffer pH 7.2. The polymer and medication solution were then thoroughly combined with constant stirring. Finally, 0.01 percent v/v benzalkonium chloride was added as a preservative, and the volume was make up to 100 ml. The final formulation was stirred for 1 hour. The created formulations were sterilised in an autoclave (121^{0}C and 15 pressure) for 20 minutes before being stored aseptically for further testing (Jain et al., 2021; Makwana et al., 2016).

Table 1: Formulation of in-situ gel.

Ingredients	A1	A2	A3	A4	A5	A6
Aceclofenac (mg)	100	100	100	100	100	100
Sodium alginate (gm)	1	1	0.5	0.5	1.5	1.5
HPMC E5	0.5	1	0.5	1	1	0.5
Distilled water	100	100	100	100	100	100

Evaluation Parameter:

1. Clarity test:

Visual inspection in good light, against a black and white background, with the contents set in motion with a swirling action, was used to determine clarity. It was also observed for the formation of turbidity or the presence of any unwanted particles dispersed in the solution(Kotreka et al., 2017; Makwana et al., 2016; Jain et al., 2021).

2. pH measurement:

pH was measured with a pH metre that had previously been calibrated using standard buffers of pH 4 and pH 7 according to the established procedure (Ranch et al., 2019; Makwana et al., 2016; Vijaya et al., 2017).

3. Gelling capacity:

A drop of the prepared formulation was placed in freshly prepared simulated tear fluid (Composition of simulated tear fluid Sodium chloride (NaCl) 0.670 g, Sodium bicarbonate 0.2 g, Calcium chloride dihydrate 0.008 g, Purified water 100 mL and 0.1 N Hcl for pH adjustment upto pH 7.4) to determine its gelling capacity. and was visually observed for gelling time. Coding for the gelling capacity described in Table 2 (Kurniawansyah et al., 2020; Mandal et al., 2012).

4. Rheological studies:

The viscosity of the in situ gel preparations in their sol and gel form were studied using a Brookfield rheometer(Mandal et al., 2012; Liu et al., 2010).

5. Drug content:

1 ml of the developed formulation was dissolved in 100ml phosphate buffer (pH=7.4) followed by spectrophotometrically estimation of the aliquot to determine drug concentration (Makwana et al., 2016; Mandal et al., 2012; Gupta and Vyas, 2010).

6. In-vitro diffusion studies:

Dissolution studies of samples were performed using Franz diffusion apparatus and simulated tear fluid as a dissolution medium. The temperature was maintained at 37±0.5 °C with the speed of rotation maintained at 100rpm. The samples were taken at various time intervals and spectrophotometrically analysed for drug content (Mundada and Shrikhande, 2008; Séchoy et al., 2000).

7. Sterility studies:

Sterility testing was conducted as per Indian Pharmacopoeia by using Membrane filter (0.22 micron). The study was performed by incubating optimized in situ gel preparation (A5) for a period of 14 days in fluid thioglycolates medium at 35^0C and soybean casein digest medium at 25^0C. Presence of growth of bacteria or fungus if any, is noted down (Puranik et al., 2015; I.P. 2010).

RESULT AND DISCUSSION:

1. Clarity test:

The formulations (A1-A6) were created by combining different concentrations of sodium alginate with different ratios of HPMC. All of the formulations were clear, with no turbidity, suspended particles, or impurities.

2. pH measurement:

The pH of the all formulation in situ gel solution was found to be around 6.45–6.57. The pH of the formulation A5 is 6.57, which is within the acceptable range for ophthalmic preparations.

3. Gelling capacity:

Gelling capacity is coded as shown in Table 2. According to that A1, A3, A4 occurs Gelation immediate, remained for few hours and A2, A5, A6 occurs Gelation immediate, and for extended period.

4. Rheological studies:

The formulations viscosity was directly proportional to their polymeric content. Addition of higher concentration of HPMC led to increase in the viscosity of formulations and exhibited more pseudo-plasticity. The higher concentration of sodium alginate and HPMC among the developed formulations A5 produces good results, and this batch is chosen as the optimised batch.

5. Drug content:

The drug content of the in situ gel was found to be in between 42.73- 95.93. The drug content of the developed formulation A5 is 95.93, and this batch is selected as optimized batch.

6. In-vitro diffusion studies:

In the case of aceclofenac in situ gel, the percentage drug release was found to be 93.72 percent in 12 hours. Thus, the in vitro dissolution test demonstrated the sustained release nature of aceclofenac in situ gel.

7. Sterility studies:

Due to the absence of turbidity, the in situ gel preparation (A5) passed the sterility test. After 14 days of incubation in soya bean casein digest and fluid thioglycolate media, there was no microbial growth.

Table 2: Results of insitu gel.

Formulation code	Appearance	Clarity	pH	Gelling capacity	% Drug content
A1	Light yellow	Clear	6.54	++	59.76
A2	Light yellow	Clear	6.49	+++	71.46
A3	Light yellow	Clear	6.45	++	42.73
A4	Light yellow	Clear	6.52	++	45.93
A5	Light yellow	Clear	6.57	+++	95.93
A6	Light yellow	Clear	6.55	+++	89.80

Table 3: Coding for the gelling capacity.

Observation	Coding
Gelation occurred in few minute and remained for few hours	+
Gelation immediate, remained for few hours	++
Gelation immediate, and for extended period	+++
Very stiff gel	++++

Table 4: Rheological studies of formulation.

Formulation code	Viscosity of solution (Pa s)	Viscosity of in-situ gel (Pa s)
A1	0.161	792
A2	0.175	820
A3	0.132	415
A4	0.189	919
A5	0.195	956
A6	0.159	602

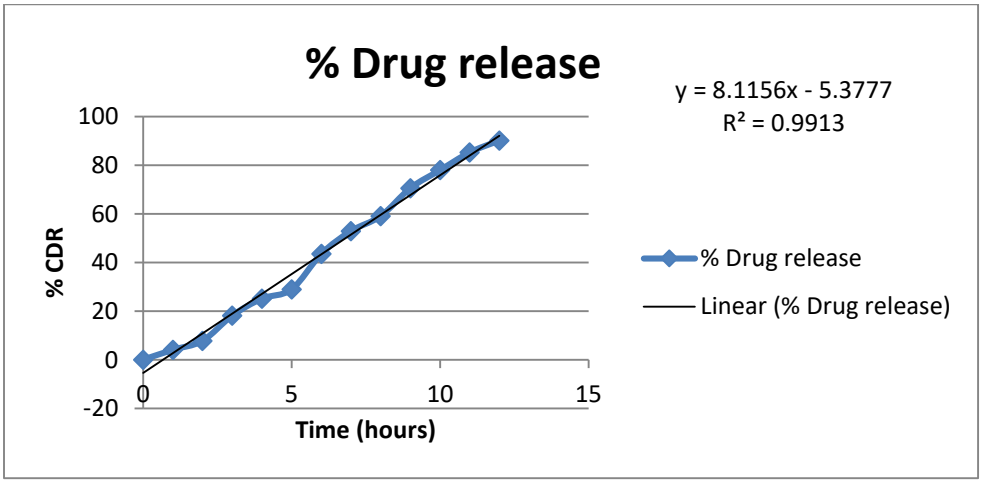

Fig. 4: Dissolution study of insitu gel

CONCLUSION:

Aceclofenac in situ ophthalmic gel was successfully developed for the treatment of ocular inflammatory infections. Thus, the above findings show that the alginate and HPMC mixture can be used as an in situ gelling vehicle to improve ocular bioavailability. This new formulation is a viable alternative to traditional eye drops due to its ability to improve bioavailability via sustained drug release and a longer pre-corneal residence time. Its ease of administration and reduced frequency of administration are also

significant, resulting in better patient acceptance.

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