



**EJPPS – European Journal of Parenteral and Pharmaceutical Sciences Volume 28 Issue 1**

**<https://www.ejpps.online/post/vol28-1-formulation-and-evaluation-of-controlled-release-bromfenac-sodium-ocular-insert>**

**DOI: <https://doi.org/10.37521/ejpps.28102>**

**Peer Review Article: Formulation And Evaluation of Controlled Release Bromfenac Sodium Ocular Insert**

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# **Formulation And Evaluation of Controlled Release Bromfenac Sodium Ocular Insert**

## **INTRODUCTION**

According to the World Health Organization, cataract operations are performed on one million people per year [1]. After cataract surgery, however, most patients still experience physiologically severe postoperative ocular inflammation. Uncontrolled intraocular inflammation causes discomfort, delayed recovery, poor visual results, and even more severe problems such as cystoid macular oedema and synechiae due to inflammatory cells and cytokines entering the aqueous humour.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat non-infectious ocular inflammation after ophthalmic surgery. As a result, NSAIDs appear to be potentially useful drugs for cataract surgery. [2]

The U.S Food and Drug Administration has approved four ophthalmic NSAIDs to treat postoperative ocular inflammation followed by cataract surgery: bromfenac sodium, diclofenac sodium, Ketorolac tromethamine, and nepafenac.[3] The first approved NSAID for treating anterior chamber inflammation during cataract surgical treatment is bromfenac ophthalmic solution. Bromfenac is a more potent drug than other drugs for treating ocular inflammation. [4]

The drug-loaded eye drop is easy to use. However, it has the inherent disadvantage that most medication is almost immediately diluted away in the tear film when the eye drops are introduced into the cul-de-sac and quickly exhausted from the precorneal cavity's constant tear flow. This process occurs more intensively in swollen eyes than in normal eyes and lachrymal-nasal drainage. [5,6] To avoid the previously stated side effects and increase the drug's effectiveness, a novel approach of an ocular insert that increases the drug's contact time in the eye should be chosen, thus improving patient compliance by increasing bioavailability and reducing frequent administration. [7]

Ophthalmic inserts are skinny discs of polymeric substances that fit into the upper or lower conjunctiva sac. They have compensations over the conventional dosage forms and possess amplified ocular residence, discharge the drugs at a slow and consistent momentum, are capable of delivering precise dosing, lack preservatives, have augmented shelf life, and reduced systemic incorporation. [8]

Our research intended to fabricate bromfenac sodium ocular inserts to amplify the contact time and offer a controlled release model that could advance patient compliance, cut dosing frequency, and attain superior curative usefulness.

## **MATERIALS AND METHODS**

Bromfenac sodium was purchased from Enaltec Labs Pvt. Ltd. Madhya Pradesh, India. HPMC was procured from Bestcare Formulation Pvt. Ltd. Thirubuvanai and glycerol was acquired from Fischer labs. All other reagents and solvents used were of an analytical grade.

### **Formulation optimisation of the ocular insert:**

The bromfenac ocular inserts were prepared using the solvent casting method with polymers and plasticizers [8, 9]. The eleven batches (F1 to F11) of the test formulations were prepared using drugs and polymer-combinations, as shown in Table 1. The polymer was dissolved in methanol: chloroform (1:1) (total 20 ml) solution under stirring conditions. The weighed amount of bromfenac (10 mg) was added to the above solution and stirred for 12 hours at controlled room temperature to get uniform dispersion. After proper mixing, the resultant casting solution (5 ml) was poured into a clean glass

petri dish (area 50.27 cm<sup>2</sup>) and left at room temperature for 48 hours, covered with an inverted funnel for slow and even evaporation. The dried films were cut into circular pieces of 8 mm in diameter containing 0.100 mg of the drug and stored in a hermetically sealed container (desiccators) at controlled room temperature.

Table 1: Optimisation of ocular film

| Formulation | Drug<br>(mg)<br>± 2% | Polymer      |         | Plasticizer |                  | Solvent( final volume 20 ml) |                        |
|-------------|----------------------|--------------|---------|-------------|------------------|------------------------------|------------------------|
|             |                      | HPMC<br>(mg) | EC (mg) | PEG<br>(mg) | Glycerol<br>(mg) | Methanol+<br>Chloroform      | Ethanol+<br>Chloroform |
| F1          | 10                   | 1.5          | -       | 1.5         | -                | 1:1                          |                        |
| F2          | 10                   | 3            | -       | 3           | -                | -                            | (Ethanol)              |
| F3          | 10                   | 3            | -       | 3           | -                | -                            | 1:1                    |
| F4          | 10                   | 7            | -       | 7           | -                | -                            | 1:1                    |
| F5          | 10                   | -            | 3       | 3           | -                | 1:1                          | -                      |
| F6          | 10                   | -            | 5       | 5           | -                | 1:1                          | -                      |
| F7          | 10                   | 3            | -       | -           | 0.5              | 1:1                          | -                      |
| F8          | 10                   | 5            | -       | -           | 0.5              | 1:1                          | -                      |
| F9          | 10                   | 7            | -       | -           | 0.5              | 1:1                          | -                      |
| F10         | 10                   | 8            | -       | -           | 0.5              | 1:1                          | -                      |
| F11         | 10                   | 10           | -       | -           | 0.5              | 1:1                          | -                      |

## Physicochemical evaluation of ocular inserts

### Thickness

Thickness was measured in triplicate using a calibrated Vernier calliper at different regions of the ocular insert, and the average was calculated.

### Weight variation

The weight of the ocular insert was calculated in triplicate by using a calibrated digital balance (A&D Company, Japan). They were separately weighed, and their mean weight was computed.

### pH:

The pH of the ocular inserts was determined in triplicate by allowing them to dissolve in a closed petri dish at controlled room temperature for 30 mins in 5 ml of distilled water. The dissolved solution was tested by using a calibrated pH meter (Eutech)

### Folding endurance:

This was determined by repeatedly folding a small strip of ocular film in the same place till it broke. The number of times film could be folded simultaneously without breaking gives the values of folding endurance.

### Moisture loss:

The percentage moisture loss test was carried out to check the film's integrity under dry conditions. Films were weighed and placed in a desiccator containing anhydrous calcium chloride. After three days, the films were taken out and reweighed using a calibrated digital balance (A&D Company, Japan); the percentage moisture loss was calculated using the following formula:

Percentage Moisture loss = (Initial weight - final weight)/ Initial weight ×100

**Development of calibration curve**

About 10 mg of bromfenac sodium was dissolved in 10ml of the standard flask containing distilled water. The solution was diluted to reach concentrations of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml. A 10µg/ml solution was scanned from the 400 to 200nm spectrum to find the  $\lambda$  max. At  $\lambda$  max (268nm), the absorbance of each solution of varying concentrations was measured by plotting absorbance vs. concentration.

**Drug content:**

Drug content was estimated by placing an ocular insert in 100 ml of distilled water with a stirring condition for 5 minutes using a magnetic stirrer at controlled room temperature. The solution was filtered to measure the absorbance in a UV–Visible Spectrophotometer (UV-1700, Shimadzu) at 268nm.

**In vitro drug release studies**

The in vitro drug release was studied for ophthalmic inserts using an egg yolk membrane as corneal epithelium. The membrane was tied at the one end of the open cylinder, which acted as a donor compartment. An ocular insert was placed inside this compartment with 10 ml of distilled water, ensuring the whole surface of the membrane was in contact with the receptor compartment containing 50 ml of water (pH7). The content of the receptor compartment was stirred continuously at 25 rpm using a magnetic stirrer. Samples of 5ml were reserved from the receptor partition at the episodic gaps (20, 40, 60, and 80 minutes) and substituted by an equal volume of distilled water. The samples were examined in a UV Visible Spectrophotometer (UV -1700, Shimadzu)) at 268nm against water as blank. [7, 10]

**Fourier Transform Infrared Spectroscopy (FT-IR) analysis:**

The compatibility studies were carried out to check any interactions between drugs and excipients. The FT-IR spectrum of bromfenac sodium alone and with polymers is determined using an FT-IR (4100, JASCO) instrument scanning range from 4000- 400 cm<sup>-1</sup>. [11]

**Sterility testing**

This was done for detecting the presence of viable forms of microorganisms in the preparation. The preparations of ocular inserts were sterilized by UV radiation. Soyabean Casein Digest Medium was prepared as follows. About 40 g of soybean casein digest medium was suspended and boiled to dissolve the medium completely. It was sterilized by autoclaving at 15 lbs pressure at 121°C for 15 min. Three sterility test bottles were used in the study and labelled as "positive control," "negative control," and "test" and incubated for seven days to observe microbial growth.

## RESULTS AND DISCUSSION

The result of the optimization of the ocular insert is shown in Table 2.

The use of plasticizer PEG gave hard, thin films, which were brittle when peeling was attempted, as shown in Figure 1.

Using the ethylcellulose polymer whitish films forms-as shown in Figure 2.

The HPMC: Glycerol (in the ratio of 10:0.5), and solvent system of methanol: chloroform (in the ratio of 1:1) furnished an optimum film formation, as shown in Figure 3. Hence the formulation F11 was selected for further evaluation and In vitro studies. Three batch of the optimized formulation (f11) was prepared.

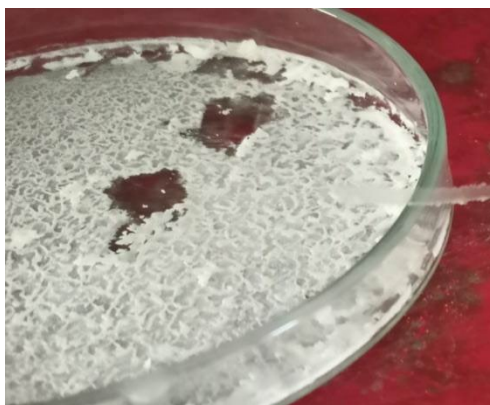
**Table 2.** Results of optimisation of the ocular insert

| Results      |                              |
|--------------|------------------------------|
| Formulations |                              |
| F1           | Thin film                    |
| F2           | Recrystallised               |
| F3           | Hard film                    |
| F4           | Brittle film                 |
| F5           | Whitish film                 |
| F6           | Whitish thin film            |
| F7           | Films were difficult to peel |
| F8           | Very thin film               |
| F9           | Thin film                    |
| F10          | Thin film                    |
| F11          | Good film                    |

**Figure 1.** Effect of PEG on film formation (we observed brittle film)



**Figure 2.** Effect of Ethylcellulose on film formation (we observed white, uneven film)



**Figure 3.** Effect of HPMC on film formation (F11) (we observed the transparent film peeling evenly and entire from the casting plate.)



### Physicochemical evaluation

Formulation (F11) with bromfenac sodium, HPMC, and glycerol shows perfect ocular insert fabrication. They were observed as translucent thin films. The texture and appearance were smooth, uniform, and without noticeable cracks or defects.

The physicochemical assessment data are offered in Table 3. The thickness of the films varies from 0.1mm to 0.2mm. All the ocular inserts from formulations (F11) exhibited uniform thickness with low standard deviation values, ensuring the uniformity of the films. Hence, formulations were not chunky enough to generate annoyance while insertion and being in a cul-de-sac.

The results of the average weight of formulation (F11) of the ocular insert, as shown in Table 3, vary from 3.0 mg to 3.2 mg and indicate that there was no significant weight variation indicating an excellent distribution of the drug, polymer, and plasticizer. (Table 3)

The drug content of the formulation (F11) was found to be 0.101 mg to 0.106 mg, and the average is shown in table 3. The results showed that the harmonised distribution of the drug and the process used to fabricate the ocular insert gave precise results.

The ocular film's pH was determined using a pH meter; the ocular film was dissolved in 5ml of distilled water, and pH was measured. The pH of the films was 7.9 to 8.1, and the average is shown in Table 3, indicating that the inserts would not modify the pH of the tear solution in the eye.

The folding endurance of formulation (F11) was good, and the maximum and minimum folding endurance for the ocular films was 91 and 67, respectively, and the average is shown in Table 3. This result shows enough strength of the ocular insert to withstand handling shock.

The moisture loss study over three days at controlled room temperature revealed that the maximum moisture loss was 1.8% and minimum moisture loss was 1.2%, and the average is shown in Table 3. By observing the physical appearance of the dried ocular inserts over the three days of the study, there was no noticeable alteration in the physical status, and they maintained their integrity under dry conditions.

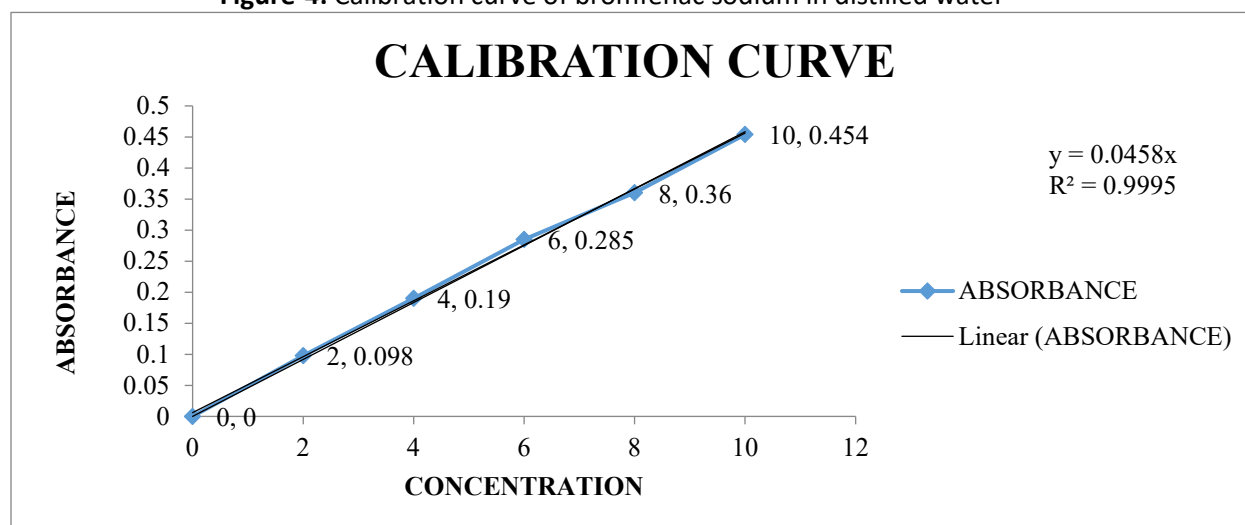
**Table 3:** Physicochemical evaluation of bromfenac sodium ocular inserts (F11)

| PARAMETERS           | AVERAGE $\pm$ SD |
|----------------------|------------------|
| Thickness(mm)        | 0.133 $\pm$ 0.06 |
| Weight variation(mg) | 3.1 $\pm$ 0.10   |
| Drug content(mg)     | 0.103 $\pm$ 0.01 |
| pH                   | 8.0 $\pm$ 0.21   |
| Folding endurance    | 77 $\pm$ 12.34   |
| % Moisture loss      | 1.5 $\pm$ 0.30   |

## CALIBRATION CURVE FOR BROMFENAC SODIUM

The calibration curve for bromfenac sodium was developed using distilled water using UV Visible Spectrophotometer UV -1700 (Shimadzu), and the results are given in Figure 4. The  $\lambda$  max was found to be 268 nm, at which the absorbance of standard solutions (2, 4, 6, 8, and 10 $\mu$ g/ml) were measured. Calibration between the concentration and absorbance was developed with a regression coefficient of 0.998. It ensures the dose-dependent linear response of the drug.

**Figure-4:** Calibration curve of bromfenac sodium in distilled water

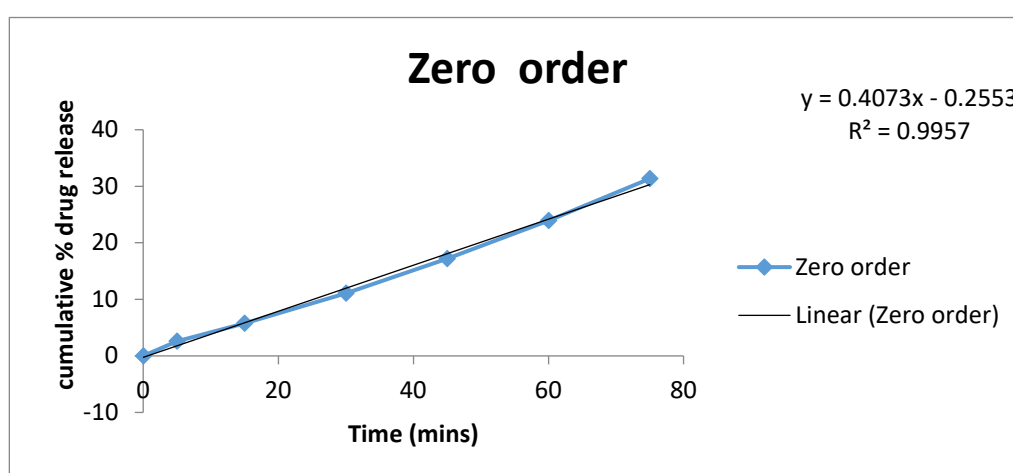


## In vitro drug release studies

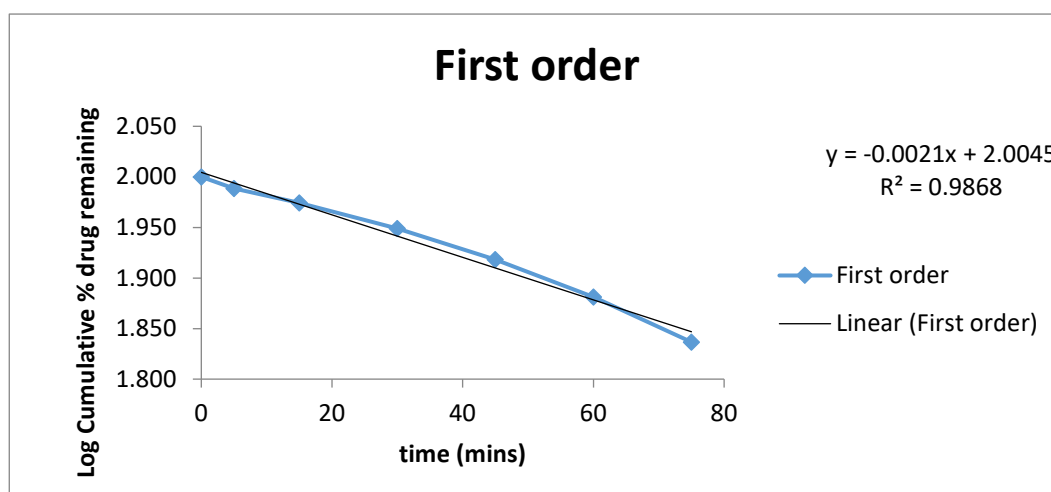
Formulation F11 released all of the bromfenac content within 1 hour and 15 minutes. In controlled drug delivery, drug release kinetics should follow zero-order. Therefore, the film of bromfenac sodium was fabricated to discharge the drug in zero-order modes by incorporating hydrophilic polymer HPMC. The zero-order of formulation F11 was linear, as indicated by their higher regression value. Therefore, the drug release from formulation F11 follows zero-order kinetics.

For the exact mechanism of drug release from the ocular insert, the data were computed and graphed according to the zero-order plot, First order, Higuchi plot, Hixson and Kors-Peppas plot, as shown in figures 5,6,7,8 and 9, respectively. The regression values of all the plots suggested that the curves were pretty linear, indicating the diffusion as a mechanism of release from ocular inserts.

**Figure 5:** Zero order plot of cumulative % drug release Vs Time

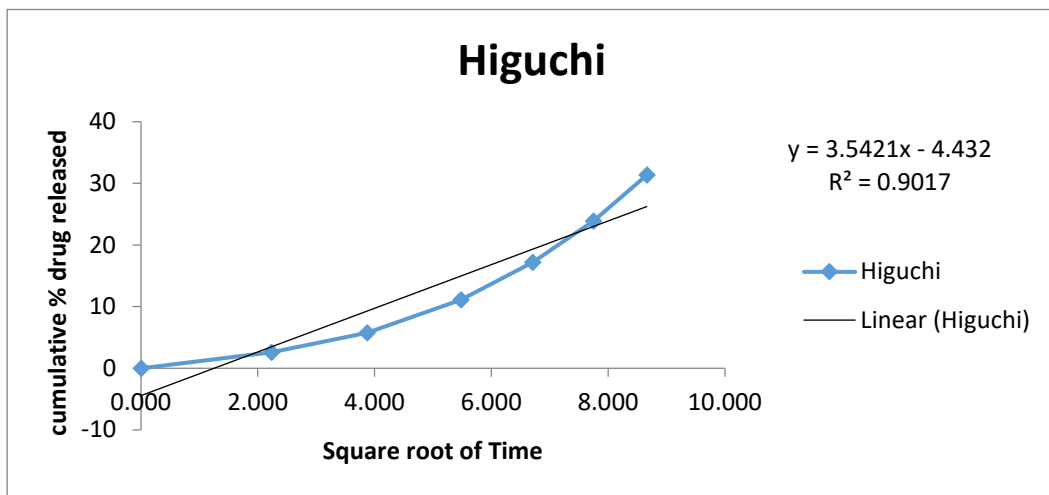


**Figure 6:** First order plot of log cumulative % drug release Vs time

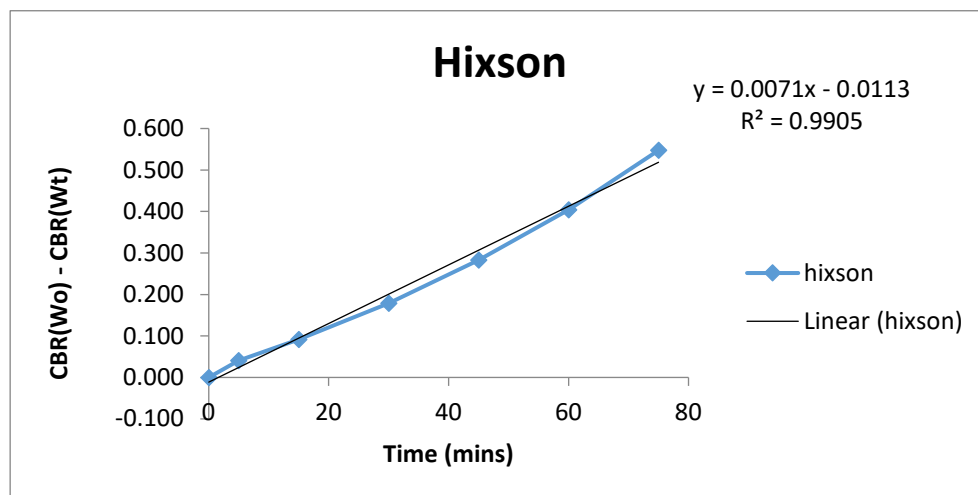




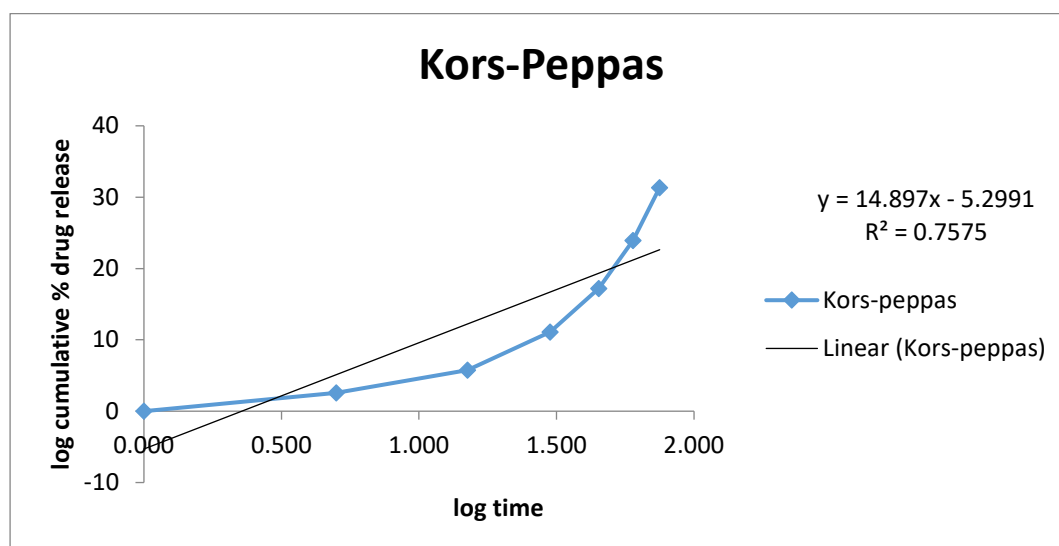
**Figure 7:** Higuchi plot of cumulative % drug released Vs square root of time



**Figure 8:** Hixson plot of CBR (Wo) - CBR (Wt) Vs time



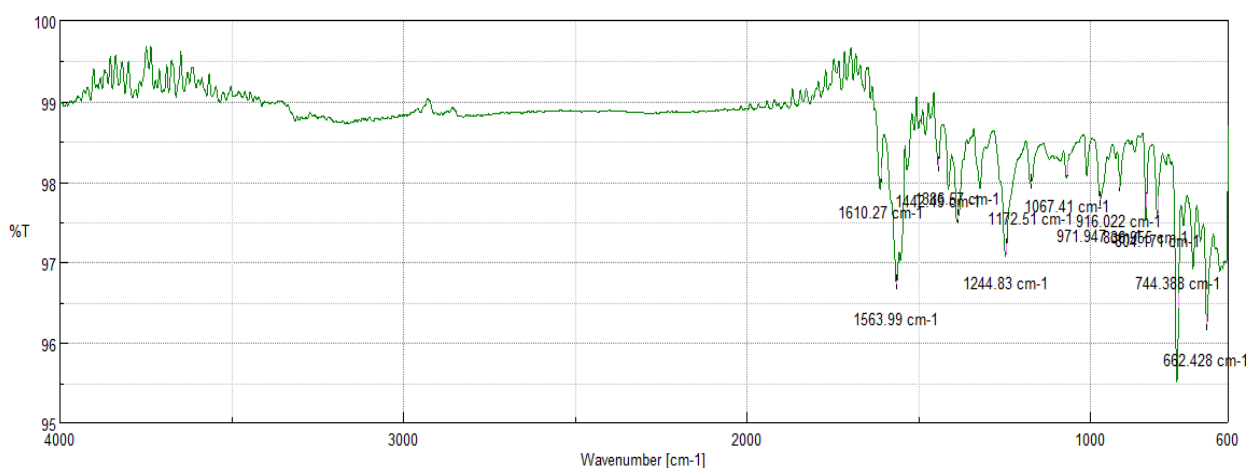
**Figure-9:** Kors-Peppas plot of log cumulative % drug release



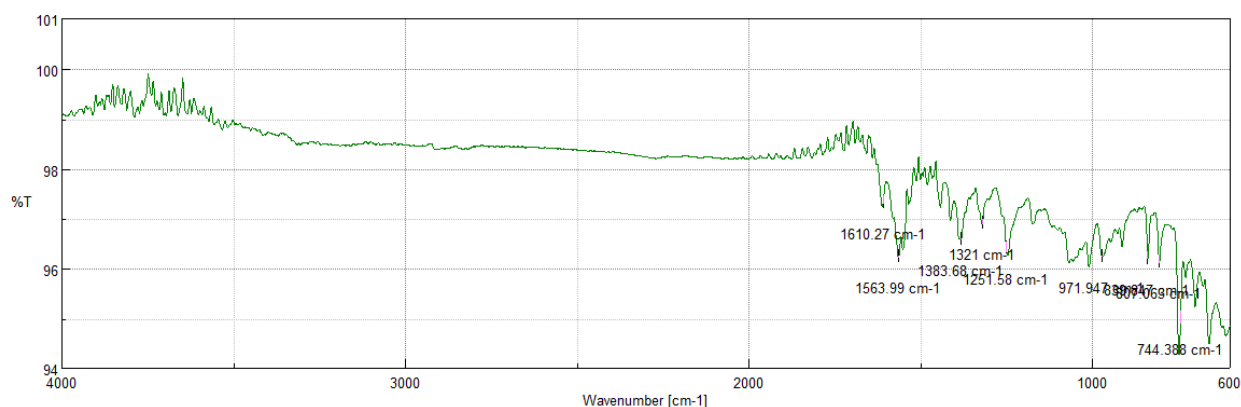
### Fourier Transform Infrared Spectroscopy (FT-IR) analysis

The FT-IR spectra of the pure drug bromfenac sodium and drug-loaded ocular inserts were recorded. From the obtained IR peaks, it was observed that there were no extra peaks and the interpretation analysis confirmed that both the drug and polymer were compatible with each other, and there were no signs of compound interaction. The results are shown in Table 4, Figures 10 and 11. C-Br stretching of the Halo compound, C-N Stretching of the Amine group, C-N Stretching of an aromatic amine group confirms the presence of the drug in the formulation with significant peak values of 662 cm<sup>-1</sup>, 1251 cm<sup>-1</sup>, 1321cm<sup>-1</sup>, respectively and the same shown in Bromfenac Sodium spectrum.

**Figure 10:** FT-IR Spectra of bromfenac sodium



**Figure 11:** FT-IR Spectra of bromfenac sodium and HPMC



**Table 4:** Interpretation of infrared spectra of bromfenac sodium

| FUNCTIONAL GROUP | INTERPRETATION (cm <sup>-1</sup> ) |         |           |
|------------------|------------------------------------|---------|-----------|
|                  | DRUG                               | HPMC    | DRUG+HPMC |
| Aromatic ring    | 1442.49                            | -       | 1442.49   |
| ketone           | 1610.27                            | -       | 1610.27   |
| C-N stretching   | 1244.83                            | -       | 1244.83   |
| C=O stretching   | 1708.26                            | -       | 1708.26   |
| Aromatic halide  | 1244                               | -       | 1244      |
| CH 2 Stretch     | -                                  | 2884.02 | 2884.02   |
| -C-O Stretch     | -                                  | 1126.22 | 1126.22   |

## Sterility testing

The outcomes of the sterility study are shown in Figures 12 and 13. The Positive (+ve) control test bottle (medium and *E. coli*) was observed with turbidity, indicating the growth of microorganisms. It indicates that this medium was favourable for the growth of microorganisms. The negative (-ve) test bottle (medium) was observed without the growth of microorganisms. Hence the sterility of the medium was shown to be maintained. The product test bottle (medium and ocular insert) was observed without microorganism growth. Hence the ocular inserts were sterile and had maintained sterility over the test period.

**Figure 12:** Sterility test on Day 1



**Figure 13:** Sterility test on Day 7



## CONCLUSION

The present research aimed to formulate and evaluate bromfenac sodium ocular insert. Ocular inserts of Bromfenac sodium were prepared by solvent casting technique using hydroxypropyl methylcellulose and glycerol. With no significant interaction between drug and polymer, it was concluded that the HPMC was the suitable film-forming polymer, and glycerol produces flexible and softer films. The In vitro drug release studies show that the film releases the drug in a controlled manner for up to 75 minutes and follows a diffusion mechanism. The ocular films comply with all the evaluation parameters of ocular inserts and appear to be promising, which would offer benefits such as increasing residence time, prolonging drug release, and reducing the frequency of administration.

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