

# DEVELOPMENT AND ASSESSMENT OF NOVEL IN-SITU OCULAR GELS OF KETOROLAC TROMETHAMINE

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## ABSTRACT:

In situ gel are viscous polymer-based liquid that exhibit sol-to-gel phase transition on the ocular surface due to change in specific physicochemical parameter like ionic strength, pH, or temperature. A major problem in ocular therapeutics is the attainment of optimal drug concentration at the site of action, which is compromised mainly due to pre-corneal loss resulting in only a small fraction of the drug being ocularly absorbed. The effective dose administered can be altered by prolonging the retention time of medication in the eye by using in situ gel, thereby preventing the tear drainage. The object of the present study is to formulation and evaluation of the in situ ocular gelling system of ketorolac tromethamine. These gelling systems involve the use of gelrite as a polymer. The formulation was evaluated for clarity, pH measurement, gelling capacity, drug content estimation, rheological study, in vitro drug release, ocular irritancy studies (as per Draize test) and ex-vivo corneal permeation studies using isolated goat cornea. The developed formulation showed sustained release of drug for up to 6 hrs. the formulation was found to be non-irritating with no ocular damage. Various batches of ketorolac tromethamine bio adhesive *in-situ* gelling ocular inserts were prepared using sodium alginate and chitosan with glycerine as a plasticizer by solvent casting method. The formulated bio adhesive *in-situ* gelling ocular insert were then evaluated for physical appearance, thickness, weight variation, folding endurance, percentage moisture loss, percentage moisture absorption, tensile strength, percentage flatness, bio adhesive strength, force of adhesive, drug content, *in vitro* drug release, sterility test, *in vitro* antimicrobial efficacy, and stability study.

**KEY WORDS:** Bio adhesive *in-situ* gelling ocular inserts, chitosan, *in vitro* drug release, ketorolac tromethamine, sodium alginate, ketorolac tromethamine, Draize test, gelrite, ex-vivo corneal permeation studies, in situ gel.

## INTRODUCTION:

The eye is an interesting organ. The tear flow and blinking reflex maintains a good environment and removes foreign material from the eye. In ocular drug delivery, the physiological constraints imposed by protective mechanism of the eye lead to low absorption of drugs and sometimes short duration of therapeutics effect. One of the reasons for relatively low bioavailability of conventional eye drops is their short precorneal contact time. When drug solution is administered in the form of drops, effective tear drainage and blinking results in a 10-fold decrease in drug concentration in 4 to 20 min. The drug absorption is also dependent upon the chemical nature of the drugs since the corneal permeability depends upon molecular size and hydrophobicity of drugs. By tear drainage the main part of administered drug is transported via the naso-lachrymal duct to the gastrointestinal tract where it may be absorbed, sometimes causing the systemic side-effects. Rapid elimination of administered eye drops often results in a short duration of therapeutic effect making a frequent dosing regimen. In order to increase the effectiveness of the drug, a dosage form should be selected, which

increases the contact time of the drug in the eye. This may increase bioavailability, reduce systemic absorption, and reduce the need for frequent administration leading to improved patient compliance. Ocular therapy would be significantly improved if precorneal residence time is increased and the most common way to achieve this is by increasing the viscosity of the solution. Gels and ointments moderately affect the contact time of the drug and have long residence time. They have a low patient compliance as they blur the vision and are recommended for bedtime use.

Ophthalmic inserts are thin disks or small cylinders made with appropriate polymeric material and fitting into the lower or upper conjunctival sac. Ophthalmic inserts offer many advantages over conventional dosage forms, such as increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, and exclusion of preservatives, increased shelf life, and reduced systemic absorption.

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug, used to treat seasonal allergic conjunctivitis. At present, it is available in the form of eye drops, which need to be administered 1 or 2 drops every 15 to 30 min. initially in acute infection and 1 or 2 drops administered 4 times daily or more in severe conditions. To overcome these limitations associated with dosage regimen, an attempt has been made to formulate bio adhesive *in-situ* gelling ocular inserts that may not only improve the efficiency of the therapy but also patient compliance. Several polymeric systems have been used to fabricate ocular inserts for better ocular bioavailability and retention to drug of which gelling systems have shown advantages of convenient administration and increased contact time. The purpose of this study was to develop a bio adhesive *in-situ* gelling ocular insert of ketorolac tromethamine using polymeric system of sodium alginate as gelling and chitosan as bio adhesive agent. The prepared dosage regimens provided ease in the application and capable to sustained drug release with reduced frequency of administration.

The available drug delivery systems are fairly primitive and inefficient. Medication is applied to the surface of eye for two purposes, to treat the outside of eye for infection (conjunctivitis) or to provide intraocular treatment through the cornea for diseases (glaucoma). Most ocular diseases are treated with a topical application of solution into the lower cul-de-sac as eye drop. Eye drops that are conventional ophthalmic delivery systems often result in poor bioavailability and therapeutic response due to high tear fluid turnover and dynamics that cause rapid precorneal elimination of the drug. A high frequency of eye drop instillation is also associated with patient non-compliance. Inclusion of excess drug in the formulation to overcome bioavailability problems is associated with side effects issues if the drug solution drained from the eye is systemically absorbed from the nasolacrimal duct. One way of prolonging the availability of drug in the precorneal area involves increasing the viscosity of the dosage form by adding water-soluble polymers. Here alternative approach was aimed to increase precorneal residence time of drugs that the polymeric solutions are change in *in-situ* gel because of pH, physiological temperature and ionic composition of the lachrymal fluid.

Ketorolac tromethamine (KETOROLAC) is a potent and effective aryl-acetic acid NSAID and is no irritating to the eye at 0.5% w/v concentration. Aqueous ocular drops of ketorolac are effective and safe for topical use following cataract surgery and intraocular lens implantation. Ketorolac is also a viable alternative to corticosteroids in treating ocular inflammation in the presence of pathogens. Ophthalmic solutions of ketorolac (0.5%) are effective in the treatment of chronic aphakic and pseudophakia macular edema. The topical ophthalmic dose of ketorolac is 1 drop qid in allergic conjunctivitis and in cystoids macular edema. The objective of the present work was to develop a pH-triggered *in situ* gelling system for sustained ophthalmic delivery of ketorolac and simultaneously determine the rheology behaviour, characterisation of gel. A combination of Carbopol (940) and hydroxyl propyl- methyl cellulose (HPMC K15M, K4M) was used as vehicle for the formulation of eye drops of ketorolac (0.5%, w/v) that would gel when instilled into the eye, and provide sustained release of ketorolac during treatment of seasonal allergic conjunctivitis and in some ocular inflammation situations.

## MATERIAL AND METHOD:

Ketorolac was a gift sample from Ranbaxy Laboratories Limited, (Gurgaon, India). Carbopol 940 and HPMC K15M, K4M (Methocel) purchased from SD fine-chem. Ltd, Mumbai. All other reagents used were of analytical grade.

Ketorolac tromethamine was obtained as a gift sample from Symed Labs; Hyderabad. Chitosan and sodium alginate were obtained as a gift sample from Coloron Laboratory, Mumbai.

### Differential scanning calorimetry (DSC) characterization

Thermal characterization of pure drug and physical mixture was performed with Calorimeter. Samples were weighed ( $2.00 \pm 0.5\text{mg}$ ) and placed in sealed aluminium pans. The equipment was calibrated with indium. The samples were scanned at  $20^\circ\text{C} / \text{min}$  from  $25^\circ\text{C}$  to  $300^\circ\text{C}$ .

### Selection of vehicle

The solubility of ketorolac was evaluated in various buffers, e.g., acetate buffer I.P. (pH 4.6, 4.8, 5.0, 5.5, and 6.0), citrophosphate buffer B.P. (pH 5.0, 6.0, 6.2 and 7.0) and phosphate buffer USP (pH 5.5, 6.0, 6.5, and 7.2) to select a suitable vehicle. Solutions of ketorolac (0.5%, w/v) in the buffers in which it was soluble were prepared and tested for stability to light, temperature, and autoclaving. Solubility of ketorolac was evaluated using a U.V. spectrophotometer at 321 nm.

### Preparation of In-situ gelling system

A) Aqueous solutions of varying concentrations of Carbopol 940 (CP) and HPMC of different grades (formulation codes K 1, K 2, K 3 ... K 28) were prepared and evaluated for gelling capacity and viscosity in order to identify the compositions suitable for use as *in situ* gelling systems. The gelling capacity was determined by placing 1 drop of the formulation in a vial containing 2ml of artificial tear fluid freshly prepared and equilibrated at  $37^\circ\text{C}$  and visually assessing gel formation and noting the time for gelation and the time taken for the gel formed to dissolve. The composition of artificial tear fluid used was NaCl 0.670 g, sodium bicarbonate 0.200 g, calcium chloride  $\cdot 2\text{H}_2\text{O}$  0.008 g, purified water q.s. 100.0 g. The viscosity at was measured using a Brookfield viscometer (DVULTRA model) in a small volume adapter used for purposes of comparative evaluation.

B) Buffer salts were dissolved in 75 ml of purified water, HPMC K15M, K4M was added and allowed to hydrate. Carbopols940 was sprinkled over this solution and allowed to hydrate overnight. The solution was stirred with an overhead stirrer, Tween 80 was added while stirring. Ketorolac was dissolved in purified water, benzalkonium chloride (BKC) was then added and the solution was filtered through  $0.2\text{-}\mu\text{m}$  cellulose acetate membrane filter. The drug solution was added to the Carbopol - HPMC solution under constant stirring until a uniform solution was obtained. Purified water was then added to make up the volume to 100 ml. The developed formulations were filled in 5-ml capacity amber glass vials, closed with grey butyl rubber closures and sealed with aluminium caps. The formulations, in their final pack were subjected to terminal sterilization by autoclaving at  $121^\circ\text{C}$  and 15 psi for 20 min.

C) The ketorolac tromethamine bio adhesive *in-situ* gelling ocular inserts were prepared based on sodium alginate and water-soluble chitosan by using solvent casting technique. Polymeric solutions were prepared by dissolving sodium alginate and chitosan at distinct compositions along with ketorolac tromethamine and glycerine in distilled water.

Chitosan was added in aqueous solution of sodium alginate and with constant stirring. The plasticizer was added thereafter and the drug polymer solutions were stirred for 12 h and allowed to stand overnight to remove any entrapped

air bubbles. The pH range of the solutions was found to be 5 to 8. The solutions were then poured into glass rings placed over mercury in the glass Petri dishes. Solvent was allowed to evaporate by placing the Petri dishes in oven ( $40 \pm 2^\circ\text{C}$ ). Dried films were carefully removed from the Petri dish and then cut into oval shaped inserts with the help of a sharp-edged die (13.2 mm in length and 5.4 mm in width). Each ocular insert contained 2 mg of the drug.

Insert code	Drug	Polymers		Plasticizer
	Ketorolac tromethamine (mg)	Sodium alginate (%)	Chitosan (%)	Glycerin (%)
F1	2	1.5	1.5	10
F2	2	2.0	1.5	10
F3	2	1.5	2.5	10
F4	2	2.5	1.5	10
F5	2	2.0	2.0	10

## EVALUATION:

### **Physical appearance**

The visual appearance of the film was conducted. The colour of the film as well as the texture was observed. Drug distribution within the film was also visualized.

### **Thickness**

The films were evaluated for the thickness of each film using a micrometre of sensitivity of 0.001 mm. The average of 10 readings was taken. The mean thickness of standard deviation was calculated.

### **Drug content**

Drug content was estimated by triturating ocular inserts in 20 ml of phosphate buffer pH 7.4 with the help of a mortar and pestle. The solution was filtered and 1 ml of the solution was withdrawn, diluted, and measured by a UV-Visible Spectrophotometer (Model-1700, Shimadzu, Japan).

### ***In vitro* drug release**

*In vitro* drug release study was carried out by using biochemical donor-receptor compartment model. The commercial semi permeable egg membrane, pre-soaked overnight in the freshly prepared dissolution medium (STF pH 7.4) and was tied to one end of a cylinder (open at both the sides), which acted as donor compartment. The ocular insert was placed inside the donor compartment in contact with the semi-permeable membrane. The donor compartment was attached to a stand and suspended in 25 ml of the dissolution medium maintained at  $37 \pm 1^\circ\text{C}$  in the way that touches the receptor medium surface. The dissolution medium was stirred at a low speed using magnetic stirrer. The aliquots of 5 ml were withdrawn at regular intervals for 12 h. and replaced by an equal volume of dissolution medium every time. The samples were analysed on UV spectrophotometer.

### **Sterility test**

Ultraviolet radiation was used to sterilize the ocular inserts and sterility testing was carried out under aseptic conditions. Alternate thioglycolate and soybean casein digest media was used to check sterility of formulation.

Preparation of alternative thioglycolate medium

Dissolve 29.3 g alternative thioglycolate medium in 1000 ml distilled water by boiling and sterilized by autoclaving at 15 lbs pressure at 121°C for 15 min. According to IP 2007 procedures, two containers were selected for sterility test. In each test, three sterility test tubes were used in the study and labelled as “positive control”, “negative control”, and “test”.

#### Preparation of soybean casein digest medium

About 40 g 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. According to IP 2007 procedures, two containers were selected for sterility test. In each test, three sterility test tubes were used in the study and labelled as “positive control,” “negative control”, and “test”.

#### *In vitro* antimicrobial efficacy

The microbiological studies were carried out to ascertain the biological activity of ophthalmic inserts against microorganisms. *Staphylococcus aureus* and *Escherichia coli* were used as the test microorganisms. A layer of nutrient agar (20 ml) seeded with the test microorganism (0.2 ml) was allowed to solidify in the Petri plate. Cups were made on the solidified agar layer with the help of sterile borer of 8 mm diameter. Later, volume of the formulations (optimized formulation and marketed eye drops) containing equivalent amounts of drug was poured into the cups. After keeping Petri plates at room temperature for 4 h, the plates were incubated at 37°C for 24 h. The diameter of zone of inhibition was measured by using an antibiotic zone finder.

#### Stability study

A short-term stability study of the optimized formulation is carried out as per International Conference on Harmonization guideline at temperature 40°C and relative humidity (RH) at 75 % for in stability chamber.

#### Physical appearance

The prepared formulation F1-F5 batch ocular inserts were translucent, colourless, smooth in texture, uniform in appearance, and show no visible crack or imperfection.

#### Surface pH

Surface pH is a very important parameter to be evaluated to check the isotonic of ocular insert with tear fluid. The surface of formulations F1-F5 was measured using digital pH meter. The surface pH values were shown in. The surface pH of formulations F1-F5 ocular inserts were found to be in the range of  $5.5 \pm 0.10$  to  $7.0 \pm 0.115$ , which were well within the pH of lachrymal secretion indicating no irritation.

#### Drug content

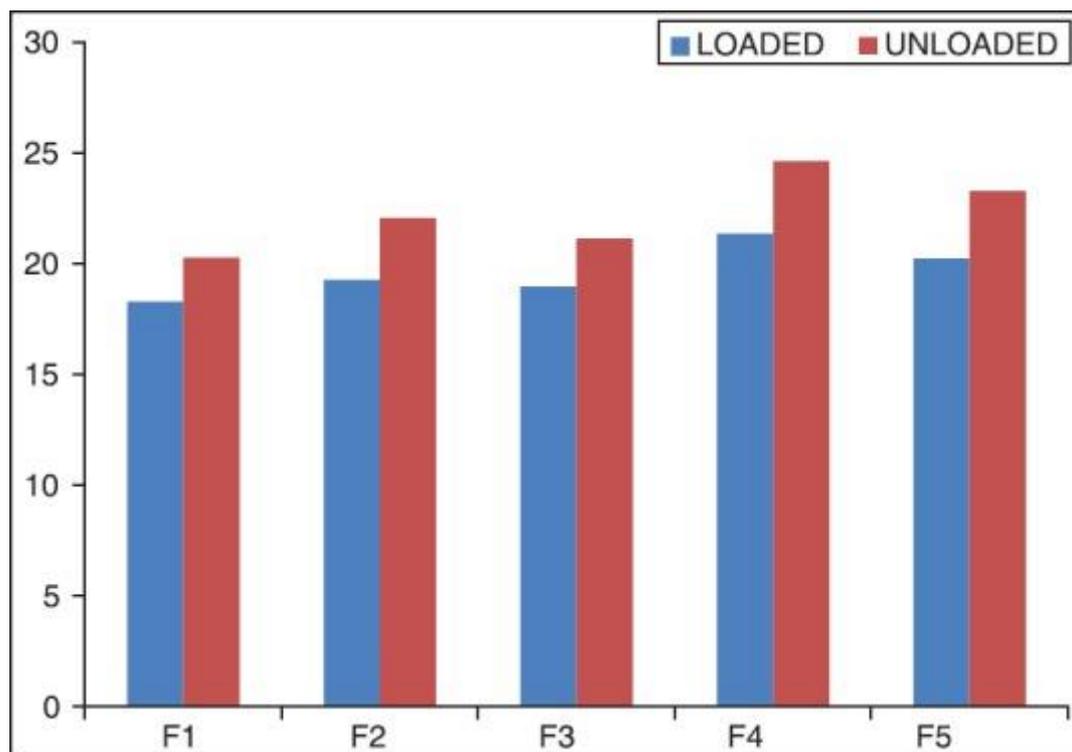
The range of drug contents was observed from  $96.23 \pm 2.20$  to  $101.24 \pm 0.28$ . Results of the content uniformity test complied with the IP 2007 requirements. These results showed that these values indicated homogeneous distribution of drug and the method for the preparation of inserts gave reproducible results.

#### Tensile strength

Tensile strength measures the ability of film to withstand rupture. Ocular insert with good tensile strength would resist tearing due to stress generated by blinking action of the eye. The tensile strength of formulation F1-F5 ocular inserts

was shown in and the graph was shown in. The tensile strength of formulation F1-F5 was found to be a range of  $1.82 \pm 0.040$  to  $2.65 \pm 0.028$  g/mm<sup>2</sup>. Tensile strength of ketorolac tromethamine inserts increased as the total amount of polymer was increased. However, the tensile strength could be related to the sodium alginate content as the inserts with higher sodium alginate content showed greater tensile strength.

Formulation	Loaded	Unloaded
F1	$1.82 \pm 0.040$	$2.02 \pm 0.045$
F2	$1.96 \pm 0.035$	$2.04 \pm 0.055$
F3	$2.37 \pm 0.028$	$2.55 \pm 0.015$
F4	$2.46 \pm 0.015$	$2.65 \pm 0.028$
F5	$2.19 \pm 0.035$	$2.34 \pm 0.030$

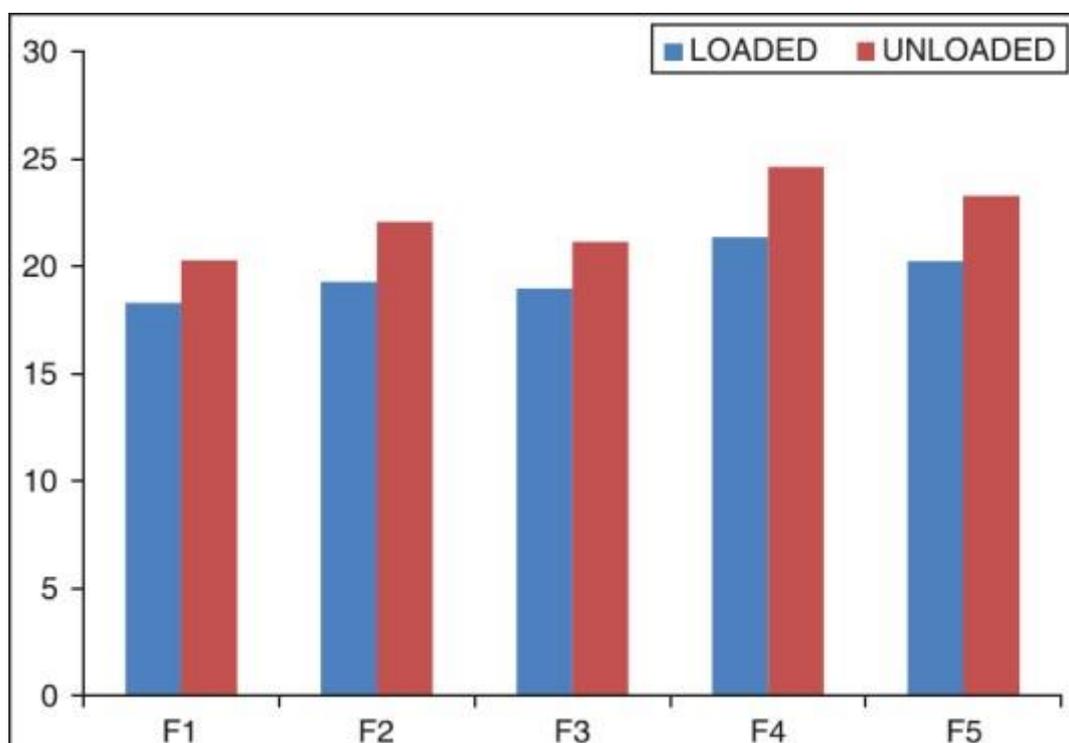


### Percentage elongation

The percentage elongation of formulation F1-F5 ocular inserts was shown in and the graph was shown in. The percentage elongation of formulation F1-F5 ocular inserts was found to be a range of  $18.29 \pm 0.011$  to  $24.62 \pm 0.028$ .

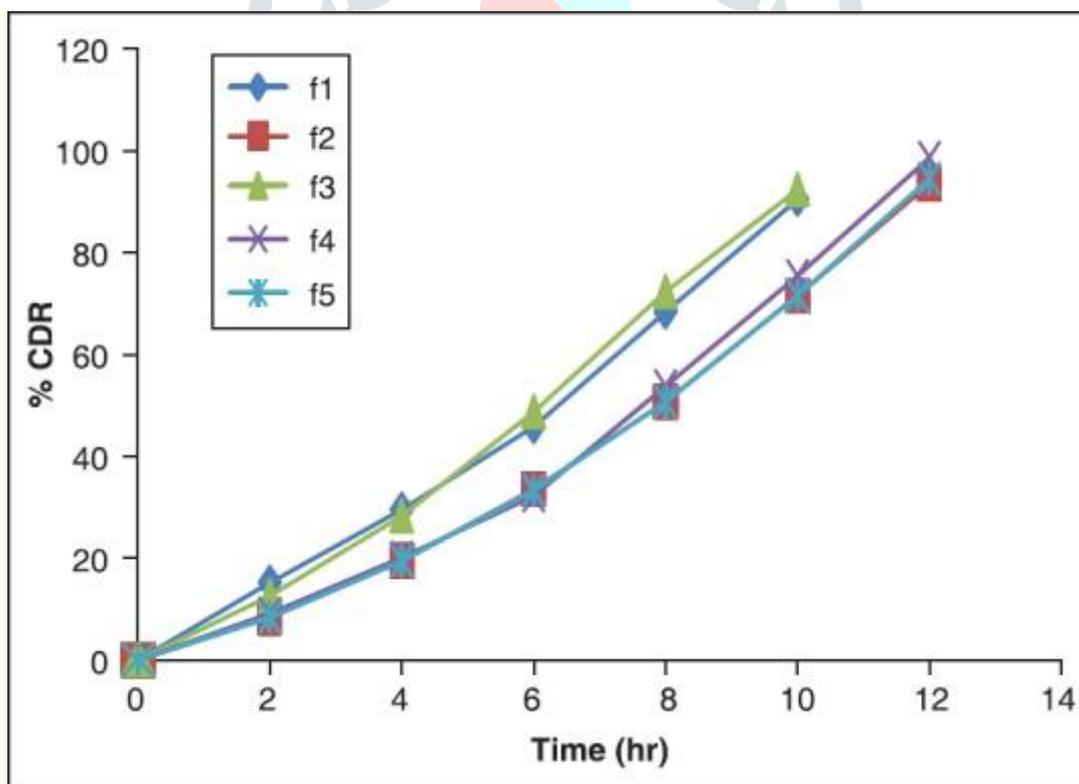
The percentage elongation of ocular inserts reduced with increase a concentration of chitosan and the percentage elongation of ocular inserts increased with increased a concentration of sodium alginate. Percentage elongation was maximum for formulation F4 followed by F5, F3, F2, and F1 formulation.

Formulation	Loaded	Unloaded
F1	$18.29 \pm 0.011$	$20.27 \pm 0.02$
F2	$19.27 \pm 0.03$	$22.06 \pm 0.3$
F3	$18.96 \pm 0.14$	$21.13 \pm 0.15$
F4	$21.35 \pm 0.035$	$24.62 \pm 0.028$
F5	$20.23 \pm 0.32$	$23.27 \pm 0.09$



### *n vitro* drug release

The effect of polymer concentration on drug release was studied for formulations F1-F5 prepared using as polymer sodium alginate and chitosan. The release profile of these formulations was shown in.



Formulation F1 containing 1.5% sodium alginate and 1.5 % chitosan was prepared ocular inserts. The formulation F1 was shown  $90.44 \pm 0.98\%$  drug release at the end of 10 h. Formulation F2 containing 2.0% sodium alginate and 1.5 % chitosan was prepared ocular inserts. The formulation F2 was shown  $93.55 \pm 0.72\%$  drug release at the end of 12 h. Formulation F3 containing 1.5% sodium alginate and 2.5% chitosan was prepared ocular inserts. The formulation F3 was shown  $92.38 \pm 1.09\%$  drug release at the end of 10 h. Formulation F4 containing 2.5% sodium alginate and 1.5%

chitosan was prepared ocular inserts. The formulation F4 was shown  $98.62 \pm 1.32\%$  drug release at the end of 12 h. Formulation F5 containing 2.0% sodium alginate and 2.0% chitosan was prepared ocular inserts. The formulation F4 was shown  $94.52 \pm 1.63\%$  drug release at the end of 12 h.

The drug release study, however out of these five formulations, F4 batch was maximum sustain drug release and also having maximum folding endurance, swelling index, percentage drug content, optimized tensile strength, and percentage elongation.

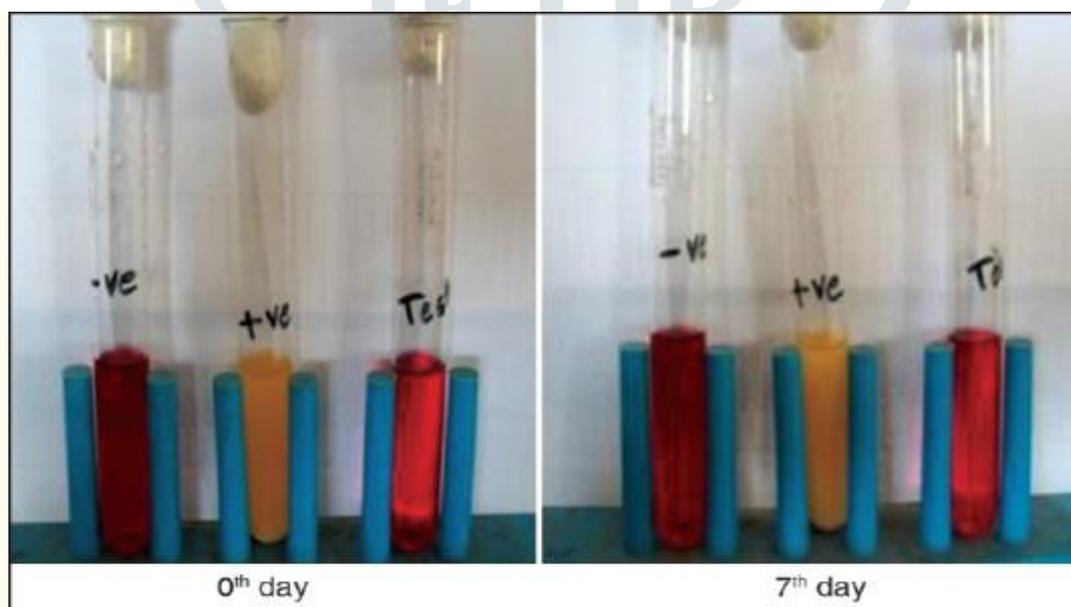
Hence, on the basis of drug release profile and physicochemical parameters F4 formulation evolved as the best formulation.

### Sterility test

Positive (+ve) test tube (Medium and *E. coli*): Microorganism seen. So that media suitable for growth of microorganism.

Negative (-ve) test tube (Medium): No growth of microorganism seen. So that sterility maintained.

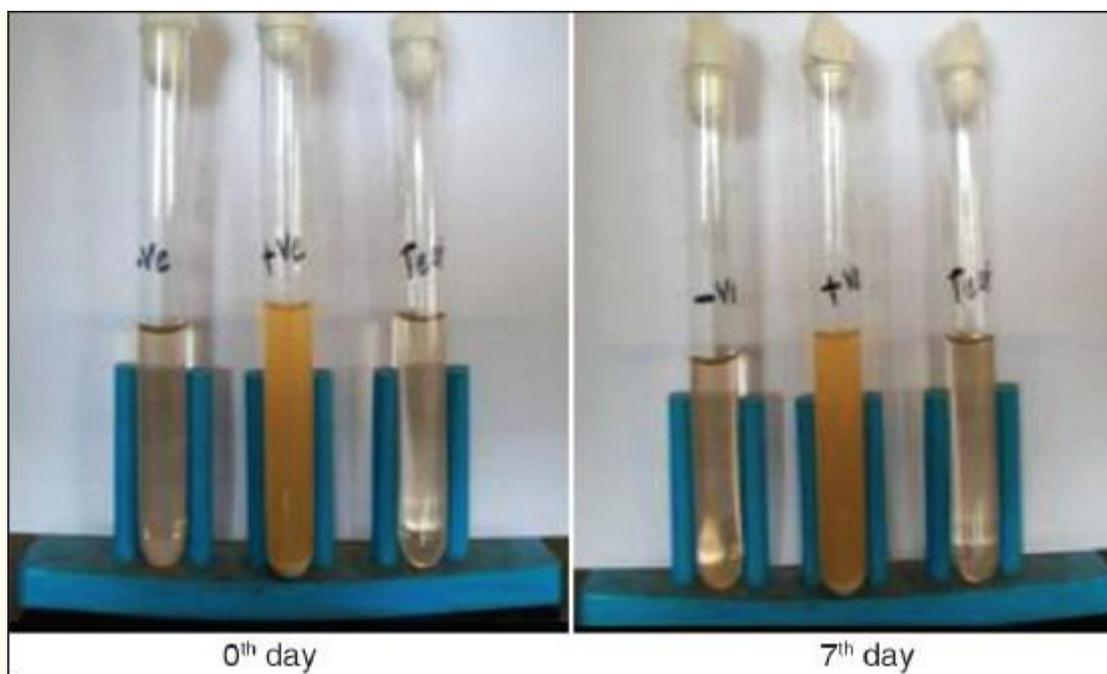
Control test tube (Medium and ocular insert): No growth of microorganism seen. So that product was sterilized.



Positive (+ve) test tube (Medium and *E. coli*): Microorganism seen. So that media suitable for growth of microorganism.

Negative (-ve) test tube (Medium): No growth of microorganism seen. So that sterility maintained.

Control test tube (Medium and ocular insert): No growth of microorganism seen. So that product was sterilized.



### *In vitro* antimicrobial efficacy

The microbiological studies were carried out to ascertain the biological activity of ophthalmic inserts against microorganisms. *Staphylococcus aureus* and *Escherichia coli* were used as the test microorganisms.

shows that the disc containing ocular insert shown zone of inhibition by using *Staphylococcus aureus* and *Escherichia coli*.



### Stability test

A short-term stability study was carried out. A sufficient number of optimized ocular inserts (packed in aluminium foil) were stored in the stability chamber at temperature 40°C and 75 % RH for 1 month. After one month, the ocular inserts were taken out and were evaluated for thickness, folding endurance and *in vitro* drug release at 10<sup>th</sup> h. The evaluation parameters for stability studies was shown in [Table 5](#) and it was found that there was no significant change in the physicochemical properties from 0<sup>th</sup> to 30<sup>th</sup> day. Hence, the formulation was found to be stable.

Formulation	Days	Parameters evaluated for the stability study		
		Thickness (mm)	Folding endurance	Q10 (%)
F4	0	271±0.503	170±1.155	74.43
	15	270±0.025	168±1.132	72.28
	30	270±0.0141	167±2.019	71.565

### Ocular irritancy

In-vivo eye irritation testing was carried out using rabbits and as per Draize test protocol. Optimized two formulations K11 & K26 were used for this test. The formulations were found to be non-irritating with no ocular damage or abnormal clinical signs to the cornea, iris or conjunctivae observed. Hence the formulation was suitable for the eye instillation.

### CONCLUSION:

Various batches of ketorolac tromethamine bio adhesive *in-situ* gelling ocular inserts were prepared using solvent casting method and evaluated. F4 was found to be better as it was smooth, translucent, and flexible. Physicochemical parameters like weight and thickness uniformity, folding endurance, tensile strength and percentage elongation was satisfactory and surface pH, swelling index, percentage flatness, percentage moisture absorption, percentage moisture loss, bio adhesive strength, force of adhesion showed optimum results and also better drug content uniformity in comparison with other formulations. The formulation F4 was shown 98.62 % drug release at the end of 12 h. So that F4 formulation was maximum sustain drug release than other formulation. This optimized formulation was subjected to sterility and stability test. There was no evidence of microbial growth and hence the ocular insert passed the sterility test and there was no significant change in the physicochemical properties from 0<sup>th</sup> to 30<sup>th</sup> day. Hence, the formulation was found to be stable. From above results it can be concluded that ketorolac tromethamine bio adhesive *in-situ* gelling can be delivered in controlled manners for extended period of time in the form of ocular inserts. Release pattern of drug from these inserts can be altered by using different formulation variables. The said promising formulation (F4) would be able to offer benefits such as increase residence time, prolonged drug release, reduction in frequency of administration and thereby definitely prove to improve the patient compliance.

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