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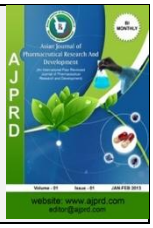

Open Access Research Article

# Ketorolac Tromethamine for Sustained Ocular Delivery; Novel In-Situ Gels Development and Evaluation

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## A B S T R A C T

**Objective:** Ophthalmic ketorolac is used to treat itchy eyes caused by allergies. It also is used to treat swelling and redness (inflammation) that can occur after cataract surgery. Ketorolac is in a class of medications called nonsteroidal anti-inflammatory drugs (NSAIDs).

**Methods:** Ocular bioavailability is always poor from conventional ophthalmic drops due to spillage and nasolachrymal drainage. Ocular in situ gels can increase the drug residence time thus increasing bioavailability. Polyacrylic acid (Carbopol 934) was used as the gelling agent in combination with hydroxypropylmethylcellulose (Methocel K4M) which acted as a viscosity enhancing agent. Compatibility studies of the drug excipients were carried out using differential scanning calorimetry. The prepared formulations were characterized for clarity, pH, drug content, sol-to-gel transition by scanning electron microscopy, in-vitro and in-vivo drug release, ocular irritation and stability.

**Results:** FTIR spectras revealed that, there was no interaction between LEV and excipients. The formulated gels were transparent, uniform in consistency and had spreadability with a pH range of 7.1 to 7.4. Rheological studies revealed that the formulations were psuedoplastic in nature, drug content of sterile in situ gels was found to be 92-98%.Release kinetic study showed that the formulation followed first order diffusion controlled and the optimized formulations was having good antibacterial efficacy.

**Conclusion:** 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.

**Keywords:** Ketorolac tromethamine ,In-situ gels , Ocular delivery , Bio adhesive in-situ gelling , Draize test , Sustained release.

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## 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.[1]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[2] , Ocular drugs are mostly applied locally to the surface of the eye as eye drops for

treatment of either the external ocular infections such as conjunctivitis, blepharitis, keratitis sicca, or intraocular diseases such as glaucoma, proliferative vitreoretinopathy, endophthalmitis, recurrent uveitis, acute retinal necrosis and cytomegalovirus retinitis etc[3] However, due to efficient protective mechanisms of the eye (e.g. lachrymal secretion, blinking reflex) and systemic absorption in the conjunctiva, major part of the drug is rapidly eliminated from the ocular surface and only a small fraction of drug is absorbed into the eye, which results in poor bioavailability of the drugs. This needs frequent dosing of eye drops, which causes pulse kinetics of the drugs in the eye[4] .

Ketorolac tromethamine (KT) is a BCS class I drug having potent anti-inflammatory activity. Chemically it is a pyrrolizine carboxylic acid; NSAID used for the treatment of post-operative eye inflammation and conjunctivitis. Being water soluble agent; to formulate nanosystem is quite difficult by entrapment in polymeric vehicle. Generally the basic problems for topical application in the treatment of ocular infection is drug loss from pre-corneal surface, conjunctival uptake due to poor bioavailability and rapid drainage through naso-lacrimal areas. However, short precorneal contact time combined with corneal impermeability result in low bioavailability, and frequent dosing is usually needed. Nanosuspension by nanoprecipitation is the novel drug delivery approach for sustaining the drug in its crystalline state. Selection of polymers and stabilizers are very essential in the development of nanosuspensions to avoid particle aggregation, and crystal growth. Design of experiment has proven effective optimization of formulations. In present investigation; formulation was optimized by using 32 factorial design. Hence, based on above challenge, KT nanosuspension loaded in situ gel increases ocular bioavailability, and residence time on the corneal surface. The rationale of present work was to design and develop KT nanosuspension loaded in situ gel with sustained effect and greater permeability for challenging ocular drug delivery[5]The chemical structure of ketorolac tromethamine was shown in fig.(1)

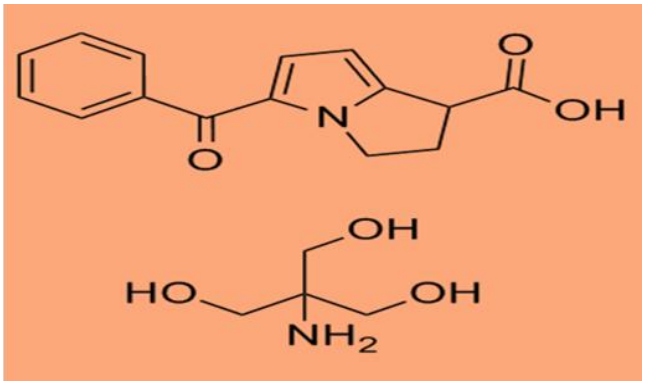



**Figure 1:** Chemical structure of ketorolac tromethamine

Ketorolac tromethamine is a nonsteroidal anti inflammatory drug, used to treat seasonal allergic conjuctivits. Ion activated ocular gels of Ketorolac tromethamine were prepared by using the polymer Gelrite. The present investigation deals with development and evaluation of ion activated ocular gels of Ketorolac tromethamine. The prepared dosage regimens provided ease in application and capable to sustained drug release with reduced frequency of administration.

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.

## MATERIALS AND METHODS

### Materials:

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.

### Methods:

### Drug-excipient compatibility studies:

DSC characterization: Calorimetric characterization of ketorolac tromethamine, Carbopol® 934, and HPMC (K4M, E4M, and E15 LV) alone and their physical mixtures were carried out using a DSC 822e instrument (Mettler Toledo Stare System, Switzer Land). Argon was used as the purging gas at a rate of 80 ml/min. The calorimeter underwent baseline calibration using no pans and, for cell constant and temperature using indium. All experiments were performed using non-hermetic aluminium pans, into which samples were accurately weighed, and then simply covered with a lid. The samples were loaded on an auto-sampler tray. The samples for the DSC study were program-heated from 25 to 200˚C, then cooled to 0˚C using liquid nitrogen, and finally heated to 200˚C again, always at the rate of 10˚C/min[6,7] .

### Preparation of formulations:

### Selection of vehicle

The solubility of ketorolac tromethamine was tested in various buffers, such as 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), in order to select a suitable vehicle. Solutions of ketorolac tromethamine (0.5%, w/v) in buffers in which it was soluble were prepared and these were tested for stability to light, temperature and autoclaving using a stability indicating high-performance thin-layer chromatographic (HPTLC) method[8] .

**Preparation of In-situ gelling system:**

Aqueous solutions of varying concentrations of Carbopols 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 Table 1. 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 0C 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 -2 H2O 0.008 g, purified water q.s. 100.0 g[9]. The viscosity at was measured using a Brookfield viscometer (DV- ULTRA model) in a small volume adapter used for purposes of comparative evaluation.

**Table 1:** Combinations of Carbopol and HPMC studied

| Formulation | HPMC grade | Concentration (w/v) | | Gelling capacity |
|---|---|---|---|---|
| | | HPMC | Carbopol | |
| K1 | K15M | 0.2 | 0.2 | - |
| K2 | K15M | 0.2 | 0.4 | + |
| K3 | K15M | 0.2 | 0.6 | + |
| K4 | K15M | 0.2 | 0.8 | +++ |
| K5 | K15M | 0.3 | 0.2 | _ |
| K6 | K15M | 0.3 | 0.4 | + |
| K7 | K15M | 0.3 | 0.6 | + |
| K8 | K15M | 0.3 | 0.8 | + |
| K9 | K15M | 0.4 | 0.2 | _ |
| K10 | K15M | 0.4 | 0.4 | ++ |
| K11 | K15M | 0.4 | 0.6 | ++ |
| K12 | K15M | 0.4 | 0.8 | +++ |
| K13 | K15M | 0.5 | 0.2 | _ |
| K14 | K15M | 0.5 | 0.4 | + |
| K15 | K15M | 0.5 | 0.6 | +++ |
| K16 | K15M | 0.5 | 0.8 | +++ |
| K17 | K4M | 0.3 | 0.2 | _ |
| K18 | K4M | 0.3 | 0.3 | _ |
| K19 | K4M | 0.3 | 0.4 | + |
| K20 | K4M | 0.3 | 0.5 | + |
| K21 | K4M | 0.4 | 0.2 | _ |
| K22 | K4M | 0.4 | 0.3 | + |
| K23 | K4M | 0.4 | 0.4 | +++ |
| K24 | K4M | 0.4 | 0.5 | ++ |
| K25 | K4M | 0.5 | 0.2 | _ |
| K26 | K4M | 0.5 | 0.3 | ++ |
| K27 | K4M | 0.5 | 0.4 | +++ |
| K28 | K4M | 0.5 | 0.5 | +++ |

**Notice:**
No gelation,
+ Gels after a few a min, dissolves rapidly,
++ Gelation immediate, remain for few hours,
+++ gelation immediate, remains for extended period

The detailed procedure for preparing the in situ gelforming system of ketorolac tromethamine is outlined in Table 2. The buffer salts were dissolved in 75 ml purified water, then Methocel K4M was added and allowed to hydrate. Carbopol® 934 was sprinkled over this solution and allowed to hydrate overnight. The solution was stirred with an overhead stirrer, then edetate disodium (EDTA) solution was added while stirring. Ketorolac tromethamine was dissolved in purified water, benzalkonium chloride (BKC) was then added and the solution was passed through a 0.2-µm 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 transferred to 5-ml amber glass vials, closed with gray butyl rubber stoppers and sealed with aluminium caps. The formulations, in their final packaging, were subjected to terminal sterilization by autoclaving at 121˚C and 15 p.s.i. for 20 min[10] .

**Table 2:** Composition of In-situ gelling system of developed formulation.

| Sr. No | Ingredients | Concentrations (% w/v | | | |
|---|---|---|---|---|---|
| | | K 10 | K 11 | K 24 | K 26 |
| 1 | Ketorolac | 0.5 | 0.5 | 0.5 | 0.5 |
| 2 | Carbopol | 0.4 | 0.4 | 0.4 | 0.5 |
| 3 | HPMC K15M | 0.4 | 0.6 | - | - |
| 4 | HPMC K4M | - | - | 0.5 | 0.3 |
| 5 | Benzalkonium Chlorid | 0.01 | 0.01 | 0.01 | 0.01 |
| 6 | Citric acid ip | 0.407 | 0.407 | 0.407 | 0.407 |
| 7 | Disodium hydrogen phosphate IP | 1.125 | 1.125 | 1.125 | 1.125 |
| 8 | Tween 80 | 0.5 | 0.5 | 0.5 | 0.5 |
| 9 | Purified water IP (qs) | 100 | 100 | 100 | 100 |

**Characterization for Ion activated ocular gels:**

**Clarity**

The clarity of the formulation before and after gelling was determined by visual examination of the formulations under light alternatively against white and black backgrounds.

**pH**

Formulation was taken in a beaker and 0.1M NaOH was added dropwise with continuous stirring. pH was checked using pH meter ( µ pH Systronics digital pH meter).

**Assay**

Accurately weighed amount KT in-situ gel equivalent to 5mg of drug was taken in a 100ml volumetric flask. Simulated Tear Fluid (STF pH 7.4) was added to it and kept on magnetic stirrer to dissolve the drug. The volume was made to 100ml with STF (pH 7.4).and filtered using Whatmann filter paper (No 42). 10ml aliquot of the above solution was taken and diluted to 100ml with STF (pH 7.4). The absorbance of sample solution was determined at 322nm against STF (pH 7.4) as blank after suitable dilution with STF.

**In-vitro Dissolution studies**

In-vitro drug in release studies of sample were carried out by using modified usp apparatus paddle method with STF (PH 7.4) as dissolution medium . A glass cylinder of 2.5cm in diameter open at both both ends[11]. Dialysis membrane previously soaked in STF (PH 7.4) was taken , dried , and tied on to on end of the glass cylinder and to this one ml of the formulation was accurately pipetted. The glass cylinder was attached to the shaft of USP apparatus II, in place of basket as shown in Fig (2).

The cylinder was then suspended in 50 mL of dissolution medium maintained at 34 ± 0.5°C such that the membrane just touched the dissolution medium. The speed of the metallic device shaft was set at 50 rpm. Aliquots were withdrawn at intervals of 1, 2, 3, 4, and 5 hours and replaced by equal volumes of dissolution medium. Aliquots were suitably diluted with STF (pH 7.4) and analyzed by UV Spectrophotometer at 322 nm. The percent release of the drug was computed as shown on Table 3 and the graph of percent drug release versus time were plotted as shown in Fig (3)[12].

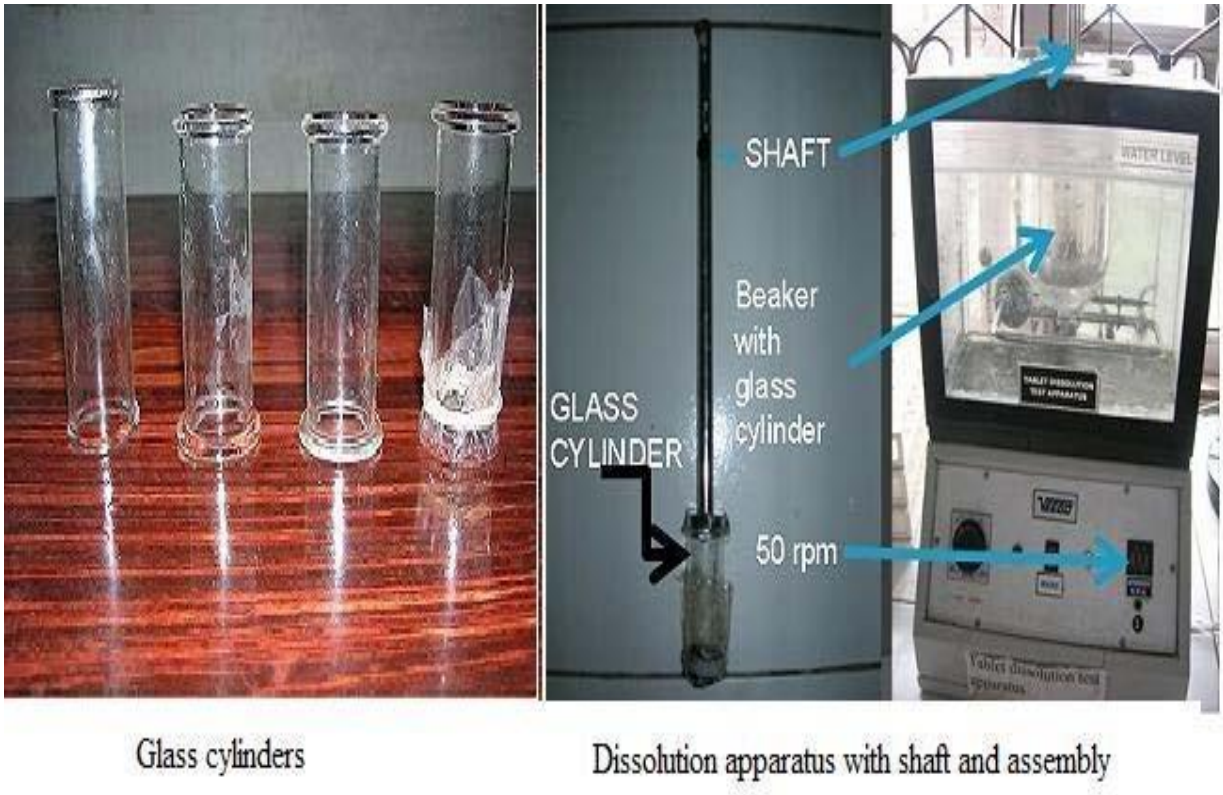



**Figure 2:** it shows the glass cylinders and dissolution assembly

**Table 3:** Comparative dissolution profile of formulations with gelrite.

| Time | Formulation code | |
|---|---|---|
| | KT-G1 | KT-G2 |
| **1** | 41.38 | 38.98 |
| **2** | 52.35 | 46.36 |
| **3** | 61.53 | 55.86 |
| **4** | 70.55 | 66.36 |
| **5** | 64.51 | 75.32 |
| **6** | 51.88 | 86.96 |

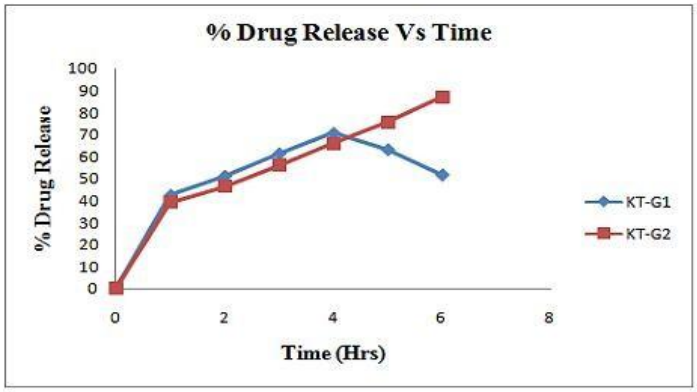



**Figure 3:** Effect of excipient ratio on dissolution rate of Ketorolac tromethamine ion activated in-situ ocular gels.

## Absorption And Bioavailability Of The Drugs From The Eye

The drug solution instilled as eye drops into the ocular cavity may disappear from the precorneal area of the eye by any or a composite of the following routes.5 shown in Fig.(4).

Tear turnover,

Productive corneal absorption,

Nonproductive conjunctival uptake,

Drug administered by instillation must Penetrate the eyes and so primarily through the cornea. Corneal absorption is much more effective than scleral or conjunctival absor-ption, in which removed by blood vessels into the general circulation occurs.

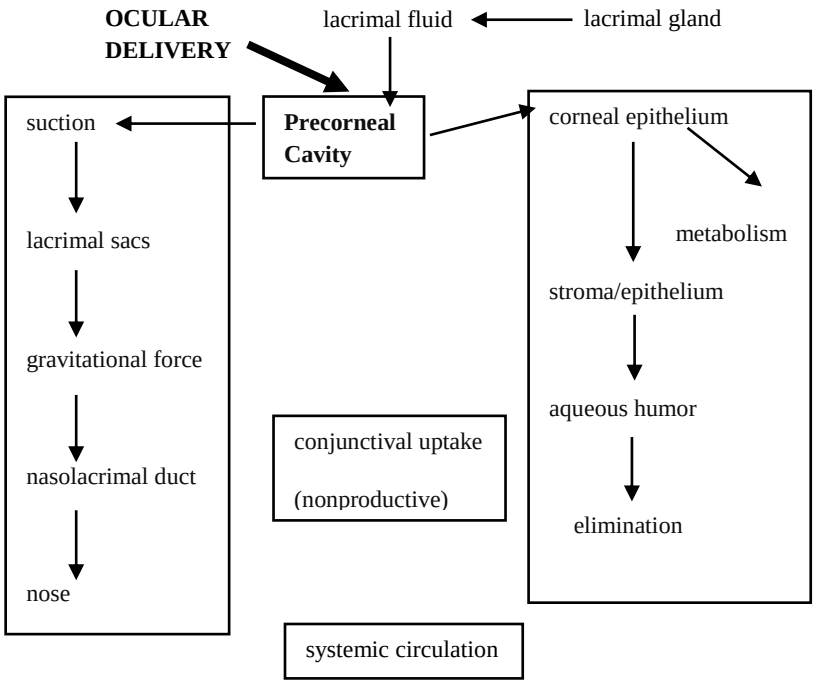



**Figure 4 :** Routes of ocular absorption of drugs

**In-situ gelling system**

Ophthalmic in-situ gelling is comprising of environmentally sensitive polymers that will be altered structurally with the small changes in specific conditions like pH, temperature and ionic strength in the environment. In-situ forming gels are liquids during instillation into the eye and then undergoes rapid gelation in the cul-de-sac of the eye to form viscoelastic gels in response to environmental changes; lastly release the drug slowly under physiological conditions[13] .Consequently, the residence time of the gel formed in-situ will be extended and the drug is released in a sustained manner which leads to enhanced bioavailability, minimized systemic absorption and reduced frequent dosing regimen resulting to improved patient compliance[14] . Furthermore, some other potential advantages such as simple manufacturing process, ease of administration, and deliverance of accurate dose have been exhibited by in-situ gelling systems[15].

**Data treatment of dissolution studies**

Various models like zero order, first order, Higuchi models, and Korsemeyer&Peppas were tested for explaining the kinetics of drug release based on the release rate data as as shown in Table 4.

**Table 4:** Different Release Rate Constants of Thermo-reversible ocular gels of Ketorolac tromethamine (Formulation code KT-T4).

| Formulation | Parameters | Zero order | First order | Higuchi | Korsemeyer |
|---|---|---|---|---|---|
| KT-T4 | k | 0.072 | 0.010 | 1.168 | 1.828 |
| | $r^2$ | 0.9921 | 0.9790 | 0.9902 | 0.9971 |

**FTIR spectroscopy**

FTIR spectra of drug, and formulation were obtained. Sample is suspended between KBr plates, and examined in0.1mm KBr sealed cell, and scan for 16 times. The instrument model used for FTIR was Prestige 21,

**Rheological Evaluation:**

Viscosity of formulation was determined before and after gellation by using Brookfield's viscometer (DV II model) in the small volume adaptor and the angular

velocity was increased gradually from 10, 20, 50 and 100 rpm. The hierarchy of the angular velocity was reversed. The average of two readings was taken to calculate the viscosity of the gels. Gellation was induced in formulation by raising the temperature to 34 ºC ± 0.5 ºC[16].

**Ocular Irritancy test**

The optimized formulation was evaluated for in vivo performance in animal model (Rabbits). The protocol is approved by college ethical committee (Ethical committee Registration number is CPCSEA/IAEC/Reg. No. 518/2009). Three rabbits (Albino rabbits) were used for this study. They were housed and maintained in the animal house at room temperature (27ºC) during the period of the study. They were fed with standard diet and water. The animals were placed in cages and the eyes were marked as test and control. The control group received no sample and the test eye received the formulation (0.5ml), and the eyes were observed for the ocular irritancy (includes the macroscopic observation of cornea, iris, and conjunctiva SHIMADZU and the FTIR cpectrum was recorded from et at 2007 3800cm-1 to 650cm-1[17] .

**Evaluation of The Prepared Ketorolac Tromethamine In-Situ Ocular Gels**

**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.

**pH Measurement:**

The pH of the prepared formulations was checked by using pH-meter.

**Determination of Gelling Capacity:**

In order to identify the compositions suitable for use as in situ gelling systems, gelling capacity of the prepared formulations was evaluated. The gelling capacity was determined as follows: the prepared in situ gelling systems were mixed with freshly prepared STF in the ratio of 25: 7 respectively (application volume 25 µm, normal volume of tear fluid in the eye is 7 µl) at 35ºC± 0.5. Gelation was assessed by visual examination [20]. The time for gelation & the time taken for the formed gel to re- dissolve were recorded. The composition of artificial tear fluid was sodium chloride 0.670 g, sodium bicarbonate 0.200 g, calcium chloride·2H2O 0.008 g, and purified water q.s.100 g[18].

**Ocular irritation studies:**

The Draize-irritancy test was designed for the ocular irritation potential of the ophthalmic product prior to marketing. According to the Draize test, the amount of substance applied to the eye is normally 100µl is placed into the lower cul-de-sac with observation of the various criteria made at a designed required time interval of 1hr, 24hrs, 48 hrs, 72hrs, and 1week after administration and rabbits are observed periodically for redness, swelling, watering of the eye[19].

**In-vitro release of Ketorolac Tromethamine from the prepared in-situ hydro gel formulations:**

A glass cylindrical tube (2.5 cm in diameter and 6 cm in length) containing the formulae to be tested was attached instead of the basket of the dissolution apparatus and tightly covered with a semi permeable membrane (0.45 µm pore size), The cylindrical tube was dipped in a 500 ml simulated tear fluid (PH 7.4), the release study was carried out at 34ºC ± 0.5, [the temperature of the eye[20], according to predetermined time regimen, aliquots of 5 ml were withdrawn and further diluted to 25 ml with STF. Ketorolac tromethamine concentration was determined spectrophotometrically at λmax 322 nm; the results were the mean values of three runs.

**Stability study of Ketorolac Tromethamine in the prepared in-situ hydro gelling systems:**

On the basis of the previous evaluation studies of the prepared Ketorolac Tromethamine formulations; F1b (0.5%Chitosan) was selected to undergo further stability studies. The selected formulation was stored in dark place at controlled room temperature (25ºC ± 2) for one year to detect any change in its characteristics which may affect efficacy or suitability for use over their shelf life. At predetermined time intervals, samples were withdrawn and examined physically for any changes and chemically for its Ketorolac Tromethamine content using the HPLC stability indicating assay. The stability study includes both physical and chemical stability.

**Isotonicity Evaluation:**

Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity. Formulations are mixed with few drops of blood and observed under microscope at 45X magnification and compared with standard marketed ophthalmic formulation[21].

**RESULTS AND DISCUSSION:**

**Evaluation of the prepared Ketorolac Tromethamine in-situ hydro gels:**

According to the results listed in table 5, clarity of all prepared formulations was found to be satisfactory. The pH was within acceptable range (from 5.5 to 6.5) and hence would not cause any irritation upon administration on to the eye. Ideally, the ophthalmic preparations should have possessed the pH in the range of 4.5 – 11[22]. Percent drug content in all formulations was found to be within the acceptable pharmacopeial range of 98.35 to 101.32% indicating uniform distribution of drug [23].

**Table 5:** Results of different evaluations studies applied on the prepared KT in-situ hydro gel formulations at different polymer concentrations

| Formula number | Composition | | Appearance (clarity) | pH Mean ± SD | Drug Content (mg/ml) Mean ± SD |
|---|---|---|---|---|---|
| | Polymer type | Polymer conc. | | | |
| **f1a** | chitosan | 0.26 | clear | 6.2±0.006 | 98.45±0.014 |
| **f1b** | chitosan | 0.50 | clear | 6.2±0.010 | 99.44±0.025 |
| **f1c** | chitosan | 1.0 | clear | 6.2±0.008 | 100.05±0.015 |
| **f2a** | carbopol | 0.12 | clear | 5.5±0.000 | 101.03±0.003 |
| **f2b** | carbopol | 0.20 | clear | 5.5±0.014 | 99.45±0.015 |

**Drug-excipient compatibility studies**

DSC characterization: The successful formulation of a stable and effective dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. DSC can be used to investigate and predict any physicochemical interactions between components in a formulation and, therefore, can be applied to the selection of suitable chemically compatible excipients. In the absence of any interaction, the thermograms of mixtures show patterns corresponding to those of the individual components. In the event that an interaction occurs, this is indicated in the thermogram of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components. Polymorphism is the ability of a substance to crystallize into two or more different crystalline forms. Any polymorphic changes in the drug may change its melting point, bioavailability, and release kinetics. Polymorphic changes in the drug, ketorolac tromethamine, were also studied by DSC by examining the melting characteristics of the drug in the presence and absence of other additives[24].

Fig. (5) A to D show the DSC thermograms of physical mixtures of ketorolac tromethamine with Carbopol® 934 and different grades of HPMC (K4M, E4M, and E15 LV). The DSC thermograms of physical mixtures showed characteristic endothermic peaks corresponding to those of the individual components and there was no appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the individual components. However the characteristic peak of HPMC E4M at 106˚C was not found in Fig. 5C, and this may be due to the formation of eutectic mixtures, and the characteristic peak at 105˚C for HPMC K4M in Fig. 5B was screened to move afterward. These findings indicate that no interaction occurs between ketorolac, HPMC (K4M, E4M, and E15 LV), and Carbopol® 934. Therefore, HPMC and Carbopol® 934 can be used as excipients in the formulation of ketorolac in situ gelling systems. There were no additional peaks to demonstrate the different crystalline or amorphous forms of ketorolac tromethamine or significant changes in the melting characteristics of ketorolac in the presence and absence of other additives indicating that no polymorphic changes in ketorolac tromethamine had taken place.

Fig. (6) A to E compare the DSC thermograms of ketorolac tromethamine, Carbopol® 934, and HPMC (K4M, E4M, and E15LV) alone. Ketorolac tromethamine showed a long and sharp characteristic endothermic peak at 170˚C due to its phase transition. The DSC thermogram of Carbopol® 934 showed endotherms between 50 to 100˚C corresponding to the evaporation of moisture and a poorly resolved change in the baseline of Carbopol® 934 at 129–139 ˚C, as previously reported[25]. An additional phase transition at lower temperatures, detected by DSC, may be related to the residual solvents that act as plasticizers but evaporate easily when the temperature increases, the polymer then showed the characteristic phase transition at 133˚C. The occurrence of several phase transitions was also seen in linear poly acrylic acids using DSC[26]. The lower phase transitions were related to the plasticizing effect of the remaining solvent used for synthesis. These remaining residual solvents, which alter the hydrogen bonding interactions among the carboxylic acids groups, may be responsible for the appearance of a secondary transition at lower temperatures in Carbopol® 934[27]. DSC thermograms of different HPMC grades, K4M, E4M, and E15 LV, showed a small and sharp characteristic endothermic peak at 105˚C, 106˚C, and 75˚C, respectively. Additional phase transitions were also found in all HPMC grades at a temperature between 40˚C and 50 ˚C. These secondary transitions may also be related to the residual solvents, which evaporate easily when the temperature increase.

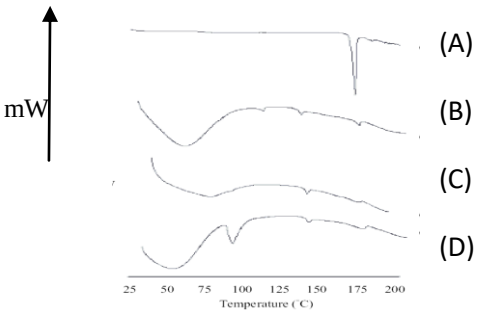



**Figure 5:** Comparison of DSC thermogram of (A) KT with the physical mixture (B) KT + HPMC-K4M+CP (C) KT + HPMC E4M+CP and (D) KT + HPMC-E15LV

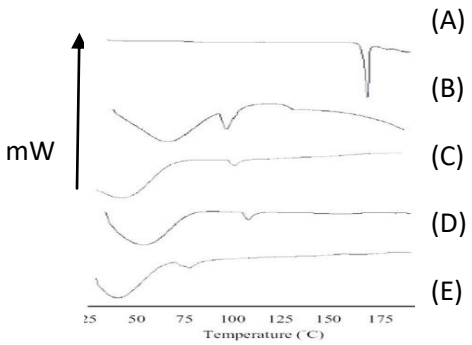



**Figure 6:** DSC thermogram of (A) Ketorolac tromethamine, (B) Carbopol® 934, (C) HPMC-K4M, (D) HPMC-E4M and (E) HPMC-E15LV

**Ocular Irritancy studies**

Ocular irritation studies indicate that KTG2 was a non irritant. The formulation was very well tolerated by the eye. No ocular damage or abnormal clinical signs to the cornea, iris, or conjunctivae were visible as shown in table 6

**Table 6:** Ocular irritation study as per the draize test protocol

| Eye part | Cornea | Iris | Conjunctiva | Total |
|---|---|---|---|---|
| **Score point** | 0 | 0 | 0 | 0 |

**Determination of gelling capacity:**

Results listed in table 7 showed that formulae F1a and F2a, gelled after a few minutes, dissolved rapidly (unacceptable formulations). But Formulae F1b and F2b, gelled instantaneously (less than a minute), and retained their consistency for a few hours on contact with STF (acceptable formulations). F1c, gelled instantaneously (less than a minute) and remained for an extended period (unacceptable formulations) as this may cause irritation to the eye upon application. These results can be easily correlated with the polymer concentration into the prepared in situ hydrogel formulations as follows, formulations of low polymer concentration (low viscosity) showed low gelling capacity (sign+) and formulations of moderate polymer concentration (moderate viscosity) showed acceptable gelling capacity (sign++),While the formulations of high polymer concentration (high viscosity) showed high gelling capacity (sign+++).

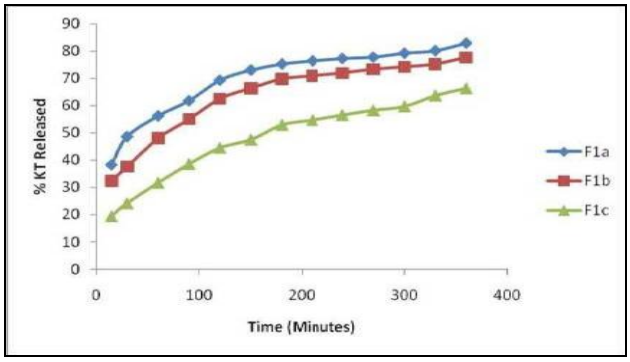
**Table 7**: Results of gelling capacity study applied on the prepared KT in-situ hydro gel formulations at different polymer concentrations

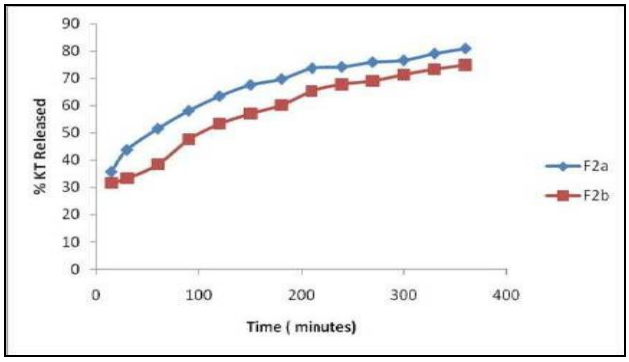
| Formula number | Gelling capacity |
|---|---|
| F1a | + |
| F1b | ++ |
| F1v | +++ |
| F2a | + |
| F2b | ++ |

Notice:
+: Gels after few minutes and rapidly dissolves.++: Immediately gels and remains for few hours.
+++: Immediately gels and remains for an extended time period.

**In-vitro release of Ketorolac Tromethamine from different formulations:**

Fig (7) shows that the percentage of drug released after 320 min from F1a, F1b, and F1c was 82.9%, 77.66%, and 66.33% respectively. Fig (8) shows that the percentage of drug released after 320 min from F2a, and F2b were 81.02%, and 74.87% respectively. It is clear from these results that all formulations showed initial burst release due to the hydrophilic nature of the prepared in situ gel formulations, slowing the release rate later on can be explained on the basis of the diffusion process of the drug through the formula that markedly retarded due to increase of the its viscosity in contact with the release media. In other words; the release of drug from the prepared in situ hydro gels is inversely proportional to the gel strength. The results of the drug release study can also be inversely related to the polymer concentrations in the prepared formula.




**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 10th h. The evaluation parameters for stability studies was shown in Table 8 and it was found that there was no significant change in the physicochemical properties from 0th to 30th day. Hence, the formulation was found to be stable.

**Table 8:** short- term stability study

| Formulation | Days | Parameters Evaluated ForThe Stability Study | | |
|---|---|---|---|---|
| | | Thickness (mm) | Folding endurance | Q10 (%) |
| F4 | 0 | 271±0.503 | 170±1.115 | 74.43 |
| | 15 | 270±0.025 | 168±1.132 | 72.48 |
| | 30 | 270±0.141 | 167±2.019 | 71.363 |

## CONCLUSION:

Ketorolac is a potent and effective aryl-acetic acid NSAID and is nonirritating to the eye, was successfully formulated as pH triggered in-situ gel forming eye drops(0.5%w/v) using carbopol 940 as a gelling agent in combination with HPMC (K15M/K4M) as a viscosity enhancing agent. The formulation was liquid at the formulated pH (6.0) and underwent rapid gelation upon raising the pH to 7.4. The gel formed in situ afforded sustained drug release over an 8-hour period. The developed formulation is a viable alternative to conventional eye drop by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability of sustain drug release. Clarity of all the formulations was found to be satisfactory. Terminal sterilization with autoclaving had no effect on the physicochemical properties of the formulations. The pH was within acceptable range and formulation does not cause any reduction upon administration of the formulation in rabbit eye during the draize test. The in-vitro release studies were carried out for all formulations using STF as the dissolution medium. The data of these studies and results indicates that (K-10, 11, 24, 26) showed better sustaining effect amongst all formulations.

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## CONFICTS OF INTEREST

The authors declare no conflict of interest in this research article.

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