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Sustained Ophthalmic Delivery of Ketorolac Tromethamine from an ion activated *In Situ* gelling system

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Abstract

The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid pre-corneal elimination of the drug may be overcome by the use of *in situ* gel forming systems that are instilled as drops into the eye and then undergo a sol-gel transition in the cul-de-sac. Hence, the purpose of the present work was to formulate and evaluate an ophthalmic delivery system for a nonsteroidal anti-inflammatory drug, Ketorolac tromethamine, based on the concept of ion activated *in situ* gelation. The sodium alginate was used in different concentrations (0.2-2.0 % w/v) as the gelling agent in combination with tamarind seed polysaccharide (TSP) (0.2-1.5 % w/v) which acted as a viscosity enhancing agent. Compatibility studies of the drug excipients were carried out using Differential Scanning Calorimetry (DSC). The prepared formulations were characterized for clarity, pH, antimicrobial efficacy, drug content, *in vitro* drug release and stability. *In vitro* release studies indicated that the sodium alginate / tamarind seed polysaccharide (TSP) solution retained the drug better than the sodium alginate or tamarind seed polysaccharide (TSP) solutions alone. The clarity, pH and drug content of the developed formulation were found to be satisfactory. The developed formulation was therapeutically efficacious, stable, non-irritant, and provided sustained drug release over an 8-h period. The formulation with benzalkonium chloride and edetate disodium improved the rate of corneal absorption but not the extent. The developed system is an alternative to conventional ophthalmic drops, patient compliance, industrially oriented and economical.

Key-Words: *In Situ* Gelation; Sustained Ophthalmic Delivery; Tamarind Seed Polysaccharide; Ketorolac Tromethamine

Introduction

Inflammation is the manifestation of vascular and cellular response of the host tissue to injury. Injury to the tissue may be inflicted by physical or chemical agents, invasion of pathogens, ischemia, and excessive (hypersensitivity) or inappropriate (autoimmunity) operation of immune mechanisms. Inflammation facilitates the immune response and the subsequent removal of antigenic material and damaged tissue. As soon as the injury is recognized, the mechanisms to localize and clear foreign substances and damaged tissues are initiated. Further the response is amplified by activation of inflammatory cells and production of chemical mediators like acidic lipids[1]e.g. Prostaglandins (PGs), thromboxanes, leukotrienes; vasoactive amines, cytokines etc .

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Ketorolac, 5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid, is a racemic mixture. The anti-inflammatory activity of the levorotatory (l) isomer of the drug is twice that of dextrorotatory isomer[2] (d). It is commercially available as the tromethamine salt which has higher aqueous solubility compared to Ketorolac. Ketorolac is applied topically in the management of seasonal allergic conjunctivitis, postoperative ocular pain and inflammation[3].

The objective of the present work was to develop a pH-triggered *in situ* gelling system for sustained ophthalmic delivery of Ketorolac tromethamine (KT), a potent and effective nonsteroidal anti-inflammatory drug (NSAID). Many NSAIDs have been tested as ocular anti-inflammatory agents in order to reduce the well-documented ocular side effects caused by corticosteroids[4, 5]. KT, an aryl-acetic acid NSAID, is nonirritating to the eye at a concentration of 0.5% w/v[6]. Aqueous ocular drops of KT are an effective and safe anti-inflammatory agent for topical use following cataract surgery and intraocular lens implantation[7,8]. KT is also known to be a viable

alternative to corticosteroids in treating ocular inflammation in the presence of pathogens[9]. An ophthalmic solution of KT (0.5%) has been shown to be effective in the treatment of chronic aphakic and pseudoaphakic macular edema[10]. Beneficial effects of KT (0.5%) topical solution in reducing postoperative pain after laser *in situ* keratomileusis have been reported[11]. The topical ophthalmic dosage of KT is one drop 4 times a day in allergic conjunctivitis and in cystoids macular edema.

The extent of absorption of an ophthalmic drug is severely limited by physiological constraints. The conventional liquid ocular formulation is eliminated from the precorneal area immediately upon instillation because of lachrymation and effective nasolacrimal drainage. Various preparations, such as ointments[12], suspensions[13], inserts[14], and hydrogels, have been developed for ophthalmic delivery system not only to slow down the drug elimination but also to lengthen the residence time of vehicle on ocular surface[15]. However, they have not been used extensively because of some drawbacks, such as blurred vision with ointments or low patient compliance with inserts[16].

An ideal ophthalmic formulation should be administrated in eye drop form, without causing blurred vision or irritation. This problem can be overcome using *in situ* gel-forming drug delivery systems prepared from polymers that exhibit sol-to-gel phase transitions due to a change in a specific physicochemical parameter in the cul-de-sac[17]. *In situ* gelation approach combines advantages of both solutions and gels, such as accuracy and ease of administration of the former and prolonged precorneal retention of the latter[18, 1 9.]

A combination of sodium alginate and tamarind seed polysaccharid[20,21,22] (TSP) was investigated as a vehicle for the formulation of eye drops of KT (0.5%, w/v) which would gel when instilled into the eye, and provide sustained release of the drug during treatment of seasonal allergic conjunctivitis and some forms of ocular inflammation.

Preservation of the ketorolac aqueous drops with benzalkonium chloride, EDTA, chlorbutanol, phenylmercuric acetate and phenylmercuric nitrate was associated with increased corneal permeation[23]. On the other hand preservation with thiomersal was found to decrease the corneal permeation of ketorolac. Presence of ascorbic acid, sodium sulphite in ketorolac tromethamine ophthalmic solution had a negative impact on the corneal permeation of ketorolac, while sodium metabisulphite favored corneal permeation. Among all the formulations ketorolac tromethamine ophthalmic solution (0.5% wt/vol) containing benzalkonium chloride (0.01% wt/vol) and EDTA (0.01% wt/vol) provided more extensive permeation.

Material and Methods

Materials

Ketorolac tromethamine was obtained as a gift sample from torrent research, village bhat, Gandhinagar, Gujrat, India. Sodium alginate was purchased from Colorcon Asia, Mumbai, India. Tamarind seed polysaccharide (TSP) was purchased from local market Jaipur, India. Benzalkonium chloride and Edetate disodium was purchased from Ranbaxy fine chemicals limited, New Delhi, India and all other reagents used were of analytical grade.

Drug-excipient compatibility studies

DSC characterization: Calorimetric characterization of Ketorolac tromethamine, Sodium alginate and tamarind seed polysaccharide (TSP) 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[24, 25].

2.3. Preparation of formulations:

2.3.1. 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[26].

Ketorolac tromethamine was found to be completely dissolved in saline phosphate buffer (pH 7.2) which was selected as the vehicle for the preparation of *in situ* gelling systems.

Preparation of in situ gelling systems

Aqueous solutions of different concentrations of Sodium alginate and tamarind seed polysaccharide (TSP) (formulation codes F1, F2, ……F12) were prepared and evaluated for their gelling capacity and

viscosity in order to identify the compositions most suitable for use as *in situ* gelling systems (Table 1).

The *in situ* gelling system of tamarind seed polysaccharide was prepared as per the procedure described by Zhidong, Liu et al (2006)[27]. For preparing the *in situ* gel-forming system the following steps were followed.

- The buffer salts were dissolved in 75 ml purified water
- The sodium alginate solutions were prepared by dispersing the required amount (0.2-2.0 %w/v) in 75ml saline phosphate buffer (PBS pH 7.2) with continuous stirring until completely dissolved.
- The alginate/ TSP solutions were prepared by dispersing the required amount of tamarind seed polysaccharide (TSP) (0.2-1.5 % w/v) in the desired concentration of sodium alginate with continuous stirring until completely dissolved. Then edetate disodium was added into the alginate/TSP solutions.
- 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 alginate/TSP solution under constant stirring until uniform, clear solution was obtained.
- Saline phosphate buffer (PBS pH 7.2) was then added to make the volume up to 100 ml.
- Finally, the prepared formulations were filtered through membrane filter (pore size 0.22 to 0.45µm) and filled into 5-ml sterilized 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.
- The detailed procedure for preparing the *in situ* gel forming system of Ketorolac tromethamine is outlined in Table 1.

Evaluation of formulations

The developed formulations were evaluated for drug content by UV Spectrophotometry at 316 nm (1700 Shimadzu), clarity by visual observation against a black and white background in a well lit cabinet, pH By Equiptronics digital pH meter, antimicrobial efficacy by agar diffusion employing 'cup plate techinique' , *in vitro* drug release by diffusion method and stability.

Selection of formulations

Gelling capacity and rheology are the main prerequisites of the in situ gelling systems. Therefore based on these two properties the formulations F8, F9 and F10 were selected and evaluated for further studies. The general appearance of the formulations was observed which included colour and clarity of solution. The pH of the prepared formulations was checked using a pH meter.

In situ gelling capacity

The gelling capacity of the formulation was determined by placing the formulation in a vial containing artificial tear fluid in the proportion of 25:7. The composition of the simulated tear fluid (STF) was: NaCl 0.67 g, NaHCO3 0.2 g, CaCl2.2H2O 0.008 g and water up to 100 g[28]. The gel formation was assessed visually and the time was noted for the gelation and also noted the time taken for the gel formed to dissolve.

Rheological studies

Viscosity of the instilled formulation is an important factor in determining residence time of drug in the eye. The prepared solutions were allowed to gel in the simulated tear fluid and then the viscosity determination were carried out by using Brookefield DV-II+ Rheometer with spindle LV-3 with angular velocity run from 6 to 100 rpm.

Determination of drug content

The drug content was determined by taking 1ml of the formulation and diluting it to 100 ml with phosphate buffer pH 7.2. Aliquot of 5ml was withdrawn and further diluted to 25ml with phosphate buffer pH 7.2. Ketorolac tromethamine concentration was determined at 316 nm by using UV-Visible spectrophotometer (UV-1700, Shimadzu Corporation, Japan)

Antimicrobial efficacy studies

Antimicrobial efficacy was determined by agar diffusion employing 'cup plate techinique' on selected formulations[29]. Wells were made with borer in the solidified medium previously seeded with test organism (Pseudomonas aeruginosa[9] and *Staphylococcus aureus)*. After allowing diffusion of the solution for 2 hours, the agar plates were incubated at 37^{o}C for 24 hrs, and then observed for zone of inhibition.

***In vitro* drug release studies**

A number of approaches have been used by different workers to conduct *in vitro* drug release from controlled ocular drug delivery systems, including bottle method, diffusion method, modified rotating basket/paddle method and technique involving flow

through apparatus[30], drug release studies were performed using a diffusion technique[31] with some modification.

In vitro release studies of Ketorolac tromethamine from the formulations were studied through cellophane membrane using a modified USP XXIII dissolution testing apparatus[32]. The dissolution medium used was simulated tear fluid freshly prepared of pH 7.2, cellophane membrane previously soaked overnight in the dissolution medium was tied to one end of a specifically designed glass cylinder (open at both ends of 5 cm diameter) a 1ml of the formulation was placed in to this assembly . The cylinder was attached to the metallic drive shaft and suspended in 50ml of simulated tear fluid (STF) maintained at 37±1ºC temperature so that the membrane just touched the receptor medium surface. The shaft was rotated at 50 rpm, at specified intervals of time (hourly), 1ml of the sample solution was withdrawn from the receptor compartment and replaced with the fresh STF. The samples were analyzed after necessary dilutions by UV-Visible spectrophotometer at 316 nm. The *in vitro* release studies were also carried out for the marketed conventional ophthalmic drops of Ketorolac tromethamine (0.5% w/v) (eye drop acular, cipla) in order to compare the release profile of the drug with the prepared *in situ* gelling system.

The drug release data were fitted to various models like Higuchi's model (cumulative percent release against square root to time), Zero order model (cumulative percent release against time), First order model (log cumulative percent release against time) and Krosmeyer's peppas model (log cumulative percent release against log time) Hixson crowell (cubeth root of % drug remained against time) kinetics to know the release mechanism. The model fitting for the drug release for the samples were calculated by using Disso software PCP Disso V3 software and Microsoft Excel. Mathematical equations that represent the release kinetics:

Q = kt - zero order kinetics (cumulative percent release against time),

Log Q = kt/2.303 - first order kinetics (log cumulative percent release against time)

$Q = k\sqrt{t}$ - Higuchi model (cumulative percent release against square root to time),

$\sqrt[3]{Q}=kt$ - Hixson crowell model (cubth root of % drug remained against time)

F= ktn - Korsmeyer's peppas model (log cumulative percent release against log time)

Where, Q is the amount of drug released at a time (t) k is the rate constant.

F= fraction of drug released at time (t)

Stability studies

The selected formulations were stored at ambient humidity conditions between 2-8ºC, ambient temperature and at 40ºC for a period of one month. The samples were withdrawn at frequent intervals and evaluated for the parameters viz. pH, appearance, gelation studies and drug content.

Results and Discussion

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[33, 34].

Figure 1-3 show the DSC thermograms of Ketorolac tromethamine, sodium alginate and tamarind seed polysaccharide (TSP) powder alone. Ketorolac tromethamine showed a long and sharp characteristic endothermic peak at 170˚C due to its ionic transition. The DSC thermogram of sodium alginate showed endotherms between 100 to 200˚C. Figure 4 shows the DSC thermograms of physical mixtures of Ketorolac tromethamine with sodium alginate and TSP. 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. These findings indicate that no interaction occurs between Ketorolac, sodium alginate and TSP. Therefore, sodium alginate and TSP 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.

Preparation of formulations

Selection of vehicle

Buffers play a pivotal role in formulating ophthalmic drops. They contribute significantly to the chemical stability and clinical response and also influence the comfort and safety of the product and, hence, it is important to selecting a suitable buffer to ensure product stability and desired drug solubility. The studies in various buffer solutions indicated that the drug was soluble in acetate buffers of pH 5.0, 5.5 and 6.0, citrophosphate buffers of pH 5.0, 6.0, 6.2, 7.2 and 7.4 and phosphate buffers of pH 5.5, 6.0, 6.5 and 7.2 at the dosage level desired (0.5% w/v). The solutions were stable to elevated temperatures and autoclaving. However, their instability to light as shown by discoloration of the exposed solutions necessitated their packing in amber vials. Saline phosphate buffer, pH 7.2 was selected as a vehicle for the formulation of *situ* gelling systems of Ketorolac tromethamine, which can precipitates at a pH below 5.0, at the dosage level desired, and so it is easily neutralized by the buffering action of the tear fluid.

Preparation of *in situ* gelling systems

The use of sodium alginate in *in situ* gel-forming systems is substantiated by the ability of its aqueous solutions to transform into stiff gels when the pH is raised. A reduction in sodium alginate concentration without compromising the gelling capacity and rheological properties of the delivery system may be achieved by the addition of viscosity-enhancing polymers such as tamarind seed polysaccharide (TSP). The two main prerequisites of an *in situ* gelling system are a high viscosity and gelling capacity (speed and extent of gelation). The formulation should have an optimum viscosity that will allow easy instillation into the eye as a liquid (drops), which would undergo a rapid sol-to-gel transition. In addition to facilitate sustained release of drug to the ocular tissue, the gel formed *in situ* should preserve its integrity without dissolving or undergoing decomposition for a prolonged period of time. Table 1 shows the gelling capacity and viscosity of formulations F1 to F12. A concentration of 0.8% sodium alginate and 0.8% tamarind seed polysaccharide (TSP) (code F10) was selected as it had a satisfactory viscosity and gelling capacity. To study the effect of benzalkonium chloride (0.01%, w/v), as preservative, alone and in combination with edetate disodium (0.01%, w/v), as permeation enhancer, on the *in vitro* drug release, the final formulations F8, F9 and F10 were selected. The formulae for F8, F9 and F10 are listed in Table 2.

Evaluation of formulations

The clarity, pH and drug content of the formulations were found to be satisfactory. All the formulations prepared were clear, transparent in colour without any turbidity or impurities and pH of the formulations were between 6.0-6.3, which is an acceptable range for ophthalmic preparations. The formulations were liquid at room temperature and they underwent rapid transition to the gel phase at the pH of the simulated tear fluid (pH 7.4). Terminal sterilization by autoclaving had no effect on clarity, pH, viscosity and gelling capacity of F8, F9 and F10 (Table 3 and Figure 5).

Viscosity enhancing polymers such as tamarind seed polysaccharide (TSP) were included in the formulations in order to achieve the desired rheological behavior. Moreover gum polymers possess mucoadhesive property which may help in prolongation of the stay of drug in cul de sac. The viscosities (m.Pa.s.) of all the formulations at 6-100 rpm as shown in (Table 3), reveals the shear thinning nature of the solutions. The some formulations with greater gel stability (F8, F9, and F10) were found to possess higher viscosities at angular velocities 6-60 rpm (Figure 5).

Antimicrobial studies

The zones of inhibition observed in agar diffusion study on the formulations (Table 4 and 5) were found to be similar, which proves the sustained release of the drug from the *in situ* formed gels.

In vitro drug release studies

Results of *in vitro* drug release studies by diffusion through cellophane membrane on the three formulations F8, F9 and F10 are given in the (Figure 6). The *in vitro* drug release conditions may be very different from those likely to be encountered in the eye. However, the results clearly show that the gels have the ability to retain Ketorolac tromethamine for a prolonged period of time (8h) and premature drug release does not occur. The addition of edetate disodium in formulation F9 did not alter the release profile of Ketorolac tromethamine. A more prolonged release was observed with F10 which showed the maximum *in situ* formed gel stability, which may be due to the higher concentration of sodium alginate along with TSP. In the cul-de-sac, the gels will probably undergo faster dissolution due to the shearing action of the eyelid and eyeball movement or dissolution in the cul-de-sac will proceed more slowly than that seen in the *in vitro* experiments, as the normal

resident volume of the lachrymal fluid in human eye is 7.5–10 µl [35]. The higher regression coefficient values (Table 6) for each formulation suggested that the formulations behaved matrix type of drug release, whereas formulation F10 showed zero order drug release kinetics. This indicates that the gels have the ability to retain Ketorolac resulting in sustained drug release. All the formulation the best fit model was higuchi matrix equation and suggesting diffusion controlled release may be due to the swelling nature of polymer. The n value obtained from peppas equation were less than 0.5,which indicated that all the formulation showed drug release by Fickian diffusion mechanism.the results were shown in table 6.

The comparative *in vitro* drug release profile (Figure 6) between the formulation F10 and marketed conventional ophthalmic drops showed 24 % and 30 % respectively after initial 1hrs. At the end of 4 hrs the drug release was found to be 90.6% from the marketed product and 71 % from the F10 indicating that the drug release was significantly prolonged by using the *in sit*u gelling systems.

Stability studies

The results of stability study of selected formulations (F10) were indicated in Table 7. The samples were withdrawn at frequent intervals and evaluated for the parameters viz. pH, appearance, gelation studies and drug content.

Conclusion

Ketorolac tromethamine a nonsteroidal anti-inflammatory drug used in the treatment of ocular infections was successfully formulated as an ion activated *in situ* gel forming ophthalmic solution using sodium alginate in combination with tamarind seed polysaccharide (TSP) as a viscosity enhancer which sustained the drug release over a period of 8 hours.

In the present study, we found that the optimum concentrations of sodium alginate and tamarind seed polysaccharide (TSP) solutions for ocular drug delivery system were 0.8 % and 0.8 % (*w*/v), respectively. When sodium alginate and tamarind seed polysaccharide (TSP) solutions were combined, the gel strength under physiological conditions was significantly increased and the combined solution was easy to administer during ocular instillation. The formulation also promises to reduce the frequency of drug administration, thus improving patient compliance. As the concept involved is novel and the methodology used for the preparation is simple as that of conventional ophthalmic liquid dosage form, it is industrially oriented and economical. The polymers used are inexpensive and easily available.

The developed formulation is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to produce sustained drug release.

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Table 1: Composition of Ophthalmic *in situ* gelling systems of Ketorolac tromethamine

Ingredients	Formulation											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ketorolac tromethamine (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium alginate (%w/v)	0.2	0.4	0.6	0.8	1.0	2.0	0.8	0.8	0.8	0.8	--	--
tamarind seed polysaccharide (TSP) (%w/v)	--	--	--	0.2	0.2	0.2	0.3	0.4	0.6	0.8	1.0	1.5
Purified water (ml) q.s	100	100	100	100	100	100	100	100	100	100	100	100
Gelling capacity	–	-	-	+	++++	++++	++	+++	+++	+++	-	-
Viscosity (m.Pa.s.)(6 rpm)	210	228	316	874	3960	4210	1192	1349	1424	1488	915	1052

Notice: -, No gelation; +, Gels after a few a min, dissolves rapidly; ++, Gelation immediate, remain for few hours; +++, gelation immediate, remains for extended period, ++++, gelation immediate but very thick gel

Table 2: Formulae of the developed formulations

Ingredients	Formulation		
	F8	F9	F10
Ketorolac tromethamine (%w/v)	0.5	0.5	0.5
Sodium alginate (%w/v)	0.8	0.8	0.8
tamarind seed polysaccharide (TSP) (%w/v)	0.4	0.6	0.8
Benzalkonium chloride (%v/v)	0.01	--	0.01
Edetate disodium	--	0.01	0.01
Citric acid I.P.	0.4	0.4	0.4
Disodium hydrogen phosphate I.P.	1.125	1.125	1.125
Purified water (ml) q.s	100	100	100

Table 3: Evaluation of In Situ Gelling Formulations

Formulation	F8	F9	F10
Appearance	Transparent	Transparent	Transparent
clarity	clear	clear	clear
pH	6.0	6.3	6.2
Drug content	97.75% w/v	99.52% w/v	99.98% w/v
Gelling capacity	+++	+++	+++

Table 4: Comparison of antimicrobial activity of the in situ gels with standard against pseudomonas aeruginosa in cup and plate technique

Conc.(ug/ml)	Standard zone of inhibition(cm)	Tests zone of inhibition(cm)		
		F8	F9	F10
20	3.8	3.3	3.5	3.5
40	4.2	3.7	3.0	3.7
60	4.4	3.0	3.1	3.1
80	4.6	3.3	3.3	3.3
100	4.8	3.7	3.8	3.5

Table 5: Comparison of antimicrobial activity of the in situ gels with standard against staphylococcus aureus in cup and plate technique

Conc.(ug/ml)	Standard zone of inhibition(cm)	Tests zone of inhibition(cm)		
		F8	F9	F10
20	3.4	3.2	3.4	3.4
40	3.9	3.7	3.7	3.8
60	4.3	4.2	4.2	4.2
80	4.6	4.3	4.5	4.5
100	4.9	4.8	4.8	4.7

Table 6: Regression co-efficient analysis and best model fit analysis for the formulations

Formulation	Zero order r^2	First order r^2	Higuchi r^2	Kosermeyer peppas r^2	n value
F8	0.9638	0.8745	0.9829	0.994	0.342
F9	0.989	0.956	0.984	0.901	0.1686
F10	0.994	0.986	0.966	0.951	0.4876

Table 7: Stability studies of Ketorolac tromethamine In situ gel of F10 formulation at room temperature and 40°C after 1 month

Formulation (F10)	Room temperature	40°C
pH	6.2	6.1
Appearance	Clear and transparent	Clear and transparent
Gelation studies	+++	+++
Drug content	99.46% w/v	99.23 % w/v

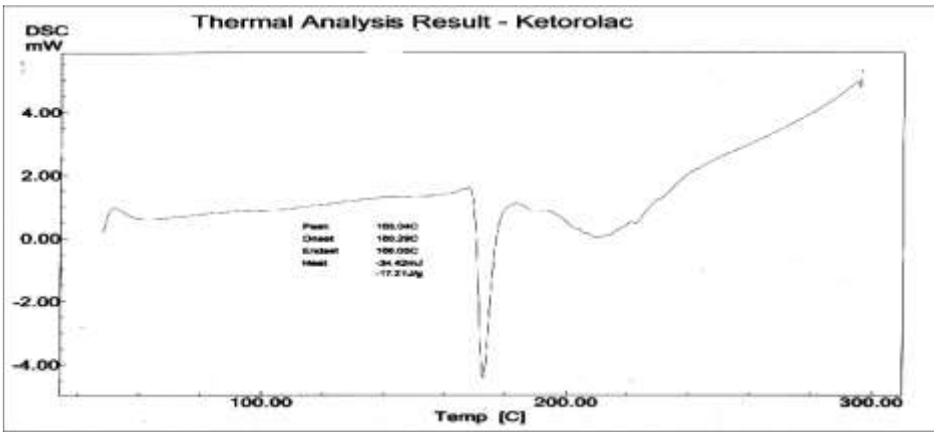

Fig. 1: DSC thermogram of Ketorolac tromethamine

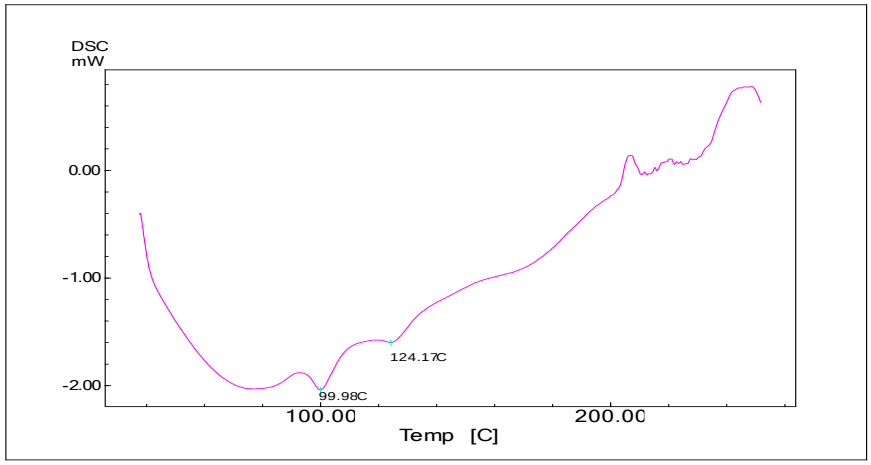

Fig. 2: DSC thermogram of sodium alginate

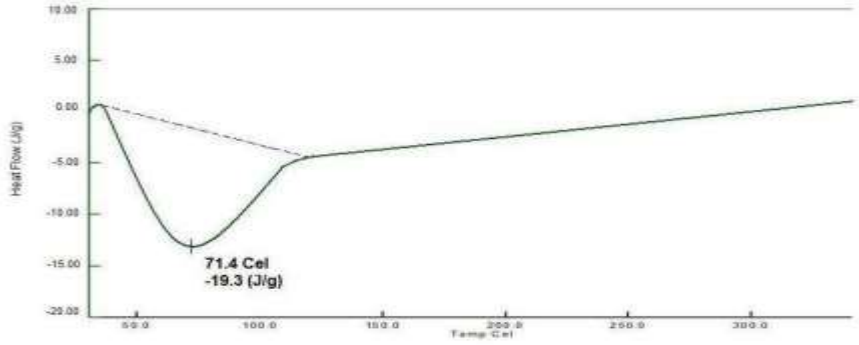

Fig. 3: DSC thermogram of tamarind seed polysacharide powder

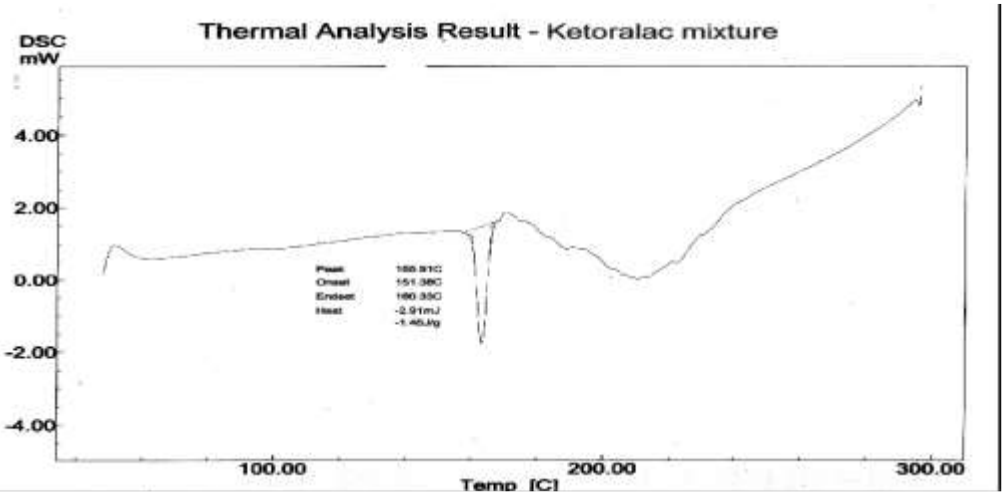

Fig. 4: Comparison of DSC thermogram of KT with the physical mixture (sodium alginate + TSP)

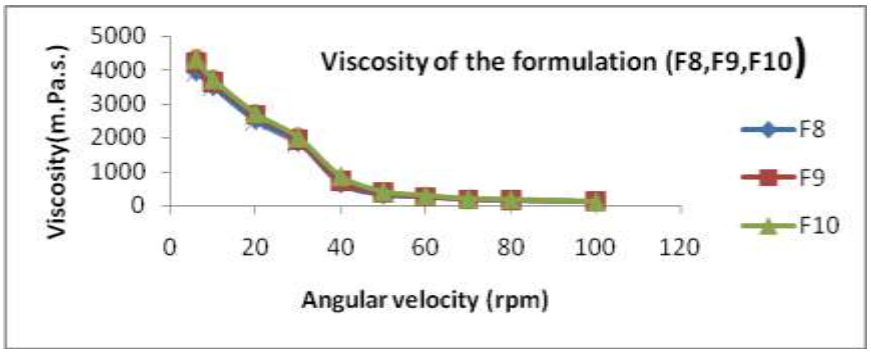

Fig. 5: Rheological profile of in situ gelling formulations (F8, F9, and F10)

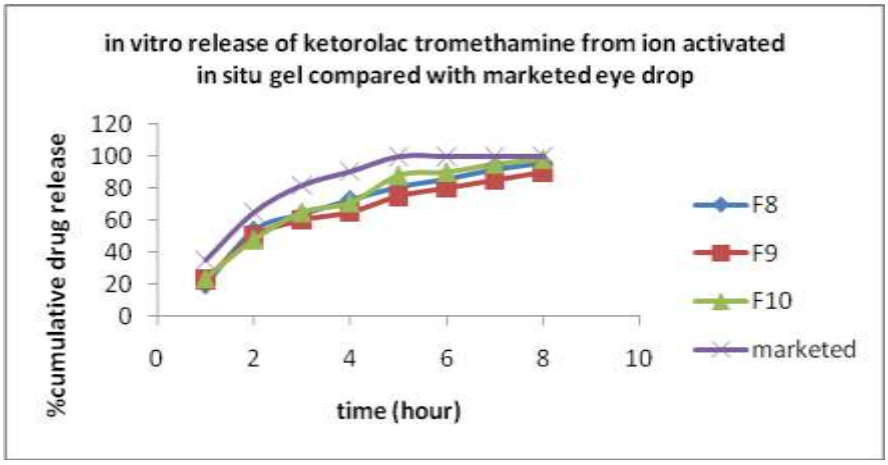

Fig. 6: comparative In vitro release profile of in situ gel formulations with marketed Preparation (Acular 0.5% w/v).

How to cite this article

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