Formulation and evaluation of pH-induced in situ gels of a non-steroidal anti-inflammatory drug (NSAID) "Ketorolac"

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Abstract

The conventional liquid ophthalmic delivery systems exhibit short pre-corneal residence time and the relative impermeability to the cornea which leads to poor ocular bioavailability. The aim of the present work was to formulate and evaluate an ophthalmic delivery system for a nonsteroidal anti-inflammatory drug, Ketorolac, based on the concept of pH Inducedin situ gelation. The sodium alginate was used as the gelling agent in combination with HPMC (0.25- 0.75 % w/v) which acted as a viscosity enhancing agent. Compatibility studies of the drug excipients were carried out using FTIR studies. The prepared formulations were characterized for clarity, pH, Gelation studies, drug content, in vitro drug release. In vitro release studies indicated that the F8 formulation containing 0.3%w/v of sodium and HPMC (10cps & 15cps) with 0.5%w/v each shows sustained drug release upto 8hrs & follows zero order kinetics with supercase II transport mechanism. The clarity, pH and drug content of the developed formulation were found to be satisfactory. The developed system is an alternative to conventional ophthalmic drops, patient compliance, industrially oriented and economical.

Key-Words: Ketorolac, Sodium alginate, HPMC, FTIR.

1) Introduction: Today, topical ophthalmic application is considered the preferred way to achieve therapeutic levels of drug agents used to treat ocular diseases. The conventional preparations for this route fall in to several categories: solutions, suspensions, semisolids, and others. Bioavailability, particularly for ocular solutions, ranges from 1 to 10 % of the total administered dose. This is due in part to the rapid precorneal clearance kinetics resulting from reflex tearing and blinking, where half-life times of instilled isotonic solutions approximate only 15 seconds in the human.[1]

The eye drop dosage form is easy to instill but suffers from the inherent drawback that the majority of the medication it contains is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul-de-sac and is rapidly drained away from the precorneal cavity by constant tear flow, a process that proceeds more intensively in inflamed than in the normal eyes, and lacrimal-nasal drainage. Therefore, only a very small fraction of the instilled dose is absorbed into the target tissues, and relatively concentrated solution is required for instillation to achieve an adequate level of therapeutic effect[2].

The frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of medication. This gives the eye a massive and unpredictable dose of megdication, and unfortunately, the higher the drug concentration in the eye drop solution, the greater the amount of drug lost through lacrimal-nasal drainage system. Subsequent absorption of this drained drug, if it is high enough, may result in undesirable systemic side effects.[3] The topical application of ophthalmically active drugs to the eye is the most prescribed route of administration for the treatment of various ocular diseases. It is generally agreed that the intraocular bioavailability of topically applied drugs is extremely poor. upon instillation of an ophthalmic solution; most of the instilled

volume is eliminated from the pre-corneal area. This loss is mainly due to drainage of the excess fluid by the nasolacrimal duct or elimination of the solution by tear turnover, which will results in poor ocular bioavailability[3].

Novel Ocular Drug Delivery Systems:

Hydrogels:Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amount of water or biological fluids. The environmental conditions to which a hydrogel can be made responsive by pH, temperature, electric field, ionic strength, salt type, solvent, external stress, light, or a combination of these.Due to their elastic properties, hydrogels can also represent an ocular drainage-resistance device.

In addition they may offer better feeling, with less of a gritty sensation to patients. In particular, in-situ forming hydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and their long-term retention property as a gel after dosing.[4]

Sol to Gel Systems: Several new preparations have been developed for ophthalmic use not only to prolong the contact time of the vehicle at ocular surface, but at the same time slow down the elimination of the drug.This problem can be overcome by using in-situ forming gel ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions and pseudo plastic behavior to minimize interference with blinking.

Such a system can be formulated as drug containing liquid suitable for administration by instillation into the eye, which upon exposure to physiological conditions will shifts to the gel phase, thus increasing the precorneal residence of the delivery system and enhancing ocular bioavailability.[5]

pH-Triggered Systems[6-10]

Gelling of the solution is triggered by changes in the pH. Cellulose Acetate Phthalate (CAP) latex, cross-linked poly acrylic and derivatives such as carbomers are used. Cellulose acetate derivatives are the only polymer known to have buffer capacity that is low enough to gel effectively in the cul-de-sac of the eye. The pH change of about 2.8 units after instillation of the native formulation (pH- 4.4) into the tear films leads to an almost instantaneous transformation of the highly fluid latex into viscous gel.

Cellulose Acetate Phthalate latex is a polymer with potentially useful properties for sustained drug delivery to the eye because latex is a free-running solution at a pH of 4.4, which undergoes coagulation when the pH is raised by the tear fluid to pH-7.4.

The poly acrylic acid and its lightly cross-linked commercial forms (polycarbophil and carbopol) exhibit the strongest mucoadhesion. Carbopol is a poly acrylic acid (PAP) polymer, which shows a sol-gel transition in aqueous solution as the pH is raised above its pka of about 5.5. Different grades of carbopol are available. The manufacturer states that carbopol-934 gel has lowest cross-linking density, while carbopol-981 intermediate and carbopol-940 have the highest.

In situ gels are made from polymers that exhibit phase transition due to physicochemical change in the environment. They can be conveniently dropped as a solution into the conjuctival sac in the eye. Upon contact with the lacrimal fluid, the polymer changes its conformation to form a gel. This delivery system has the ease of administration similar to an opthalmic solution and has a long retention time because of the gel formation. Several polymers have been used for preparing pH induced in-situ gels. The present work envisaged formulating a pH-induced in situ gelling system of an non steroidal anti-inflammatory drug (NSAID) ‘Ketorolac’ to get better patient compliance by increasing residence time and bioavailability with the objectives of developing in situ gelling system of NSAID drug “Ketorolac”, optimization of pH-induced in-situ gelling system using different polymers, HPMC 10cps, HPMC 15cps, alone and in combination,interaction studies of polymers and drug before selection of the formulation by FTIR and evaluate with respect to In- vitro Gelation and Rheological studies,Drug content uniformity,In vitro Release studies andto provide a formulation with better residence time enhanced bioavailability after topical administration and improved patient compliance.

2) Materials and Methods: Ketorolac (BMR Chemicals, Hyderabad.), HPMC 10cps, HPMC 15cps (Color cone Asia Ltd., Verna, Goa), Benzalkonium chloride and SodiumChloride (MJ Biopharmaceuticals, Mumbai) were purchased and utilized in this formulation. All materials used were ofAR Grade. UV-Visible Spectrophotometer (UV-1700)(Systronics 2201, Ahmadabad), Rheometer (DV-E)(Brooke Field Viscometer) instruments and equiments were used for the work.

METHODS:

Estimation of Ketorolac by Spectrophotometric Method[11-13]

A simple method for estimation of Ketorolac by Spectrophotometric method was developed in Simulated Tear Fluid (STF). Ketorolac in simulated tear fluid of pH 7.4 shows λ_{max} at 293 nm.

The standard stock solution was prepared by dissolving 100 mg of Ketorolac in 100 ml of simulated tear fluid, to get the 1mg/ml concentration of solution.From above stock solution, 0.02ml – 0.12 ml was pipetted out in to a 10 ml volumetric flask and made up to 10 ml with Simulated Tear Fluid to give a concentration of 2-12 µ/ml, respectively.Above working standard solution was taken for building calibration curve and absorbance was taken at λ_{max} 293 nm.

Preparation of pH Induced In-Situ Gelling System[14-15]: In situ gelling liquids were prepared using different concentrations of HPMC 10cps and HPMC 15cps with combination of HPMC 10cps & HPMC 15cps. Ketorolac (0.5 w/v) was weighed separately and dissolved in the distilled water. HPMC 15cps & HPMC 10cps solutions of different concentrations (0.25%, 0.5%, and 0.75%) were prepared by dispersing the required amount in distilled water with continuous stirring until completely dissolved. The Ketorolac solution was added to the alginate solution under constant stirring until uniform, clear solution was obtained. Further, to this mixture different concentrations of HPMC 15cps & HPMC 10cps were added. Benzalkonium chloride (0.02% w/v) was added as a preservative to the previous solutions. Sufficient amount of sodium chloride was added to the mixture to maintain the isotonicity. Finally, the volume was adjusted with distilled water up to 100 ml. Partially the dissolved pluronic solutions were stored overnight in a refrigerator at 4°C for hydration and stirred periodically until clear homogenous solutions were obtained. Nine batches of formulation were prepared by using different concentrations of HPMC 15cps and HPMC 10cps.

Table 1. Formulations of Ketorolac Ocular Insitu Gels

Ingredients(%w/v)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketorolac	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium alginate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
HPMC 10cps	0.25	0.5	0.75	--	--	--	0.25	0.5	0.75
HPMC 15cps	--	--	--	0.25	0.5	0.75	0.25	0.5	0.75
Benzalkonium chloride	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
sodium chloride	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
water	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Evaluationof formulation[16-24]

Visual Appearanceand Clarity: Visualappearance andClaritywas doneunder fluorescent light against a white and black back ground for presenceofanyparticulatematter.

pH: ThepHof thepreparedin-situgellingsystemafter additionofalltheingredientswasmeasuredusingpHmeter.

Drug Content Analysis:Drugcontentanalysisof preparedin-situgellingsystems wascarriedoutusingSpectrophotometricmethod.The assay of theseformulationswascarriedoutby pipetting0.1mlofallfour optimizedformulations,anditwasdilutedupto100ml of SimulatedTearFluid(pH7.4).Theabsorbancewasmeasuredat 293 nmusingUV-Visiblespectrophotometer.

In-VitroGelation: The Gelling capacity of the formulations containingdifferentratioof HPMC 10cps andHPMC 15cps was evaluated. It was performed by placing a drop of polymeric solution in vials containing 1 ml of Simulated Tear Fluid, freshly prepared and equilibrated at 34^0C, and visually assessed the gel formed and time forgelationaswellastimetakenforthegelformedtodissolve.

Measurement of Gelation Temperature: At room temperature, ten milliliters of cold sample solution (pluronic containing formula) were put into a beaker (25 mL) and placed in a low temperature water bath. A thermometer was immersed into the sample solution for constant monitoring. The solution was heated with stirring at 200 rpm using a magnetic bar (9 × 25 mm). The temperature at which the magnetic bar stopped moving due to gelation was reported as the gelation temperature (T_{gel}). Each sample was measured in triplicate.

Rheological Studies: It is the important factor to determine the residence time of drug in the eye by considering the viscosity of the instilled formulation. The prepared solutions were allowed to gel at physiological temperature and then the viscosity determination was carried out by using Brookfield viscometer (Brookfield DV+Pro, Brookfield Engineering Laboratories, Middleboro, MA, USA). By plotting graph of shear rate versus shear stress, the flow pattern was checked.

Drug Interactionstudies in the gels by FTIR: The preparedin-situgelformulationswere testedfor the intactnessof druginthevariousformulationsbycomparingwith puredrug. Theseweredonetoensurethat, thetherapeutically active drug has not undergone any change after it has been subjectedtoprocessingstepsduringpreparationof in-situgelling systems.Thesestudieswereperformedby takingIRspectrausing KBr method.

In-VitroReleaseStudies: In vitro drug permeation studies were carried out by putting them in situ gelling formulation on Millipore membrane filter (0.15 mm) between the donor and receptor compartments of an all-glass modified Franz diffusion cell. To simulate the corneal epithelial barrier, the Millipore membrane filter was used, as isolated cornea will not remain viable beyond 4 hr. The receptor compartment of an all-glass modified Franz diffusion cell was filled with 10 mL freshly prepared simulated tear fluid (pH 7.0), and all air bubbles were expelled from the compartment. An aliquot (1 mL) of test solution was placed on the Millipore membrane filter, and the opening of the donor cell was sealed with a glass cover slip. The receptor fluid was kept at 37 ± 0.5°C with constant stirring using a Teflon-coated magnetic stir bead. Permeation study was continued for 10 hr, and samples were withdrawn from receptor and analyzed for Ketorolac content by measuring absorbance at 293 nm in a spectrophotometer.

Drug Release kinetic Studies[25-26]: In the present study, data of the in vitro release were fitted to different equations and kinetic models to explain the release kinetics of Linagliptin from the buccal tablets. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

3) Results and Discussion:

Estimation of ketorolac by spectrophotometric method:A simple Spectrophotometric method for estimation of Ketorolac was developed in Simulated Tear Fluid, which exhibited λ_{max} at 293 nm in Beer's range of 1-12 µg/ml. Shown in Figure 1 and the spectrum for ketorolac was shown in Figure 2.**STANDARD TABLE OF KETOROLAC**

CONCENTRATION(µg/ml)	ABSORBANCE(nm)
0	0
2	0.155
4	0.319
6	0.473
8	0.628
10	0.795
12	0.934

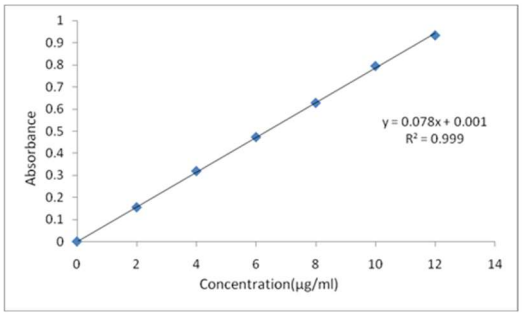


Fig. 1. Calibration curve of Ketorolac

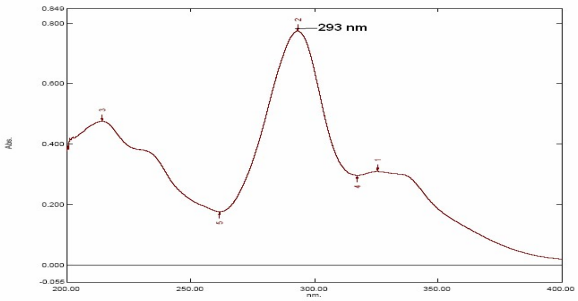


Fig. 2. UV spectrum of Ketorolac

Preparation of pH induced in-situ gelling system:

Table:2 Evaluation of pH, Drug Content Analysis,gelation temperature and gelling capacity:

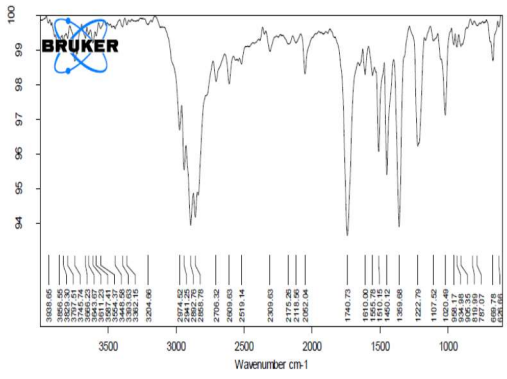
Formulations	Gelation temperature	pH	Drug content	Gelling Capacity
F1	26.92±0.15	7.5±0.01	96.14±0.22	+
F2	26.52±0.45	6.9±0.07	93.27±0.56	++
F3	25.15±0.22	6.9±0.06	98.39±0.01	++
F4	29.92±0.50	7.2±0.09	99.78±1.86	+
F5	31.18±0.33	6.9±0.04	96.65±0.52	++
F6	30.46±0.48	7.2±0.03	97.19±0.48	++
F7	38.36±0.12	7.0±0.20	96.45±1.89	++
F8	37.68±0.28	7.1±0.15	95.36±2.46	++
F9	35.43±0.72	7.3±0.05	98.52±0.66	+++

4) DISCUSSION:

Optimized in-situ gels were subjected for preliminary evaluation such as, Visual appearance, Clarity, pH and Drug content. All formulations were found transparent and clear. pH of the formulations was within limits. Drug content was found within 93.27 % to 99.78% in all optimized in-situ gelling systems.Prepared in-situ gelling systems were evaluated for in-vitro gellation capacity. All the formulations were given satisfactory results.

FTIR Studies

The prepared in-situ gelling systems were evaluated for interaction studies to ensure that there is no interaction occurred in between drug and polymers. All formulations were subjected to IR study and compared to IR absorption spectra of pure drug and studies reveal that there was no definite changes in bands were observed with respect to pure drug and was conformed that formulations did not have any drug –polymer interactions



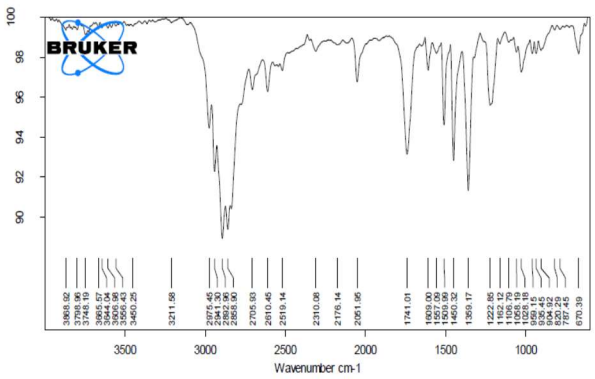


Fig. 3 IR spectra of pure ketorolac drugFig. 4.IR spectra of optimized formulation

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Rheological Studies:

Table 3: Rheological studies of all the formulations:

Shear Rate (RPM)	Viscosity (cps) of Formulations								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
2	102.1	105.0	106.5	101.0	103.0	107.1	98.6	100.2	102.2
4	96.0	97.4	99.2	94.2	98.5	99.6	91.2	94.3	97.5
6	81.2	84.5	88.4	78.5	82.3	85.4	80.4	82.1	85.4
10	63.7	66.0	68.5	61.0	64.0	69.0	61.5	64.5	66.2
20	39.5	41.2	46.4	38.0	40.2	43.2	38.0	41.6	43.7
30	29.4	31.3	36.0	29.0	31.5	34.5	27.1	30.0	32.0

During blinking the shearing force on the preparation is large. If the viscosity at high shear rate is too high, this will result in irritation. On the other hand, if the viscosity is too low, it will give rise to increased drainage. So, the formulation should have optimum viscosity for easy instillation into the eye as liquid, which will undergo a rapid sol-to-gel transition, hence the good gelling capacity.

In-Vitro Release Studies:

Table 4. In-Vitro Release Profile of Ketorolac ocular insitu gels (F1-F6)

Time(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	46.95±0.16	42.08±0.86	36.95±0.32	42.69±0.15	40.05±0.15	32.95±0.16	22.64±0.46	19.06±0.12	16.85±0.20
2	72.37±0.24	56.94±0.95	46.75±0.56	56.09±0.26	52.94±0.23	39.46±0.24	36.53±0.23	22.63±0.26	26.37±0.62
3	86.95±0.53	69.37±0.32	62.08±0.80	62.38±0.33	59.36±0.46	49.61±0.85	46.25±0.52	39.38±0.48	37.31±0.23
4	96.08±0.63	80.92±0.10	76.34±0.43	73.64±0.84	62.38±0.86	52.06±0.36	59.76±0.89	49.85±0.84	46.38±0.15
5		98.34±0.31	83.96±0.26	98.96±0.56	76.48±0.22	66.08±0.95	72.84±0.66	66.07±0.62	55.82±0.01
6			97.34±0.16		89.38±0.46	86.34±0.42	86.84±0.34	70.49±0.31	59.31±0.62
7					95.61±0.29	98.68±0.54	96.81±0.21	83.94±0.20	63.68±0.23
8								98.52±0.46	79.64±0.15

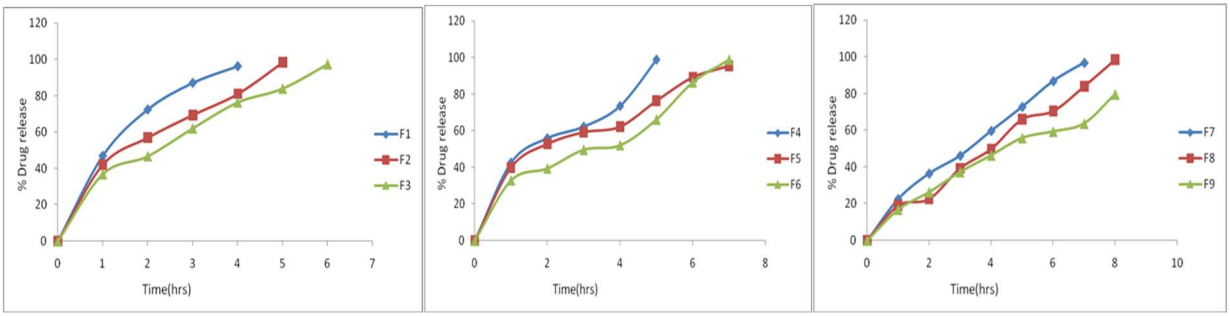


Fig 5. % Drug release for F1-F3Fig 6. % Drug release for F4-F6Fig 7. % Drug release for F7-F9

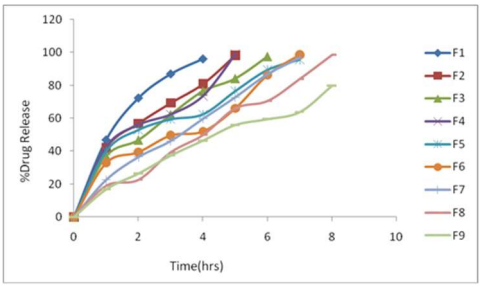


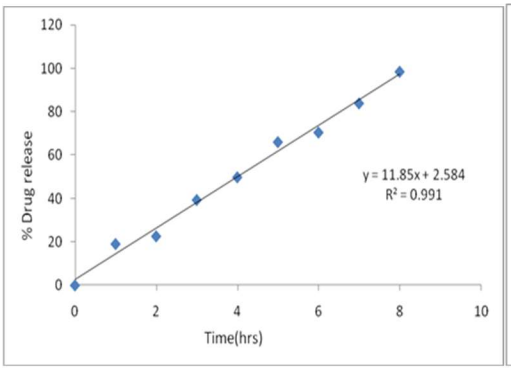
Fig 8. % Drug release for all formulations F1-F9:

Total nine formulations were designed by using two different polymers and gelling agent, among them F1 to F3 formulations, were formulated using HPMC 10cps as viscosity enhancer with three different proportions (0.25, 0.5, & 0.75%) in which maximum concentration shows sustain release upto 6hrs. Further formulations were formulated using HPMC 15cps with same proportions.

F4 – F6 formulations were formulated using HPMC 15cps as viscosity enhancer. Among them HPMC 15cps with highest concentration shows maximum sustain release upto 7hrs. Further 3 formulations were designed with combination of HPMC 10cps & 15cps.

F7-F9 formulation was formulated using HPMC 10cps & HPMC 15cps in combination. F7 formulations shows maximum drug release of 96.81% up to 7hrs. Whereas F8 formulation shows 98.52% of drug release at then of 8th hour and F9 formulation shows 79.64% drug release at the end of 8th hour due to higher proportion of polymer. So F8 formulation shows maximum drug release at the end of 8 hour hence it is chosen as optimized formulation further drug release kinetics studies were performed for F8 formulation.

Release Kinetics Mechanism for optimized formulation (F8)



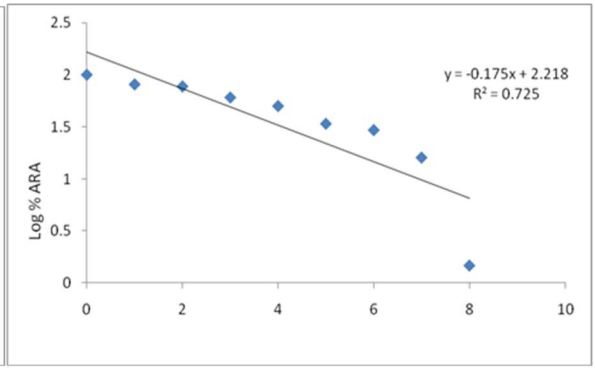
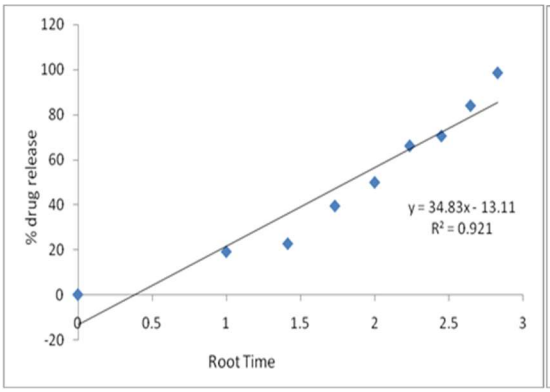


Fig 9. Zero Order KineticsFig: 10. First Order Kinetics



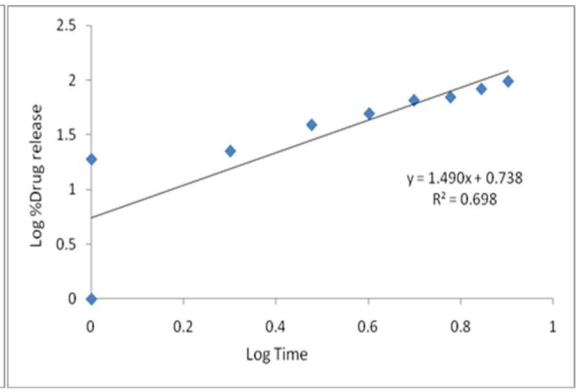


Fig: 7.10 Higuchi Release Fig: 7.11 Peppas Release

Table: 5Drug release kinetics:

R^2 values					n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F8	**0.991**	**0.725**	**0.921**	**0.698**	**1.490**

The invitro drug release data for best formulation F8 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F8 shows R^2 value 0.991. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The 'n' value is 1.490 for the optimised formulation (F8) i.e., n value was n > 0.89 this indicates Super case II transport.

5) CONCLUSION:

Ketorolac was successfully formulated as a in situ gel using HPMC as a polymer. Sodium alginate as gelling agent used in combination with HPMC as a viscosity enhancing agent. The formulation was liquid and underwent rapid gelation upon coming in contact with tear fluid. The F8 gel formed in situ afforded sustained drug release over an8-h period. The formulation were therapeutically efficacious. The developed formulation is viable alternative to conventional eye drops virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain drug release. Also important is the ease of administration afforded and decreased frequency of administration resulting in better patient acceptance.

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