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Research Article

Formulation Development and Evaluation of Ketorolac Tromethamine Gel for Topical Application in Pain Management

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Abstract

In today's world, pain and inflammation has been a matter of concern in day to day life. For the slightest disorder of pain and inflammation; patients want quick symptomatic relief. Hence there is a wide scope for delivery of analgesic, anti-inflammatory drugs through all possible routes of administration. Topical drug delivery system has been considered as fastest, easiest and safest mode of treating local inflammation. In conventional topical formulation, it was found that the drug release was for a shorter period of time. Hence there was a need for enhancing the release for an extended period of time. In present study topical formulation with penetration enhancer were used to study the effect of the drug release. For patient acceptability and quick relief from pain, development of topical gel of ketorolac tromethamine was formulated. An Experimental design of 4 formulations was set up to study influence of gelling polymer-Noveon AA-1 USP Polycarbophil with added penetration enhancers on drug delivery, to provide effective therapy to evoke a desired pharmacological effect for pain management. The effect of the above on the performance and physicochemical characteristics of formulations were assessed. The gels were evaluated based on appearance, consistency, drug content uniformity, pH, viscosity, spreadability, *in vitro* permeation studies and stability studies. Gels were physically and chemically sound with respect to their quality parameters. Developed topical gel formulation of ketorolac tromethamine was found to be an innovative approach to provide an effective therapy to evoke a desired pharmacological effect within the targeted tissues and ensuring the drugs availability in therapeutic concentration for drug release over a 5 hour period.

1. INTRODUCTION

Oral drugs take longer time to act on the process of inflammation and provide relief as they have to get absorbed and reach the site of action where as topical drugs penetrate skin readily and reach site of action within minutes and give a sigh of relief[1].

Topical drug delivery system offers several advantages like elimination of first pass metabolism, minimization of pain and possible sustained release of drugs. Gels have gained popularity due to ease of application, better percutaneous absorption, its sparkle and clarity, pharmaceutical elegance and patient acceptance[2, 3].

A Novel NSAID ketorolac tromethamine belonging to pyrrolo-pyrrole derivatives with potent analgesic and modest antiinflammatory activity; when given orally has some side effects and continuous use for more than 5 days is not recommended. Hence to overcome these disadvantages and to provide quick relief from pain, most desirable formulation would be topical preparation[4].

The study has been an endeavour to develop gel formulation ideal in all respects and have all necessary attributes that would appeal to patients thus improving patient compliance. Development of ketorolac tromethamine gel has enhanced anti-inflammatory activity which would indeed be a successful approach and a stepping stone in realizing this goal.

2. MATERIALS AND METHODS

The materials used include Ketorolac Tromethamine (gift sample from Cipla pvt ltd, Verna Goa), Noveon AA-1 USP Polycarbophil (gift sample from Lubrizol pvt ltd, Mumbai), Dimethyl Sulphoxide (gift sample from Unichem Labs, Pilerne Goa), Butylated Hydroxy Toluene (BHT) was the gift sample from Centaur Pharmaceuticals, Karaswada-Goa. Propylene Glycol, Isopropyl Alcohol (IPA), Polyvinyl Pyrrolidone K30 (PVP K30), Methyl Paraben, Propyl Paraben, Disodium EDTA and Triethanolamine (TEA) of analytical grade were procured from Loba Cheme pvt Ltd Mumbai.

2.1 Preformulation Studies

Identification of the drug was carried out by FTIR (Perkin Elmer, Mumbai, India).

2.2 Selection of Vehicle

Solubility of ketorolac tromethamine was tested in distilled water and phosphate buffer. Ketorolac tromethamine was found to be slightly soluble in phosphate buffer and freely soluble in distilled water.

Further aqueous solution of polymer-Noveon AA-1 USP Polycarbophil in distilled water formed translucent to transparent gels having pH between 6 to7.5; while that with Phosphate buffer gave translucent to whitish coloured gels having pH between7 to 8. Hence distilled water was used in the formulation. Propylene Glycol when added to the above preparation, it formed gels having good consistency as compared to that when formed with phosphate buffer. Propylene Glycol (30%) was used as solvent and humectant. TEA was added as pH control agent to maintain the pH between 6 to7.5.

2.3 Gelling Concentration

Polycarbophil was used as gelling agent as it provides excellent properties of a gel and has been extensively used to enhance the delivery of active ingredients to various mucous membranes.

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Preliminary studies were carried out to study the effective concentration of Gelling polymer Noveon AA-1 USP Polycarbophil for gel formation. Aqueous solutions of Noveon AA-1 USP Polycarbophil in varying concentration ranging from 0.5% -2 % were prepared and tested for gelling capacity. The concentration of 1.5% gelling polymer gave good viscous gel and hence was used in formulation.

Alcohol-Water mixed systems have an effect on skin permeation of drugs, probably due to increase in lipid fluidisation. Hence Alcohol-water mixed systems were used in these Gels.

The penetration enhancers promote the skin permeability by altering the skin as a barrier, either by interaction with its components or by increasing the membrane/vehicle partition coefficient. The study was carried out using combination of gelling polymers and penetration enhancers in various combinations where in 1.5 % of gelling polymer with 4 % penetration enhancer yielded best result i.e. highly penetrating with immediate gelling and for an extended period of time. DMSO, DMF and PVP K30 were used as penetration enhancers.

2.4 Formulation Development

Topical gel each containing 2% ketorolac tromethamine was prepared with polymer Noveon AA-1 USP Polycarbophil individually in combination with 3 penetration enhancers at 4% concentration.

Isopropyl alcohol was used as solvent and solubiliser. It was used in anticipation of its skin penetration enhancing effect.

Disodium EDTA was used as the chelating agent in the formulation.

BHT was used as an antioxidant which retards deterioration of drug ketorolac tromethamine by oxidation. Methyl Paraben (0.2%) and Propyl Paraben (0.02%) was used as preservative.

To find the influence of penetration enhancer on drug release an experimental design of four formulations was set up as shown in Table 1.

2.5 Preparation of Gel Formulation

The detailed procedure for preparing the topical gelling systems of ketorolac tromethamine gel was outlined as below:

The polymer was dispersed in 75 ml of water and hydrated by keeping on overhead stirrer (Remi Mechanical Stirrer, Mumbai, India) for one and half hour. Here pH should be around 3.The aqueous solution was prepared using drug, Disodium EDTA and water. Preservatives were dissolved in propylene glycol. Alcoholic solution was prepared with IPA, penetration enhancer and BHT. The alcoholic solution was added to Polycarbophil mixture. Then aqueous solution containing drug was also added. At the end propylene glycol and paraben mixture was added. Resulting mixture was slowly stirred until gelling is complete and a resilient gel is formed. At the end pH was adjusted with TEA between 6 to 7.5.

2.6 Evaluation of gels

2.6.1 Visual examination

The prepared gel formulations of ketorolac tromethamine were evaluated for physical appearance and consistency by visual assessment.

2.6.2 Estimation of ketorolac tromethamine

Ketorolac tromethamine was dissolved in sufficient volume of phosphate buffer pH 7.4 and diluted to give concentration of 100 mcg/ml. UV spectrum was obtained using UV spectrophotometry (Lambda 25 UV/Vis spectrophotometer, Perkin Elmer, Mumbai, India). The λmax was found to be 322 nm.

2.6.3 Standardization of the drug

25 mg of ketorolac tromethamine was accurately weighed and transferred to a 250 ml volumetric flask. This was dissolved completely in sufficient volume of phosphate buffer pH 7.4 and the volume was made upto 250 ml with phosphate buffer pH 7.4, to give a stock solution of 100 mcg/ml.The Calibration curve was obtained by preparing aliquots of the working standard solution of ketorolac tromethamine in phosphate buffer pH 7.4 concentrations ranging from 2, 4,6,8,10,12,14,16,18 µg/ml. The absorbances were measured at 322 nm against phosphate buffer pH 7.4 blank. This was carried out using UV Spectrophotometry. (Graph1).

2.6.4 Determination of Viscosity

Measurement of viscosity was done on formulations using Brookfield Viscometer, LVT model, fitted with spindle No.4, at speed 6 rpm, at room temperature.

2.6.7 Determination of pH

Measurement of pH was carried out on gels at room temperature using Labindia pH meter.

2.6.8 Determination of Drug Content Uniformity

To find the drug content uniformity of ketorolac tromethamine in gel, spectrophotometric method was followed.1 gm of gel was transferred to a 100 ml volumetric flask, 70 ml of phosphate buffer pH 7.4 was added and this was shaken for 15 minutes till the drug was extracted. Then the final volume was made upto 100 ml with phosphate buffer pH 7.4. This solution was filtered and then the dilution was made i.e 1 ml of the solution was diluted to 25 ml. The absorbance of resulting solution was determined at λmax 322 nm using suitable reagent blank.

2.6.9 Determination of Spreadability

The Spreadability of the gel was determined 48 hours after the preparation, by using in-house apparatus that consisted of the wooden block and two 10x10 cm glass slide plates where in one was fixed at the base to the wooden block and other was upper movable slide of 125 g to which a cup was attached using a string. 1 g of gel was spread in between the two glass plates, kept for 1 minute. 25 g of weight was added to the cup which was attached to the movable glass plate. The time was noted for upper movable slide to separate completely from the fixed slides.

The spreadability was calculated using the formula S = M*L / T where S= Spreadability, L= Length of the glass plate, M= Weight tied to the upper slide and T=Time taken to separate the slide completely from each other. Spreadability Apparatus was as shown in Fig 1. The Spreadability was measured in g.cm/s[5, 6].

2.6.10 Compatibility Studies

Chromatographic studies were performed to assess drug-excipient compatibility in order to rule out any possibility of chemical interactions under experimental conditions.Compatibility studies were conducted in solid state by Infra Red Spectroscopy and liquid state by High Performance Thin Layer Chromatography.

2.6.11 Solid state compatibility study

Infra Red spectrum of representative physical mixtures of the drug and the polymers was obtained using Perkin Elmer FTIR spectrophotometer. The software used was spectrum ES and spectrum was run from 400 to 4000cm^{-1}.

2.6.12 Liquid state compatibility study:

Solution phase compatibility study was established using High Performance Thin Layer Chromatography.The Ascending technique was adopted for the study. Each formulation was extracted with solvent mixture (2 volumes of Dichloromethane : 1 volume of Methanol), spotted on silica gel GF_{254} plate along with the spot of the pure drug solution in solvent mixture. Dichloromethane:acetone:Glacial acetic acid(95:5:2) were used as mobile phase. The distance traveled by solvent front was noted and spots were visualized in the UV chamber[7].The distance traveled by solute was also determined. The Rf values of standard and the sample were then calculated by formula given below:

$$\text{Rf Value} = \frac{\text{Distance traveled by the solute from point of application}}{\text{Distance traveled by solvent front from point of application}}$$

***2.6.13 In vitro* permeation studies**

In vitro permeation studies were carried out on all the devised formulations of ketorolac tromethamine gels using a cellophane membrane. Cellophane membrane was previously soaked overnight in phosphate buffer pH 7.4 before use. 1 g of gel was weighed and was uniformly spread over an area of cellophane membrane and it was tied or fastened to one end of hollow inverted funnel permeation cell (dialysis cell). One side of cell (donor compartment) was kept in 250 ml beaker in contact with 200 ml of phosphate buffer pH 7.4, which acts as a receptor compartment. The medium in receptor compartment was agitated using magnetic stirrer rotating at 100 rpm at temperature of 37±1^{oC}. Perfect sink

conditions were maintained. Samples (10 ml) from receptor compartment were taken at various intervals of 30 min over a period of 5 h. The volume withdrawn at each time was replaced with 10 ml of phosphate buffer. The drug concentration of withdrawn receptor fluid was measured at the λ_{max} of 322 nm using phosphate buffer pH 7.4 as blank[8, 9]

2.6.14 Stability Studies
Stability studies were performed on the formulation F1a as it satisfied all requirements of best formulation at 30°/65% RH for 1 month. The gel was then subjected to content uniformity studies (Table 4).

3. RESULTS AND DISCUSSION
Visual examination revealed that all the systems were transparent. The addition of liquid excipients improved the consistency of gels. The results for evaluation of gel parameters such as Viscosity, pH, Drug Content Uniformity, and Speadability are given in table 2.

3.1 Solid state compatibility
The study indicated that the peaks in the physical mixture spectra correlated with the peaks of the drug spectrum ranging from 400-4000 cm $^{-1}$.This denoted that the drug was compatible with the formulation components. The spectra of the physical mixtures have been documented in Fig 2 and 3.

3.2 Liquid state compatibility
The study was carried out for all the formulations along with the pure drug and the Rf values were calculated individually.The Rf values of the spots obtained from the gel formulations coincided with that of the standard (pure drug) i.e 0.85, thus confirming liquid state compatibility. Also there were no additional spots on the developed plate indicating no alteration in the drug's chemical form. (Fig 4)

***3.3 In vitro* permeation studies**
The results of *in vitro* release profile of ketorolac tromethamine gels are as indicated in table 3 and graphically shown as graph 2 and 3. Formulation F1 with the drug ketorolac tromethamine and without the penetration enhancer gave a release of 82.19±1.56%. Among the penetration enhancer used, Dimethyl Sulphoxide had the maximum release enhancing effect, giving a release of 96.67±0.05%, followed by Polyvinyl Pyrrolidone K30 and Dimethyl Formamide, each giving a release of 88.94±1.23% and 85.85±1.16% respectively. The variation in trend could be due to the effect of different excipients on the drug. From the *in vitro* permeation studies performed with synthetic membrane, it can be inferred that among the 4 formulations, the one with Noveon AA-1USP Polycarbophil and DMSO gave the highest drug release. Cumulative percentage drug release at the end of 5 hours was 96.67±0.05%. Hence it proved to be the best devised formulation. Addition of penetration enhancer caused an increase in the release of the drug. The enhancing effect of DMSO was attributed to its physicochemical properties, thus serving as a penetration enhancer.

3.4 Stability Studies
The Stability studies revealed that the physical appearance of the gel did not alter when the formulation was subjected to stability studies at 30°C/65% RH. There were no significant changes reported in the *in vitro* drug release of the drug from the formulation. The drug content was found to be in good agreement with the theoretical values (98.5% to 101.5%).

Table 1: Composition of formulations

Ingredients	Formulation Code			
	F1	*F1a	F1b	F1c
Ketorolac Tromethamine	2 %	2 %	2 %	2 %
Noveon AA-1 USP Polycarbophil	1.5 %	1.5 %	1.5 %	1.5 %
Propylene Glycol	30 %	30 %	30 %	30 %
IPA	7 %	7 %	7 %	7 %
DMSO	- -	4 %	- -	- -
PVP K30	- -	- -	4 %	- -
DMF	- -	- -	- -	4 %
Methyl Paraben	0.2 %	0.2 %	0.2 %	0.2 %
Propyl Paraben	0.02 %	0.02 %	0.02 %	0.02 %
Disodium EDTA	0.01 %	0.01 %	0.01 %	0.01 %
BHT	0.01 %	0.01 %	0.01 %	0.01 %
TEA[#]	q.s	q.s	q.s	q.s
Distilled water[*]	q.s	q.s	q.s	q.s

F1 to F1c represents the various gel formulations of ketorolac tromethamine.
** Formulation F1a is the optimized formulation in terms of in vitro release studies (Permeation studies).[#] TEA is added till pH reaches to about 6 to 7.5.[*] Distilled water is added to make up final product to 100 g.*

Table 2: Evaluation of ketorolac tromethamine gel formulations.

Formulation Code	Viscosity* (cps) (Mean ± SD)	pH* (Mean ± SD)	Ketorolac content uniformity* (mg/ml) (Mean ± SD)	Ketorolac % content uniformity* (%) (Mean ± SD)	Spreadability* (g.cm/s) (Mean ± SD)
F1	87 000 ± 100	6.90 ± 0.22	19.74 ± 1.08	98.70 ± 1.16	11.36 ± 0.26
F1a	84 000 ± 50	6.76 ± 0.12	19.78 ± 0.41	98.91 ± 0.22	12.50 ± 1.98
F1b	82 000 ± 75	6.67 ± 0.55	19.91 ± 0.84	99.58 ± 0.93	13.88 ± 0.20
F1c	79 000 ± 75	6.66 ± 1.89	19.75 ± 0.43	98.77 ± 0.56	16.66 ± 0.25

F1 to F1c represents the various gel formulations of ketorolac tromethamine.
** Each value represents average of 3 determinations.*
SD denotes Standard Deviation.

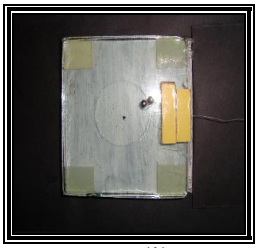
Table 3: *In vitro* release profile of ketorolac tromethamine gel

Formulation Code	*Total percent cumulative drug released at end of 5 h (%) (Mean ± SD)	*Amount of drug released at end of 5 h (mg) (Mean ± SD)
F1	82.19 ± 1.56	16.44 ± 1.26
F1a	96.67 ± 0.05	19.33 ± 0.98
F1b	88.94 ± 1.23	17.79 ± 1.85
F1c	85.85 ± 1.16	17.17 ± 1.96

F1 to F1c represents the various gel formulations of ketorolac tromethamine
** Each value represents average of 3 determinations.*
SD denotes Standard Deviation.

Table 4: Stability Study

Formulation code	Content uniformity (mg)	Percent Content uniformity (%)
F1a	19.76± 0.86	98.84± 0.08


(A)
1g of gel placed between 2 Slides and kept for 1 minute


(B)
25 g of weight added to the pan

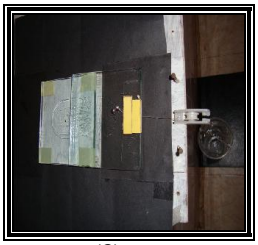

(C)
Upper movable slide separates from lower fixed slide

Fig 1: Spreadability Test

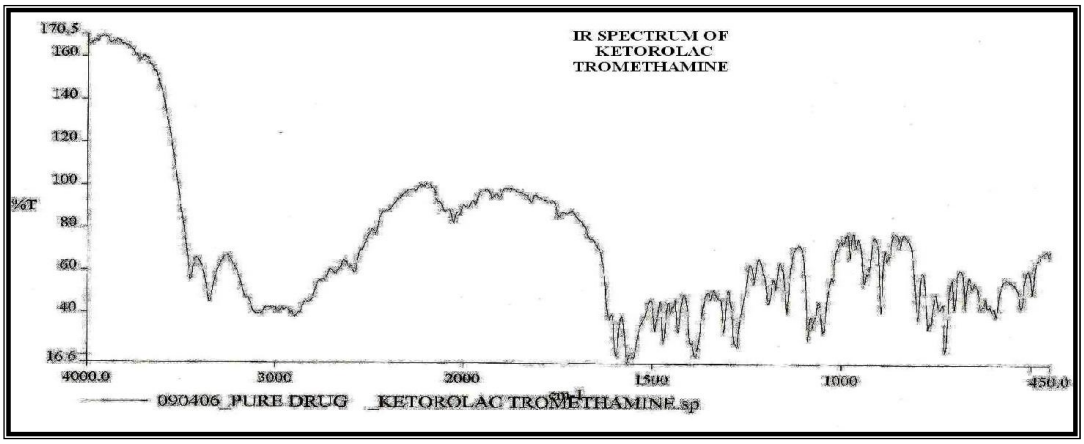


Fig 2: Spectra of ketorolac tromethamine (Pure drug)

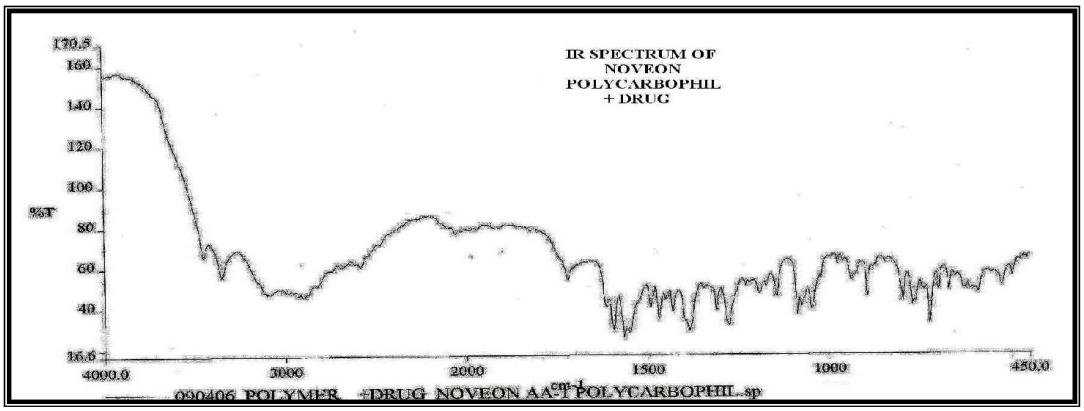


Fig 3: Spectra of Physical mixture (Ketorolac Tromethamine-Pure drug + Noveon AA-1 USP Polycarbophil-Polymer)

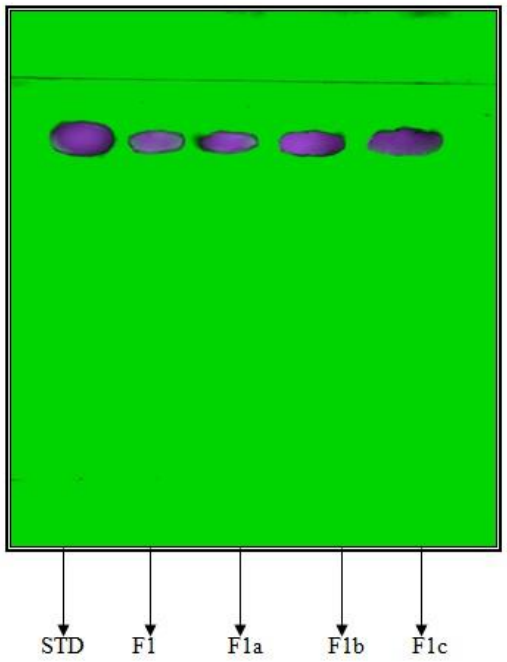
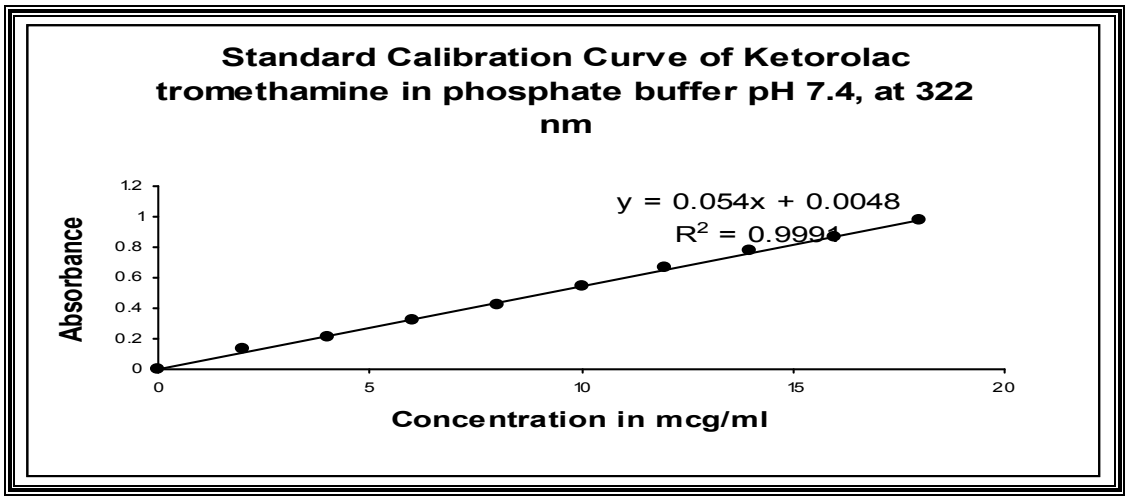
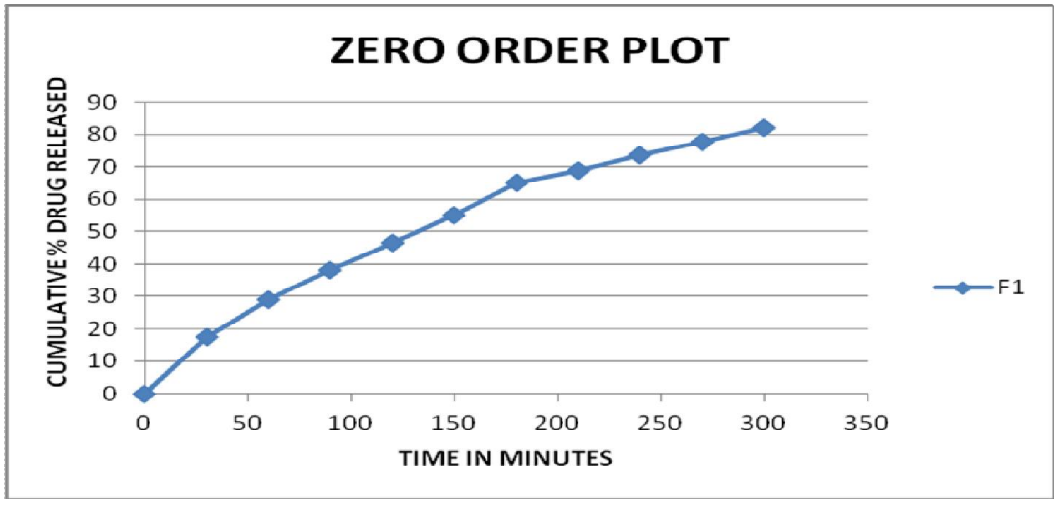


Fig 4: Liquid state compatibility- High Performance Thin Layer Chromatography



Graph 1: Standard calibration curve of ketorolac tromethamine



Graph 2: Zero Order Plot for Formulation F1

Graph 3: Zero Order Plot for Formulation F1a, F1b and F1c

4. CONCLUSION

The inferences drawn from the present study prove that devised formulations are viable alternative for reducing pain and inflammation so that ketorolac tromethamine is released for extended period of 5 hours, most efficient being Noveon AA-1 USP Polycarbophil in combination with DMSO as the drug penetration enhancer.

5. ACKNOWLEDGEMENTS

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