IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Preparation And Evaluation Of Emulgel With Ketoprofen Hydrotrope Solid Dispersions

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ABSTRACT : Oral therapy of (NSAIDS) is for the treatment of rheumatoid arthritis causes gastric irritation and ulceration. Ketoprofen has a half life of 1.5 hrs and the bioavailability of ketoprofen is 86% . The total daily dose of ketoprofen is 75 mg , hence it requires frequent dosing. Emulgel was prepared for dual controlled release of drug from emulsion and gel also avoids first pass metabolism. Different formulations were prepared using different hydrotropes sodium acetate , sodium citrate and urea in both the solid and liquid state by solid dispersion method. The prepared formulation were evaluated for various parameters like viscosity, pH, skin irritation, extrudability and invitro permeation using Franz diffusion cell . Diffusion data was fitted into various kinetic models (zero order , first order , Higuchi ,Korsemeyer peppas model). The formulation containing the combination of hydrotropes in the ratio 1:2 in 10% using almond oil as permeation enhancer was considered optimum batch and showed similar drug release to the marketed ketoprofen formulation.

Keywords: Hydrotropy, Emulgel, Frequent dosing,Extrudability, solid dispersion and Brookfield viscometer.

Introduction

Solubility is the prime requisite for a drug to dissolve which in turn effects dissolution followed by absorption. As ketoprofen belongs to BCS class II needs to enhance solubility. Though there are several techniques to increase solubility due to several advantages like simple, cost effective, safe, accurate, precise and environmental friendly the hydrotrophy is preferred for this drug.

Most of the ketoprofen adverse reactions are upper GIT complaints such as nausea, dyspepsia . Less frequent are CNS symptoms (headache, drowsiness, vertigo and insomnia). The risk of GIT bleeding and ulceration is increased when administered with corticosteroids . In order to eliminate the adverse effects of NSAIDs, the development of transdermal formulations was employed. Several topical dosage forms may be utilized to deliver NSAIDs. One of the best topical dosage forms is emulgel . The absorption of a drug in those formulation to the systemic circulation requires dissolution and release from formulation, partitioning and diffusion through SC, then partitioning from the SC into the aqueous epidermis.(1)

An emulgel is a gellified emulsion prepared by mixing an emulsion either water-in-oil (W/O) type or O/W with a gelling agent . The main advantage of the emulgel that lipophilic drugs can be easily formulated into gels. Due to solubility problems, most of lipophilic drugs cannot be formulated directly as hydrogel. For this reason; emulgel provide better stability and release of the lipophilic drug in comparison with simple hydrogel base. Other advantages for emulgel include; better stability, high loading efficiency, more production economical with low cost.(1)

Transdermal drug delivery systems are adventitious over conventional modes of drug delivery in that they avoid hepatic first pass metabolism, potentially decreased side effects and improved patient compliance . Now a days gel preparations are widely used to be applied to the skin and to mucosal surfaces of the body for local effects as well as systemic effects by penetrating the drug into systemic circulation. Normally gels are composed of a liquid phase containing thickening agents to control its flow. The liquid phase of gels permits a free diffusion of molecules through the polymers scaffold therefore the release must be equivalent to that from a simple solution.[(2)]

Materials: Ketoprofen obtained as gift sample from Vasudha pharmaceuticals ,Visakhapatnam. Remaining all the ingredients purchased from yarrow chemicals Mumbai. Almond oil obtained from local market,tagarapuvalasa ,Visakhapatnam.

Flow chart of the work

Construction of Standard graph of ketoprofen in pH 7.4 Phosphate buffer

Measuring Drug content of ketoprofen by hydrotrophic method

Selection of hydrotrophes based on equilibrium solubility studies

Preparation of solid dispersions

Preparation of ketoprofen emulgel

Evaluation of emulgel

Methods

Construction of Standard graph of ketoprofen in pH 7.4 Phosphate buffer

50mg of ketoprofen was taken and with 50ml phosphate buffer of pH 7.4 (stockI) from the stock solution of ketoprofen was subsequently diluted with buffer ofPH 7.4 to obtain a series of dilutions containing 0,20,40,60,80 and 100µg ofketoprofen per ml of solution. The absorbance of the above dilutions wasmeasured in UV-Vis Spectrophotometer at 253nm using phosphate buffer of pH7.4 as blank. The concentration of ketoprofen and corresponding absorbancevalues are plotted against each other. The above method is repeated usingwater.

Estimation of Drug Content of Pure Ketoprofen[(3)]

It was estimated by hydrotropic titration method , where 0.1M sodium hydroxide of 100ml in burette and 0.25M sodium citate of 25ml along with 1g of ketoprofen in a conical flask using phenolphthalein indicator . the percencentage purity was calculated and was found to be 99.17%

Each ml of 0.1M sodium hydroxide is equivalent to 0.02543g of ketoprofen.

Equilibrium solubility studies for selection of hydrotrophes:

The solubility of ketoprofen was determined individually in solutions of 3hydrotropic agents namely urea (U), sodium citrate (A), sodium acetate (A) atconcentrations of 10%,20%, and 30% solutions using purified water as a solvent.For determining solubility, accurately measured 3ml of a particular blend of thehydrotropic agent was taken in a 10 ml volumetric flask and excess amount ofdrug was added and mechanically shaken until saturate dissolution was formed.The volumetric flask was shaken on mechanical shaker for 12 hr. so thatequilibrium solubility was achieved, and solution was allowed to equilibrate for 24 hrs. Then solution was centrifuged at 2000rpm for 5min in ultra centrifugeand then solution was filtered through Whatman grade filter 41 filter. Aliquotwas suitably diluted with purified water and analyzed using UVspectrophotometer at 333nm.Then different combinations of above-mentioned 4hydrotropic agents indifferent ratios were tried to determine enhancement in solubility, so that totalconcentrations of hydropic agents were always 30%w/w and therefore, theseoptimized combinations of hydro tropes were selected for the preparation ofsolid dispersion.[(4)]

Preparation of Solid Dispersion:

For preparation of hydrotropic solid dispersion, accurately weighed urea, sodium acetate, sodium citrate, were taken in a beaker and were mixed properly. Then, minimum possible quantity of warm purified water sufficient to dissolve the above mixture was added (because lesser the amount of water lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely)

Preparation of Ketoprofen Emulgel Formulations Using Different Carbomers and Hydrotrpes by Solid Dispersions[5]:

Emulgel was prepared by the method reported by Mohammad et al with minor modification.

Preparation of Gel: The gel for the formulations were prepared by dispersing Carbopol 934 and carbopol 940 in purified water with constant stirring at a moderate speed separately then the pH is adjusted to 6 to 6.5 using triethanolamine left for 24 hrs.

Oil Phase Preparation: The oil phase is prepared by dissolving menthol and thymol in almond oil.

Preparation of Aqueous Phase: Methyl paraben and propyl paraben was dissolved in propylene glycol and drug was dissolved in hydrotropic mixture (sodium acetate and sodium citrate). both solutions mixed with water.

Preparation of Emulsion: Both the oily and aqueous phases were separately heated to 70 to 80 C , Then oily phase was added to the aqueous phase withcontinuous stirring until cooled to room temperature and it forms o/w emulsion.

Emulgel formulation: The prepared emulsionswere added to the gel that was prepared with carbomer934 or 940 in 1:1 ratio that results in emulgel formation

Table 1 : Ketoprofen 2.5% W/W emulgel by using Carbomer 934 And 940

Ingredients	KEF 1	KEF 2	KEF 3	KEF 4	Pure ketoprofen
Ketoprofen	250mg	250mg	250mg	250mg	250mg
Sodium acetate	2000mg	1000mg	2000mg	1000mg	
Sodium citrate	1000mg	2000mg	1000mg	2000mg	
Tween 60	0.05ml	0.05ml	0.05ml	0.05ml	0.05ml
Methyl paraben	30mg	30mg	30mg	30mg	30mg
Propyl paraben	10mg	10mg	10mg	10mg	10mg
Propylene glycol	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Thymol	50mg	50mg	50mg	50mg	50mg
Menthol	50mg	50mg	50mg	50mg	50mg
Almond oil	0.015ml	0.015ml	0.015ml	0.015ml	0.015ml
Carbopol934	250mg	250mg	-	-	250mg
Carbomer 940	-	-	250mg	250mg	
Triethanolamine	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s

The KEF1 AND KEF 3 are prepared using solid hydrotrpes by solid dispersion where as KEF2 and KEF 4 are prepared using liquid hydrotropes to show that efficcay of hydrotopes is similar in both solid and liquid state.

Evaluation tests of transedermal gel[6]

The following parameters were evaluated for the prepared emulgels.

Physical appearance, pH, drug content, extrudability studies, rheological studies and invitro drug release studies were done by following standard procedures.

Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. One gram of Ketoprofen transdermal gel formulation was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values werecalculated

Extrudability study [tube test]: It is calculated by the force required to extrude the emulgel from the tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear

rate exceeding the yield value and exhibiting consequent plug flow.Gels with high consistency may not extrude from the tube whereas, low viscous gels may flow quickly, and hence suitable consistency is required in order to extrude the gel from the tube.The formulations were filled into collapsible aluminum tubes. In this study emulgel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5cm ribbon of emulgel in 10 seconds. For better extrudability, more quantity is extruded. For the measurement of extrudability, it is done in triplicate and the average values are calculated. The extrudability is then calculated by using the following formula.

Extrudability = weight applied to extrude emulgel from tube (in gm) /
Area (in cm2)

Rheological studies: The gel formulations were placed in the sample holder of the viscometer and allowed to settle for 5 min then Viscosity was determined by using brook field viscometer using spindle S62 at 100 rpm .

Figure 1:measurement of viscosity using Brookfield viscometer

In-Vitro Release Studies: The in vitro drug release studieswere carried out using a modified Franz diffusion (FD) cell the formulationwas applied on egg membrane which was placed between donor and receptorcompartment of the FD cell. Phosphate buffer PH 7.4 was used as a donorand receptor compartment of the cell was maintained at 37^0c by circulating
water jacket. This whole assembly was kept on a magnetic stirrer and thesolution was stirred continuously using a magnetic bead. A similar bank setwas run simultaneously as a control. sample (5 ml) was withdrawn atsuitable time intervals and replaced with equal amount of fresh dissolutionmedia. Samples were removed at different time intervals and analyzed spectrophotometrically at 318nm andcumulative %drug release was calculated.

Results and Discussion

Table 2 :Calibration curve for ketoprofen in pH 7.4 Phosphate buffer

s.no	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	20	0.25
3	40	0.4176
4	60	0.6521
5	80	0.7970
6	100	0.9666

The calibration curve for Ketoprofen in pH 7.4 phoaphate buffer was constructed and it has shown that increase in the concentration resulted increase in absorbance value with r^2 value0.993 and regression equation y = 0.009x + 0.034.

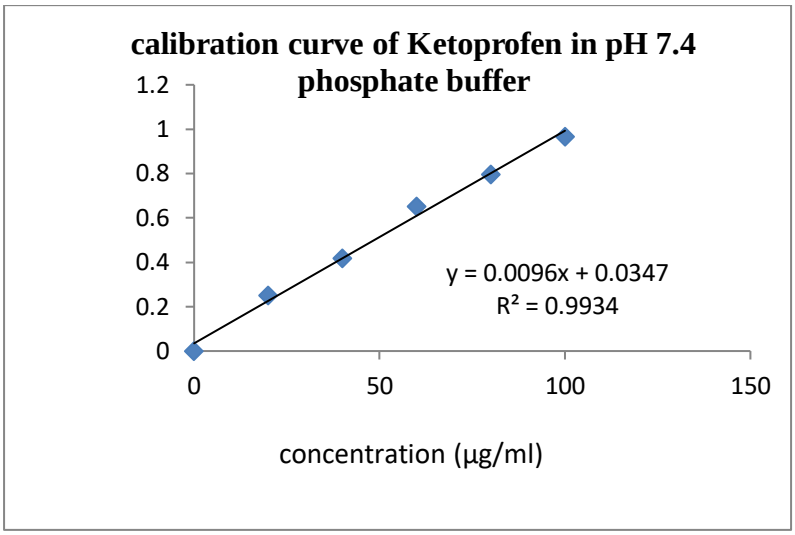

Figure 2:calibration curve for ketoprofen in pH 7.4 phosphate buffer

Table 3: Calibration curve for ketoprofen in water

s.no	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	20	0.35
3	40	0.425
4	60	0.525
5	80	0.6970
6	100	0.799

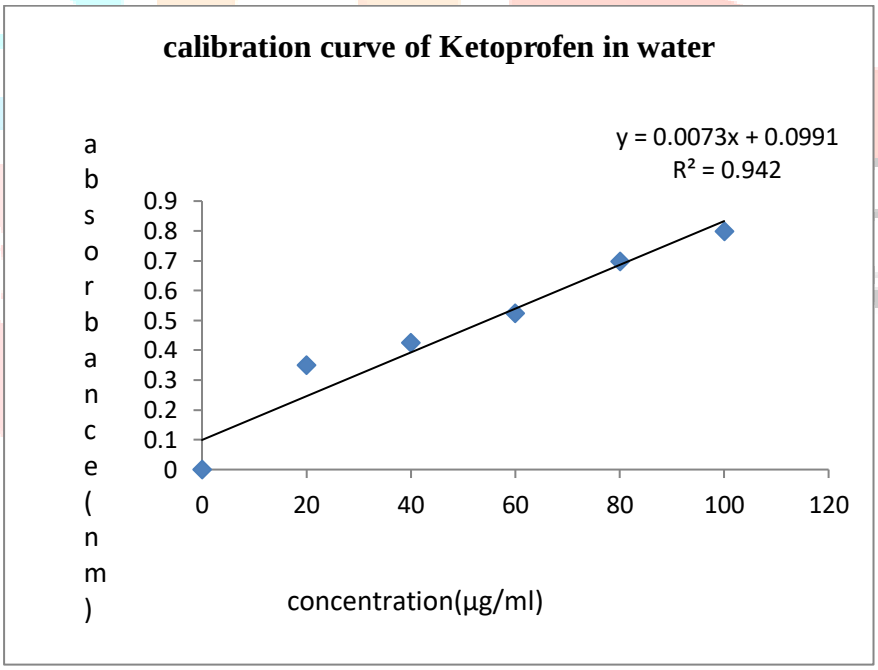

Figure 3:**calibration curve of Ketoprofen in water**

The calibration curve for ketoprofen was constructed spectrophotometrically and it has shown the increase in concentration increases absorbance with correlation coefficient 0.942.

FTIR studies:

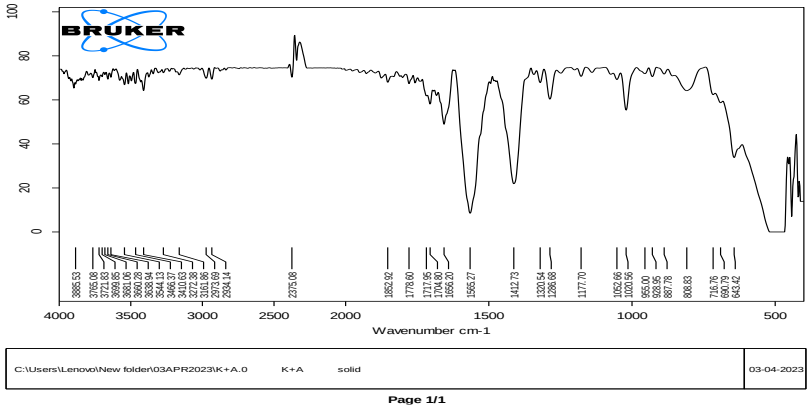

Figure 4:FTIR graph for the mixture of ketoprofen and sodium acetate

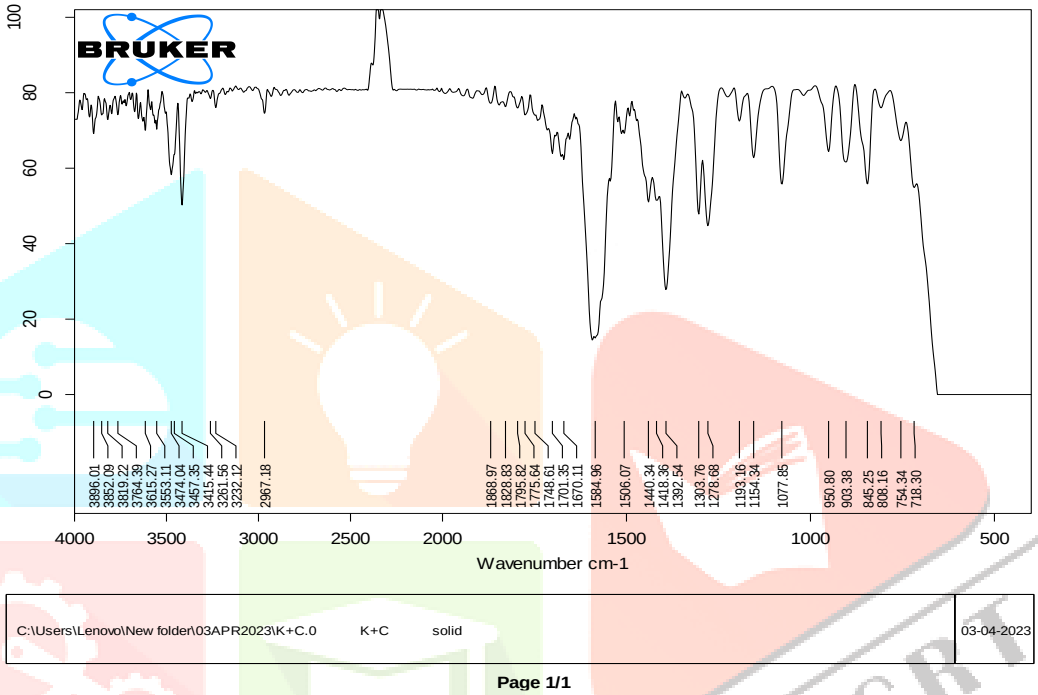

Figure 5:FTIR graph for mixture of ketoprofen and sodium citrate

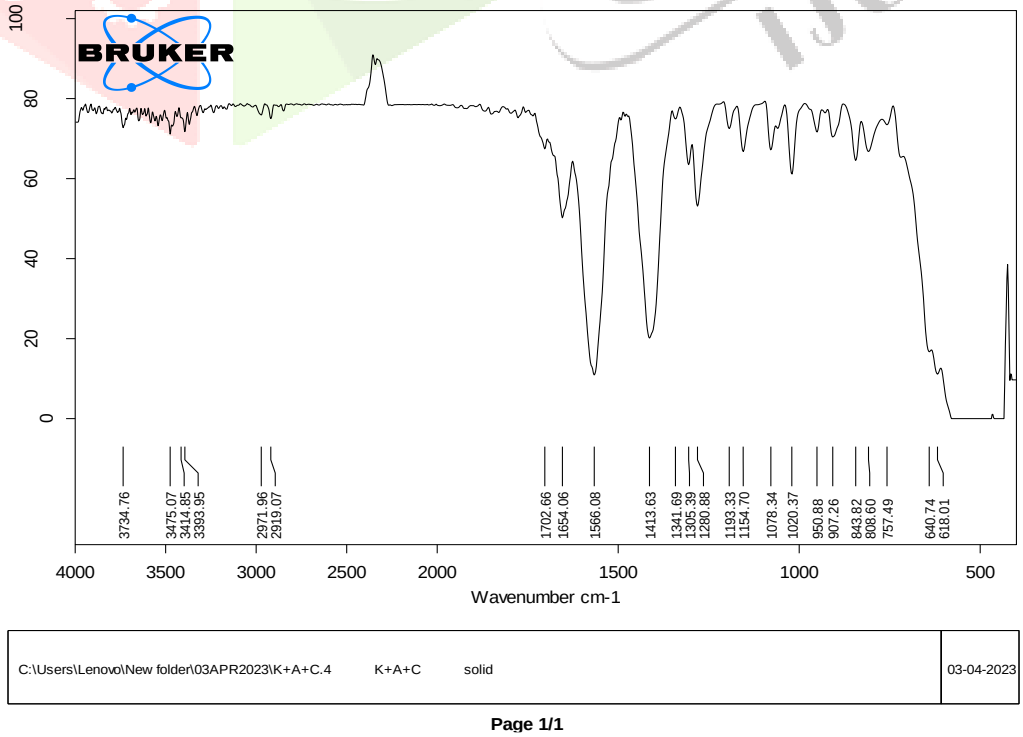

Figure 6:FTIR graph of mixture of Ketoprofen, Sodium acetate and sodium citrate

Equilibrium Solubility Studies

Table4:Solubility of Ketoprofen In different Hydrotropic agents:

Hydrotropic agents	Solubility enhancement ratio		
	10%	20%	30%
Urea	6.09	0.477	5.09
Sodium acetate	4.77	5	4.95
Sodium citrate	5	5.09	4.95

Table 5 :Solubility of Ketoprofen in mixture of different Hydrotropic Agents:

Combination	Total concentration	Individual concentration	Solubility enhancement ratio
U+A	20.00	10.00	81.81
U+C	20.00	10.00	3.40
A+C	20.00	10.00	3.54
U+C+A	20.00	5:10:5	3.09
A+C+U	20.00	7.5:10:2.5	39.54
A+C+U	20.00	10:2.5:7.5	4.454
A+C+U	20.00	10:7.5:2.5	431.81
U+C+A	20.00	5:5:10	936.36
A+C+U	20.00	7.5:2.5:10	454.54
A+C+U	20.00	2.5:10:7.5	1136.36
A+C+U	20.00	2.5:7.5:10	1127.27

Based on solubility enhancement ratio values the ketoprofen in the mixture of hydrotrophes including sodium acetate,sodium citrate and urea in the ratio 2.5:10:7.5 has highest solubility**.**The hydrotrophic mixture that contain urea become hygroscopic and hence the combination of sodium acetate and sodium citrate were used for further preparation of emulgels.

Table6: Evaluation parameters

s.no	Name of the parameter	KEF1	KEF2	KEF3	KEF4
1	pH	6.2	6.6	6.6	6.4
2	Viscosity	177-199CPS	216 -940CPS	198-218CPS	190-220CPS
3	Drug content	97.2%	96.24%	98.31%	96.17%

Fitting of diffusion data into various kinetic models:

The diffusion studies were done using franz diffusion cell and egg membrane was used as semipermeable membrane and the diffusion samples were collected from sample tube and analysed spectrophotometrically**.**

Figure 7:Zero order graph for different formulations of ketoprofen emukgel

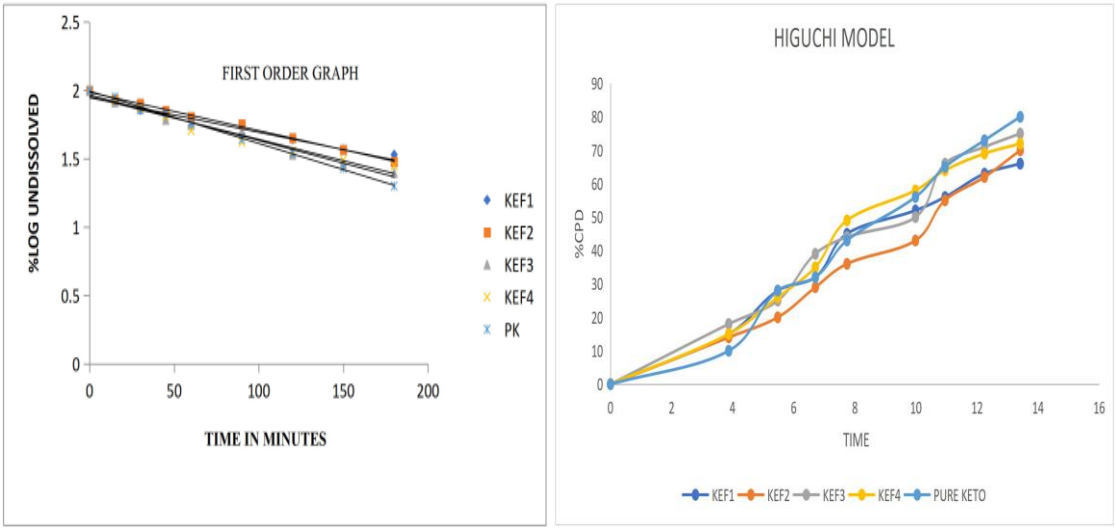

Figure 8&9 First and Higuchi graph for different formulations of ketoprofen emulgel

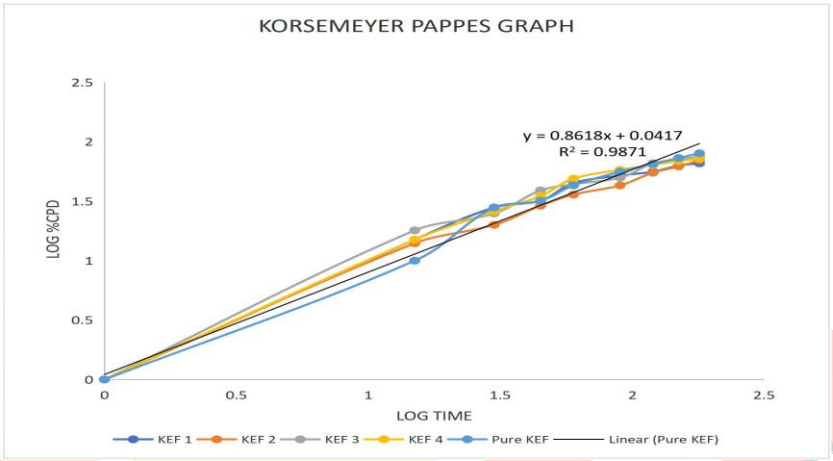

Figure10: Korse Meyer peppas graph for different formulations of ketoprofen emulgel

Table7 : R^2 values from diffusion data:

Formulation	R^2 values			n value from Korsemeyer peppas
	Zero order	First order	Higuchi	
KEF1	0.8793	0.9549	0.9843	0.8093
KEF2	0.9625	0.9959	0.9792	0.8086
KEF3	0.9215	0.9837	0.9822	0.826
KEF4	0.8829	0.9610	0.9781	0.8353
Pure Ketoprofen	0.9435	0.9972	0.9791	0.8618

Summary and conclusion

The prepared emulgels were creamy , clear no particles were formed,no phase difference was observed. the pH values were isotonic with the blood pH , better extrudability was observed in all the four formulations and the formulation with carbopol 940 and with hydrotropes in solid state has highest solubility . the hydrotropes that was prepared with urea becomes so hygroscopic hence the combination of sodium citrate and sodium acetate was selected for further preparation of emulgels. Based on r^2 values the drug release follows first order kinetics,and drug release followed diffusion and anomalous transport(from the korsemeyer peppas graphs n values were found to be $0.45<n<1$).

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