IN-VITRO RELEASE PATTERN OF KETOPROFEN USING ETHYL CELLULOSE ETHER DERIVATIVES

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ABSTRACT

The aim of this study was to formulate and evaluate polymeric tablets of Ketoprofen for the release rate, and mechanism. Formulations with different types and grades of Ethyl Cellulose Ether derivatives were prepared in several drug-to-polymer ratios (D:P ratio 10:1, 10:2 and 10:3). These formulations were compressed into tablets using the direct compression method. They were examined for the physical properties and appearance. Tablet dimensional tests i.e., (thickness, diameter) and QC tests (hardness, friability, and disintegration) were performed according to the USP methods. Invitro dissolution was performed. In order to analyze the drug release kinetics from each of the prepared matrices, five standard mathematical models were applied to the release data. The study showed that in case of tablets containing Ethocel premium polymers of 7, 10, and 100 grades show approximately 90-98% release of the drug from tablet in 24 hours compared to the Ethocel FP premium of 7, 10, and 100 which showed less release in 24 hours following nearly zero order kinetics.

Key words. Ethocel, Ketoprofen, Controlled release, Tablets.

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INTRODUCTION

The researchers made a lot of efforts in controlled drug delivery systems e.g. sustained release formulations in which the drug is released over an extended period of time in a slow manner.(1). A variety of controlled release drug products are designed for different routes of administration based on the physiological, physicochemical and pharmacokinetic properties of the drug (2). To achieve a sustained release formulation with appropriate release profile, the proper selection of polymeric materials having desired physicochemical properties is important(3). Ketoprofen is a drug belonging to the family of non steroidal anti-inflammatory drugs (NSAIDs). It is a Propionic acid derivative and is used in the treatment of rheumatoid arthritis. (3). Like other NSAIDs, Ketoprofen is used in clinics as an anti-inflammatory and analgesic drug for the treatments of rheumatoid arthritis and osteoarthritis. (4)

Ketoprofen and other NSAIDs have poor tolerability profile having some adverse effects (5) such as nausea, vomiting and epigastria headache, drowsiness and dizziness (6).

To over-come these adverse effects it was thought to prepare controlled release matrix formulations of Ketoprofen using ethyl cellulose ether derivatives (Ethocel as rate controlling agents. Is there any evidence that controlled release formulations avoid the adverse effects? If yes, include the studies and describe composition of formulations from the literature and the mechanisms through which modified formulations avoid side effects. Ethocel standard premium is the conventional granular product, but Ethocel standard FP premium is the new product, it exists in a very finally milled form, this allowing the use of direct compression to incorporate into the controlled release matrix (7).

METHODOLOGY

Material &Chemicals

Chemicals like Sodium hydroxide, monobasic potassium phosphate, (Merck, Germany), Ketoprofen, Lactose, Magnesium Stearate (BDH. England), Ethocel standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium were of analytical grade and were used without any further purification. And the equipments like Dissolution Apparatus (Pharma Test, Germany), Double Beam UV-Visible Spectrophotometer (Shimadzu, Japan), Single Punch Tablet Machine (Erweka, Germany), Hardness Tester (Erweka, Germany), Friability Tester (Erweka, Germany) were used for this research work.

Construction of Standard Calibration Curve

The standard curve was prepared by using 7.4 pH phosphate buffer solutions with the help of UV visible spectrophotometer

20 mg of ketoprofen was taken in 100ml volumetric flask for the preparation of stock solution in Phosphate buffer (pH 7.4). The drug was dissolved by using ultra-sonifier. This stock solution was used for further dilutions. 50 ml of this stock solution was taken in a 100ml volumetric flask and 50 ml of the buffer was added to it to make the volume upto 100ml. the concentration of the drug in this first dilution was 0.1 mg/ml. then from this dilution 50 ml was taken and further diluted to 100 ml with the buffer the drug concentration in solution was 0.5 mg/ml. Similarly 0.025mg/ml, 0.0125, 0.00625 mg/ml dilutions were prepared in the same way. These dilutions were then analyzed at 258nm spectrophotometrically.

Formulation Development

Tablets of 200mg ketoprofen containing 100mg drug and different grades of ethocel (7, 10, 100 premium and FP) at drug to polymer ratio of 10:1, 10:2, and 10:3 were prepared. Lactose was used as filler and 0.5 % magnisium stearate was used as a lubricant. The formulations are given in Table 1. Sixty tablets were formulated for each type of formulation according to the above drug to polymer ratio.

Table 1. Formulations of Ketoprofen Tablets

D:P Ratio	Drug	Polymer		Filler (Lactose)	Lubricant (Mg.Stearate)
10:1	100mg	7 Premium	10 mg	89 mg	0.5 %
		7 FP Premium			1 mg
		10 Premium			
		10 FP Premium			
		100 Premium			
		100 FP Premium			
10:2	100mg	7 Premium	20 mg	79 mg	1 mg
		7 FP Premium			
		10 Premium			
		10 FP Premium			
		100 Premium			
		100 FP Premium			
10:3	100 mg	7 Premium	30 mg	69 mg	1 mg
		7 FP Premium			
		10 Premium			
		10 FP Premium			
		100 Premium			
		100 FP Premium			

Characterization of the Tablets

After the tablet preparation, quality control tests were carried out for all formulations. The dimensional tests of the tablets were performed by using Vernier caliper according to USP Method. Hardness test was performed for ten tablets according to the USP Method by using hardness tester (Erweka, Germany). The friability test was carried out in a friability tester on 20 tablets from each formulation. Disintegration test was performed on six tablets from each formulation by using disintegration apparatus. Weight variation tests were also performed on 10 tablets of each formulation.

In vitro Drug Release Study

The in vitro study was carried out by using Pharma test dissolution apparatus (Hainburg, Germany). Rotating basket method was adopted for the drug release study of all tablets including conventional and SR tablets formulations. The dissolution media used was phosphate buffer (pH 7.4) for Ketoprofen. Temperature of dissolution medium was maintained at 37± 0.5 ^{o}C and the rotating speed was 100 rpm. 5 mL samples were taken at time intervals of 0.5, 1, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 10.0, 12.0, 18.0 and 24 hours and filtered by using filter paper of 0.45 µm. All the samples were analyzed using spectrophotometer and their respective absorbances were noted. The percent release was calculated for all tablets from the standard curve.

Investigation of the Drug Release Kinetics

The drug release kinetics for each matrix was analyzed by assessing the fitting of the release data to each of the following models.

Zero-order Kinetics(8)	$W=K_1t$	(A)
First-Order Kinetics(8)	$In\ (100-W)= In100 - K_2t$	(B)
Higuchi-Kinetics(9)	$W=K_4t^{1/2}$	(C)
Hixson-Crowell Kinetics(8)	$(100-W)^{1/3}= 100^{1/3}- K_3t$	(D)
Korsmeyer-Peppas equation(10)	$Mt/M\infty=K_5\ t^n$	(E)

Where

K_1-K_4= Drug Release rate constant

W= Percent Release of drug at time t

Mt/M∞= Fractional release of drug into the dissolution media

K_5= constant that incorporate geometric and structural properties of tablet

n= diffusion exponent that show the release of drug transport mechanism

When n=0.5 then drug release through quasi Fickian diffusion mechanism

When n>0.5 then the drug release through anamolus, a non Fickian or zero order release kinetic

When=1 then a non Fickian or zero order release kinetic is followed (10).

RESULTS AND DISCUSSION

From the standard curve the R^2 valve was determined which was 0.999.

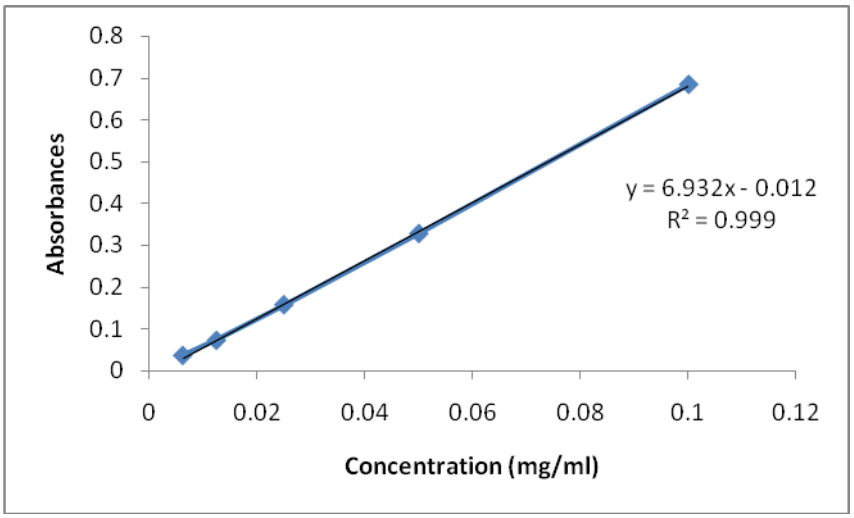

Figure 1 (Standard Curve)

Physical Tests

All the physical tests which were performed were within permissible ranges.

Dissolution

Dissolution study was conducted for all the formulations upto 24 hours by using USP method I (Basket method)

Drug Release Studies

Drug release studies were carried out on all tablet formulations. The release profiles of Ketoprofen tablets containing different grades of Ethocel polymers i.e. 7, 10 and 100 Premium and FP premium in different ratios of 10:1, 10:2 and 10:3 are given in Figures 2, 3 and 4, respectively. Figure 5 shows comparison of conventional tablet of Ketoprofen and reference SR tablets of Ketoprofen with the prepared Ketoprofen matrix tablets with drug to polymer ratio of 10:2 of different polymers.

From the figures 2, 3 and 4 it can be observed that the prepared matrix formulations of Ketoprofen show reduced release profile from that of the standard conventional tablets of the respective drugs. In case of 10:1, 10:2, 10:3 the average release percentage for Ethocel premium of 7, 10, 100 grades was 98.21% ± 0.210, 97.23% ± 0.314 and 95.25 ± 0.36 respectively and in case of 10:1, 10:2, 10:3, the average release percentage for Ethocel FP premium of 7, 10, 100 grades was 73.27% ± 0.310, 71.23% ± 0.145 and 70.457 ± 0.288. Tablets containing FP premium grades of Ethocel 7, 10, and 100 extended drug release profile due to small particle size as compared to the Ethocel premium of 7, 10, 100 grades. So the particle size of polymer is a determining factor in controlling the release of Ketoprofen from tablets

Generally the figures show that in case of tablets containing Ethocel premium polymers of 7, 10, and 100 grades show approximately 90-98% release of the drug from tablet in 24 hours compared to the Ethocel FP premium of 7, 10, and 100 which showed less release in 24 hours. It is also illustrated that there was no significant effect of drug to polymer ratio on the drug release profile. Figure 2 also show the release profile of conventional and SR standard formulations which shows that Ethocel Standard 7, 10 and 100 Premium and Ethocel Standard 7, 10 and 100FP could more efficiently extend the release of the drugs as compared to the reference conventional formulation.

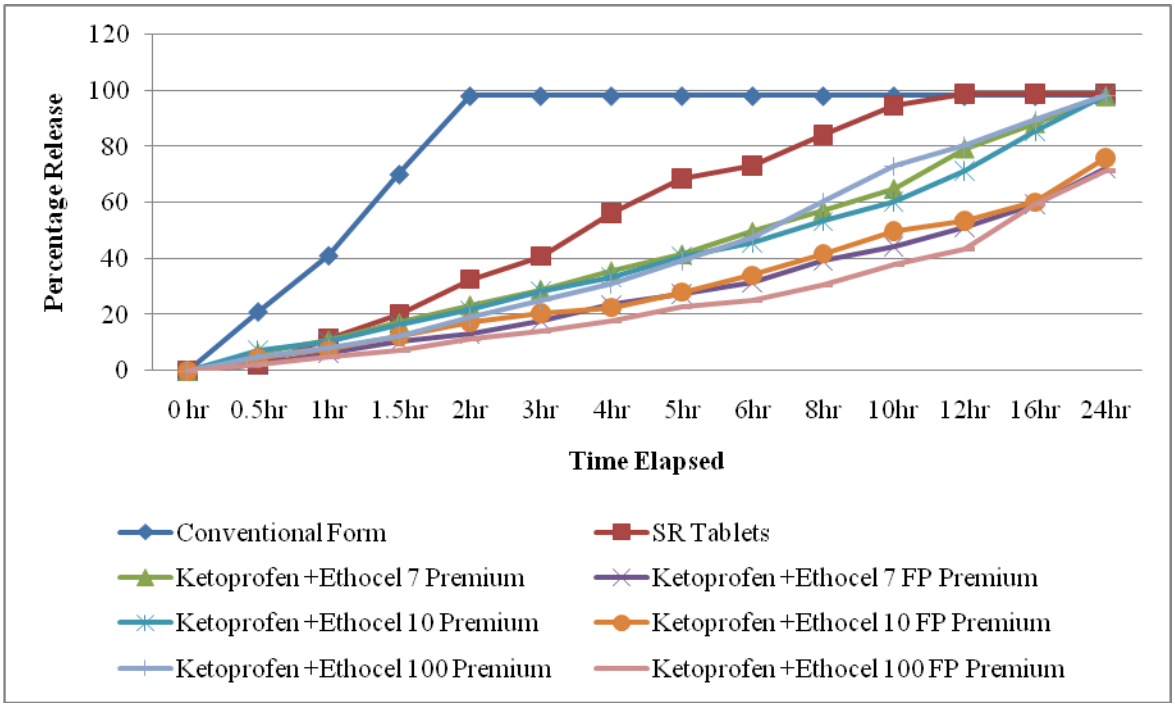

Figure No. 2 Release profile of Ketoprofen + Ethocel (10:1)

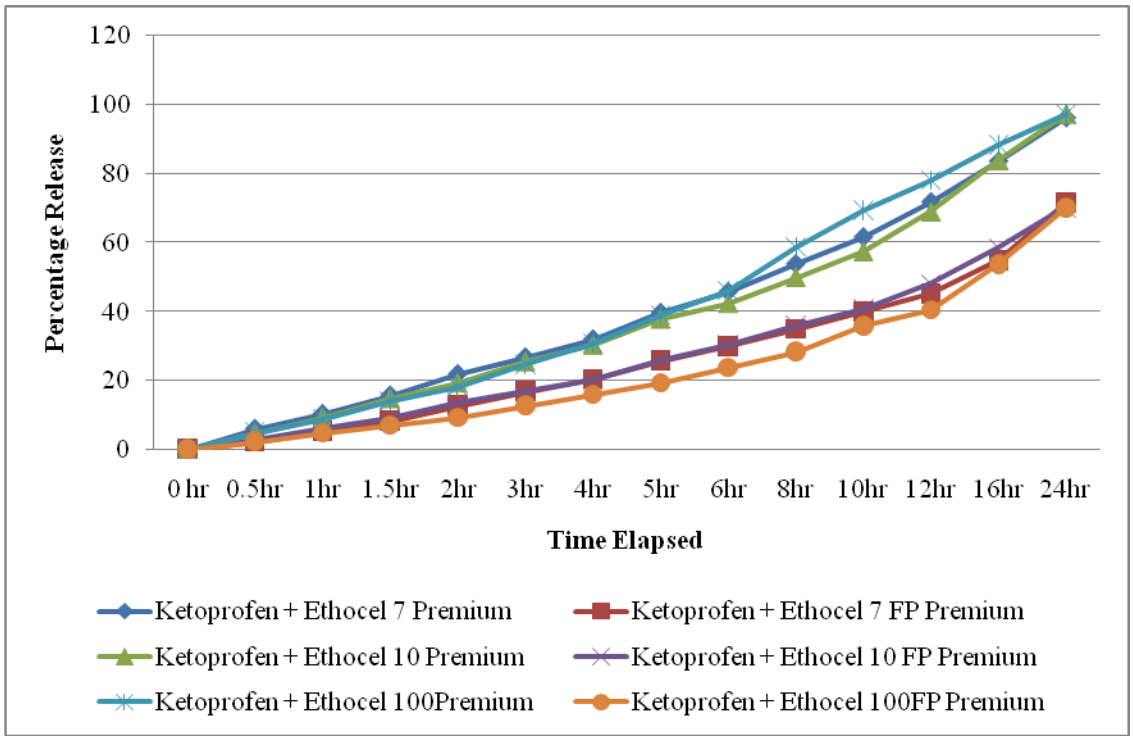

Figure No. 3 Release profile of Ketoprofen + Ethocel (10:2)

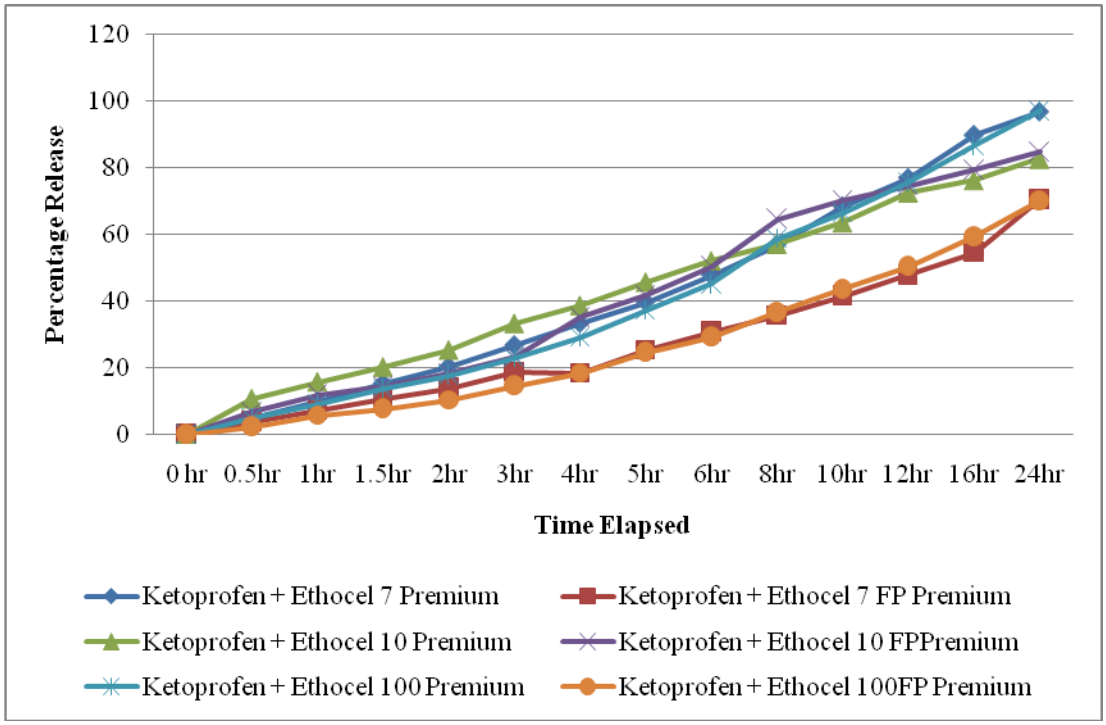

Figure No. 4 Release profile of Ketoprofen + Ethocel (10:3)

In Vitro Drug Release Kinetics

Drug release kinetics for each matrix was analyzed by using the models shown above.

Tables 2, 3 and 4 show the release kinetics of Ketoprofen tablets having different drug to polymer ratio of 10:1, 10:2 and 10:3. The n value was also greater than 0.5. it indicates that the ketoprofen formulations show anamolus-non Fickian drug-diffusion. These results confirming with the findings of Amit (11), in whose investigation on zidovudine release from guar gum matrix tablets showed a higher value of n i.e n>0.5. here the author (Amit) concluded that mechanism of the drug release was a result of coupling of two mechanisms, i.e. erosion and diffusion. Swelling of the matrix tablets occurred during the dissolution. This may be due to hydrating property of the polymer which eventually leads to the swelling of the tablet. The dissolution solvent provides a stress due to which there is relexation response in the polymer-chains and this creates an increase in the distance between the polymer-chains disruption of polymeric membrane (7). When n>0.5 then the drug release through anamolus, a non Fickian or zero order release kinetic (10). As shown in the tables 2, 3, and 4 the n values for the tablets is greater than 0.5 do nearly all matrix tablets shows anamolus, a non Fickian or zero order release kinetics.

Table No. 2. Release Kinetics of controlled release tablets of Ketoprofen-Ethocel 7P: 7FP, 10 P, 10FP, 100P, 100FP at drug to polymer ratio (D: P) of 10:1 in pH 7.4 Phosphate buffer

Formulation Ketoprofen-Ethocel	W = k1t		(100-w) = ln100-k2t		(100-w)1/3= 1001/3-k3t		W = k4t1/2		Mt / M∞ = k5 tn		
	k1 ± S D	r1	k2 ± SD	r2	k3 ± SD	r3	k4± SD	r4	k5 ± SD	r5	n
Controlled release tablets of Ketoprofen -Ethocel standard 7 Premium											
10:1	5.11 ± 2.44	0.987	0.11 ± 0.28	0.788	0.15 ± 0.36	0.924	5.51 ± 2.16	0.988	0.76 ± 2.55	0.949	0.892
Controlled release tablets of Ketoprofen -Ethocel standard 7FP Premium											
10:1	2.94 ± 1.79	0.997	0.07 ± 0.13	0.888	0.052 ± 2.14	0.973	3.37 ± 0.78	0.979	4.89 ± 7.81	0.999	0.989
Controlled release tablets of Ketoprofen -Ethocel standard 10 Premium											
10:1	5.01 ± 2.35	0.979	0.084 ± 0.31	0.815	0.31 ± 0.44	0.739	5.38 ± 2.10	0.97	0.85 ± 1.27	0.852	0.997
Controlled release tablets of Ketoprofen -Ethocel standard 10FP Premium											
10:1	3.07 ± 0.77	0.981	0.06 ± 0.21	0.954	0.19 ± 0.15	0.565	5.10 ± 0.56	0.971	1.12 ± 4.18	0.962	0.878
Controlled release tablets of Ketoprofen -Ethocel standard 100 Premium											
10:1	3.52 ± 1.20	0.972	0.06 ± 0.16	0.662	0.22 ± 0.12	0.702	4.94 ± 0.76	0.976	0.46 ± 0.56	0.854	0.740
Controlled release tablets of Ketoprofen -Ethocel standard 100FP Premium											
10:1	2.16 ± 2.18	0.976	0.05± 0.10	0.984	0.08 ± 0.64	0.967	5.38 ± 0.41	0.945	1.66 ± 4.92	0.978	0.873

Table 3. Release Kinetics of controlled release tablets of Ketoprofen-Ethocel 7P: 7FP, 10 P, 10FP, 100P, 100FP at drug to polymer ratio (D: P) of 10:2 in PH 7.4 Phosphate buffer

Formulation Ketoprofen-Ethocel	W = k1t		(100-w) = ln100-k2t		(100-w)1/3= 1001/3-k3t		W = k4t1/2		Mt / M∞ = k5 tn		
	k1 ± S D	r1	k2 ± SD	r2	k3 ± SD	r3	k4± SD	r4	k5 ± SD	r5	n
Controlled release tablets of Ketoprofen -Ethocel standard 7 Premium											
10:2	4.11 ± 1.44	0.857	0.20 ± 0.35	0.678	0.23 ± 0.25	0.834	5.51 ± 2.16	0.899	0.86 ± 0.55	0.992	0.982
Controlled release tablets of Ketoprofen -Ethocel standard 7FP Premium											
10:2	4.94 ± 1.27	0.979	0.06 ± 0.12	0.879	0.062 ± 2.14	0.990	3.37 ± 0.78	0.947	4.89 ± 9.81	0.997	0.979
Controlled release tablets of Ketoprofen -Ethocel standard 10 Premium											
10:2	5.01 ± 1.68	0.991	0.098 ± 0.32	0.816	0.16 ± 0.56	0.98	56.37 ± 2.10	0.992	0.99 ± 1.28	0.985	0.977
Controlled release tablets of Ketoprofen -Ethocel standard 10FP Premium											
10:2	4.07 ± 0.68	0.998	0.08 ± 0.22	0.992	0.161 ± 0.25	0.996	6.10 ± 0.76	0.994	3.12 ± 4.18	0.993	0.898
Controlled release tablets of Ketoprofen -Ethocel standard 100 Premium											
10:2	4.52 ± 1.18	0.98	0.1 0.10	0.692	0.15 ± 0.32	0.906	4.94 ± 0.98	0.976	0.96 ± 2.53	0.961	0.848
Controlled release tablets of Ketoprofen -Ethocel standard 100FP Premium											
10:2	3.14 ± 1.11	0.976	0.06 ± 0.65	0.918	0.05 ± 0.16	0.996	3.37 ± 0.72	0.978	1.65 ± 4.91	0.989	0.887

Table. 4. Release Kinetics of controlled release tablets of Ketoprofen-Ethocel 7P: 7FP, 10P, 10FP, 100P, 100FP at drug to polymer ratio (D: P) of 10:3 in PH 7.4 Phosphate buffer

Formulation Ketoprofen-Ethocel	W = k1t		(100-w) = ln100-k2t		(100-w)1/3= 1001/3-k3t		W = k4t1/2		Mt / M∞ = k5 tn		
	k1 ± S D	r1	k2 ± SD	r2	k3 ± SD	r3	k4± SD	r4	k5 ± SD	r5	n
Controlled release tablets of Ketoprofen -Ethocel standard 7 Premium											
10:3	511 ±0.44	0.987	0.14 ± 0.35	0.678	0.23 ± 0.25	0.724	5.51 ± 1.19	0.957	0.67 ± 1.59	0.982	0.889
Controlled release tablets of Ketoprofen -Ethocel standard 7FP Premium											
10:3	2.94 ±2.29	0.999	0.07 ± 0.11	0.859	0.052 ± 2.14	0.999	4.47 ± 0.99	0.959	4.80 ± 7.81	0.999	0.979
Controlled release tablets of Ketoprofen -Ethocel standard 10 Premium											
10:3	5.01 ± 2.35	0.998	0.098 ± 0.28	0.815	0.17 ± 0.37	0.896	7.38 ± 2.10	0.992	0.98 ± 3.28	0.955	0.996
Controlled release tablets of Ketoprofen -Ethocel standard 10FP Premium											
10:3	4.06 ± 0.76	0.998	0.08 ± 0.22	0.989	0.112 ± 0.16	0.978	5.10 ± 0.66	0.998	4.12 ± 3.18	0.998	0998
Controlled release tablets of Ketoprofen -Ethocel standard 100 Premium											
10:3	3.51 ± 1.16	0.998	0.08 ± 0.48	0.996	0.12 ± 0.30	0.896	4.98 ± 0.96	0.996	0.86 ± 1.58	0.994	0.886
Controlled release tablets of Ketoprofen -Ethocel standard 100FP Premium											
10:3	3.14 ± 2.18	0.998	0.08 ± 0.12	0.998	0.08 ± 0.12	0.998	3.40 ± 0.72	0.988	1.64 ± 4.90	0.998	0.888

CONCLUSION

The results obtained from different parameters showed that Ethocel Standard 7, 10 and 100 Premium and Ethocel Standard 7, 10 and 100FP polymers can be used successfully in order to develop directly compressed prolonged release tablets of slightly soluble drugs such as Ketoprofen. Particle size of polymer is a determining factor in controlling the release of Ketoprofen from tablets. Ethocel Standard 7, 10 and 100FP polymers extend the release rates of drug more efficiently than the conventional granular form of the Ethocel i-e. Ethocel Standard 7, 10 and 100Premium. Ethocel Standard 7, 10 and 100 Premium and Ethocel Standard 7, 10 and 100FP could more efficiently extend the release of the drugs as compared to the reference conventional formulation.

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