INVESTIGATING THE *IN VITRO* DRUG RELEASE KINETICS FROM CONTROLLED RELEASE DICLOFENAC POTASSIUM-ETHOCEL MATRIX TABLETS AND THE INFLUENCE OF CO-EXCIPIENTS ON DRUG RELEASE PATTERNS

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ABSTRACT

The objective of the study was to formulate and evaluate controlled release polymeric tablets of Diclofenac Potassium for the release rate, release patterns and the mechanism involved in the release process of the drug. Formulations with different types and grades of Ethyl Cellulose Ether derivatives in several drug-to-polymer ratios (D:P) were compressed into tablets using the direct compression method. *In vitro* drug release studies were performed in phosphate buffer (pH 7.4) as dissolution medium by using USP Method-1 (Rotating Basket Method). Similarity factor f_2 and dissimilarity factor f_1 were applied for checking the similarities and dissimilarities of the release profiles of different formulations. For the determination of the release mechanism and drug release kinetics various mathematical / kinetic models were employed. It was found that all of the Ethocel polymers could significantly slow down the drug release rate with Ethocel FP polymers being the most efficient, especially at D:P ratios of 10:03 which lead towards the achievement of zero or near zero order release kinetics.

Keywords: Diclofenac Potassium, Ethocel Standard Premium, Ethocel Standard FP Premium, controlled release tablets, release pattern and kinetics, influence of co-excipients.

INTRODUCTION

NSAID's (Non steroidal anti-inflammatory drugs) are the drugs of choice in rheumatoid arthritis and osteoarthritis but their long therapy can cause a number of serious GIT disturbances like ulcers of esophagus, stomach and duodenum, leading to perforation, obstruction and severe bleeding (Dhikav *et al.,* 2002). Diclofenac potassium is a derivative of benzene acetic acid. It is used as non-steroidal analgesic, antipyretic and anti-inflammatory drug. It is widely used for the relief of severe and moderate pain, osteoarthritis and rheumatoid arthritis (Diclofenac Potassium, 2009).

In recent years, sustained release and controlled release delivery systems have achieved a great advancement in the world of medicine. In controlled delivery systems polymers are used to control the release rate of drug into the systemic circulation from the site of absorption and are used mainly in oral preparations such as capsules and tablets. These polymers in particle form combine with the drug particles and thus the release rate of drug from its moiety or matrix tablets is controlled in a constant manner for a specific period of time either preferably up to 24 hours. The controlled release drug delivery system is concerned with the maintenance of drug plasma level in an optimum range so as to reduce the toxicity (Vert *et al*., 1991).

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In controlled release dosage forms, the drug release rate from the tablet is influenced by different factors which are directly related to both physical and chemical properties of the drug and also to its dosage form. Mostly these factors are associated with the polymers used in the formulations and show a tremendous influence in the release of drug from the polymeric tablets. These factors include the amount of polymer used, its molecular weight, concentration and the particle size but the most important factors out of these are the concentration of polymer and the drug to polymer ratio which increases the release rate of drug from cellulose matrices (Ford *et al.,* 1985, Mitchell *et al*., 1993).

Ethyl cellulose ethers are widely used in controlled release preparations. In order to control the release rate of the drug, it is uniformly mixed with the drug or used in coating a tablet, particles and granules. It is also used in bitter drug formulations so as to mask the bitter taste for compliance. Ethyl cellulose ether derivatives contain different derivatives of which Ethocel standard premium and Ethocel standard FP premium are the most interesting ones and are used in many oral and other formulations to control the release rate (Khan and Median, 2007).

MATERIALS AND METHODS

Mono basic potassium phosphate, CMC, Starch and NaOH (Merck, Germany), Diclofenac Potassium (Leeds Pharma, Islamabad), Lactose and Magnesium stearate

(BDH Chemical limited, Pool England), Ethocel standard 7, 10 and 100P and Ethocel standard 7, 10 and 100 FP Premium, Methocel K100 M Premium (Dow Chemical Co, Midland, USA), Pharma Test Dissolution Apparatus (D-63512, Hainburg), UV-Visible Spectrophotometer (UVIDEC-1601 Shimadzu, Japan), Single Punch Tablet Machine (Erweka AR 400, Germany), Hardness Tester (Erweka Apparatus TB24, Germany), Friability Tester (Erweka TA3R, Germany)

Construction of standard calibration curve of diclofenac potassium

For the preparation of a stock solution 20 mg of Diclofenac potassium was dissolved in 100 ml of phosphate buffer (pH 7.4) and was kept in an ultra sonifier until complete dissolution of the drug. From the stock solution suitable dilutions were prepared in decreasing order which were analyzed using a UV-Spectrophotometer (UVIDEC-1601 Shimadzu, Japan) at λ_{max} 276 nm (Vijayakumar *et al*., 2010) and absorbance values were recorded as given below in Table 1. Then a standard calibration curve was constructed using MS Excel as shown in fig. 1.

Table 1: Concentrations versus absorbance of diclofenac potassium in phosphate buffer (pH 7.4)

S. No.	Concentration	Absorbance
1	0.1 mg/ml	2.635
2	0.05 mg/ml	1.390
3	0.025 mg/ml	0.688
4	0.0125 mg/ml	0.343
5	0.00625 mg/ml	0.160

Preparation of matrix tablets

Tablet formulation

The controlled release tablets of Diclofenac potassium were formulated for Direct compression method along with 6 grades of polymer Ethocel 7 Premium & 7 FP Premium, 10 Premium & 10 FP Premium, 100 Premium & 100 FP Premium at a drug to polymer ratio of 10:03 and 10:01 as shown in Table 2. Several co-excipients e.g. CMC, HPMC and Starch were also added to some selected formulations in order to see their influence on the release rate and/or pattern. Magnesium stearate (0.5%) was used as a lubricant and Lactose as filler.

Tablet compression

Direct compression method is used for drugs having crystalline form which can be easily compressed. Premium and FP Premium grades of Ethocel were used as matrix polymers in this investigative study. For thorough mixing of the ingredients, Diclofenac Potassium with polymer and all the other excipients were mixed and blended geometrically in pestle and mortar except magnesium stearate (Lubricant) and was passed through mesh #08 sieve size for two to three times. After this, magnesium stearate (lubricant) was added to the mix powder and the mixed powder was again passed through #08 mesh size. Matrix tablets were compressed on a single punch machine (Erweka AR 400, Germany) having concave punches of 8 mm diameter. After compression, the resulting tablets were collected for further physical characterization and *in vitro* drug release studies.

Characterization of Diclofenac Potassium tablets

When the tablets were prepared by direct compression method, they were examined for their physical properties and appearance. Their dimensional (Thickness, diameter)

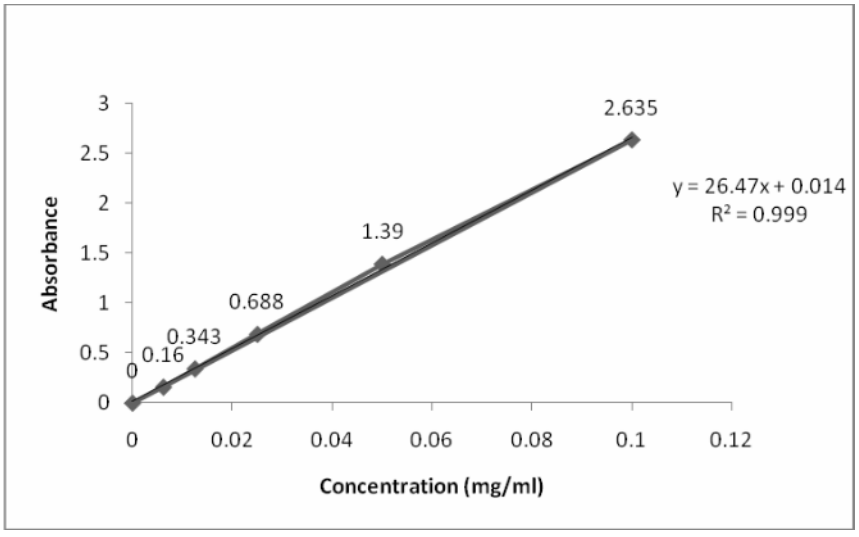

Fig. 1: Standard curve of diclofenac potassium.

and Q.C tests (hardness, friability, disintegration) were performed according to the USP methods. The thickness and diameter of the tablets were checked with the help of vernier caliper. The hardness test was determined for 10 tablets using tablet hardness machine (Erweka Apparatus TB24, Germany). Friability tests were performed for 10 tablets by friability apparatus (Erweka TA3R, Germany).

***In vitro* release study**

The different formulations of Diclofenac potassium CR tablets were subjected to *in vitro* drug release studies at 276 nm using USP Method 1 (rotating basket) with the help of Pharma test dissolution apparatus (D-63512 Hainburg, Germany). Phosphate buffer (900 ml) having pH 7.4 was used as a dissolution medium because

Table 2: Composition of 200mg Diclofenac Potassium-Ethocel Standard 7, 10 and 100 Premium and Ethocel Standard 7, 10 and 100 FP Premium (D:P Ratio 10:03 and 10:01) controlled-release matrix tablets.

Drug	D:P	Polymer	Filler (Lactose)	Lubricant	Co-excipients
Diclofenac Potassium-Ethocel Tablets without Co-excipients					
100 mg	10:03	7 P	30 mg	69 mg	0.5 %	------
		7 FP			1 mg	
		10 P				
		10 FP				
		100 P				
		100 FP				
100 mg	10:01	7 FP	10 mg	89 mg	1 mg	------
		10 FP				
		100 FP				
Diclofenac Potassium-Ethocel tablets containing Co-excipients (CMC, HPMC, Starch)					
100 mg	10:03	7 P	30 mg	48.3 mg	0.5 %	30 % of Lactose
		7 FP			1 mg	20.7 mg
		10 P				
		10 FP				
		100 P				
		100 FP				

Table 3: Parameters of kinetic models applied to release profile of directly compressed CR tablets of Diclofenac Potassium and Ethocel® standard 7P, 10P and 100P at (D:P Ratio 10:3) and Ethocel standard 7FP, 10FP and 100FP at (D:P ratio 10:3 and 10:1) in pH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Diclofenac Potassium-Ethocel (D:P) ratio	$W = k_1t$		$(100-w) = \ln 100 - k_2t$		$(100-w)^{1/3} = 100^{1/3} - k_3t$		$W = k_4t^{1/2}$		$M_t / M_{\infty} = k_5 t^n$		
	$k_1 \pm$ S D	r_1	$k_2 \pm$ SD	r_2	$k_3 \pm$ SD	r_3	$k_4 \pm$ SD	r_4	$k_5 \pm$ SD	r_5	n
Diclofenac Potassium -Ethocel® standard 7 Premium Matrix Tablets											
10:03	5.95 ± 1.53	0.955	0.09 ± 0.24	0.711	0.13 ± 0.26	0.831	6.38 ± 1.22	0.955	0.52 ± 1.22	0.958	0.860
Diclofenac Potassium -Ethocel® standard 7 FP Premium Matrix Tablets											
10:03	3.76 ± 1.14	0.942	0.05 ± 0.09	0.853	0.07 ± 0.13	0.888	4.24 ± 0.80	0.942	3.37 ± 6.81	0.985	0.909
10:01	6.21 ± 1.24	0.919	0.11 ± 0.26	0.698	0.13 ± 0.36	0.824	6.59 ± 1.16	0.919	0.66 ± 1.55	0.942	0.872
Diclofenac Potassium -Ethocel® standard 10 Premium Matrix Tablets											
10:03	5.53± 1.31	0.953	0.08 ± 0.18	0.705	0.11 ± 0.209	0.817	5.98 ± 0.92	0.953	1.44 ± 3.39	0.967	0.917
Diclofenac Potassium -Ethocel® standard 10 FP Premium Matrix Tablets											
10:03	4.56 ± 0.78	0.976	0.06 ± 0.11	0.897	0.09 ± 0.15	0.930	4.77 ± 0.64	0.976	3.66 ± 9.29	0.948	0.907
10:01	4.94 ± 1.29	0.941	0.05 ± 0.12	0.879	0.072 ± 1.24	0.910	4.37 ± 0.98	0.941	3.89 ± 8.81	0.994	0.921
Diclofenac Potassium -Ethocel® standard 100 Premium Matrix Tablets											
10:03	5.64 ± 1.27	0.949	0.08 ± 0.18	0.721	0.11 ± 0.22	0.827	6.06 ± 0.97	0.949	0.77 ± 1.79	0.944	0.869
Diclofenac Potassium -Ethocel® standard 100 FP Premium Matrix Tablets											
10:03	3.79 ± 1.16	0.927	0.05 ± 0.09	0.825	0.07 ± 0.13	0.864	4.27 ± 0.82	0.927	5.18 ± 11.5	0.980	0.940
10:01	6.12 ± 1.37	0.976	0.095 ± 0.2	0.714	0.13 ± 0.25	0.838	6.39 ± 1.11	0.976	0.94 ± 2.23	0.951	0.914

Diclofenac potassium gives a good absorbance at pH 7.4. Temperature was maintained at 37± 0.1ºC and the rotating speed was fixed at 100 rpm. Samples of 5ml each were withdrawn at specific time intervals (0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 hours) and were immediately replaced by fresh buffer which was kept at the same temperature as the dissolution medium. The samples were filtered through a membrane filter (0.45µm) before analysis on UV-Spectrophotometer to remove any particle or other impurities.

Determination of release kinetics

The release rate and release mechanism of Diclofenac Potassium-Ethocel CR tablets were elucidated by fitting the dissolution data in five kinetic models i.e.

Zero order kinetics

$$W=K_1 t \quad (1)$$

(Xu and Sunada, 1995)

First order kinetics

$$\ln (100-W) = \ln 100 - K_2 t \quad (2)$$

(Xu and Sunada, 1995)

Table 4: Parameters of kinetic models applied to release profile of directly compressed CR tablets of Diclofenac Potassium and Ethocel standard 7P; 7FP, 10P, 10FP & 100P, 100FP Premium (D:P Ratio 10:3) using HPMC as co-excipient in pH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Diclofenac Potassium-Ethocel (D:P) ratio	$W = k_1t$		$(100-w) = \ln 100-k_2t$		$(100-w)^{1/3}= 100^{1/3}-k_3t$		$W = k_4t^{1/2}$		$M_t / M_{\infty} = k_5 t^n$		
	$k_1 \pm$ S D	r_1	$k_2 \pm$ SD	r_2	$k_3 \pm$ SD	r_3	$k_4 \pm$ SD	r_4	$k_5 \pm$ SD	r_5	n
Diclofenac Potassium -Ethocel® standard 7 Premium Matrix Tablets											
10:03	11.69 ± 3.18	0.721	0.47 ± 0.64	0.786	0.46 ± 0.55	0.778	9.20 ± 1.42	0.721	0.01 ± 0.05	0.959	0.550
Diclofenac Potassium -Ethocel® standard 7 FP Premium Matrix Tablets											
10:03	10.12 ± 1.48	0.839	0.35 ± 0.56	0.881	0.37 ± 0.50	0.892	8.53 ± 0.35	0.839	0.01 ± 0.03	0.976	0.605
Diclofenac Potassium -Ethocel® standard 10 Premium Matrix Tablets											
10:03	12.11 ± 3.51	0.717	0.49 ± 0.65	0.760	0.47 ± 0.56	0.766	9.38 ± 1.58	0.717	0.01 ± 0.05	0.950	0.548
Diclofenac Potassium -Ethocel® standard 10 FP Premium Matrix Tablets											
10:03	10.54 ± 1.77	0.859	0.34 ± 0.55	0.874	0.36 ± 0.50	0.896	8.71 ± 0.48	0.859	0.01 ± 0.04	0.966	0.604
Diclofenac Potassium -Ethocel® standard 100 Premium Matrix Tablets											
10:03	11.20 ± 2.53	0.769	0.43 ± 0.62	0.833	0.42 ± 0.54	0.834	9.02 ± 0.99	0.769	0.02 ± 0.05	0.972	0.586
Diclofenac Potassium -Ethocel® standard 100 FP Premium Matrix Tablets											
10:03	10.57 ± 1.77	0.887	0.33 ± 0.54	0.852	0.35 ± 0.49	0.889	8.77 ± 0.49	0.887	0.02 ± 0.06	0.933	0.607

Table 5: Parameters of kinetic models applied to release profile of directly compressed CR tablets of Diclofenac Potassium and Ethocel® standard 7P; 7FP, 10P, 10FP & 100P, 100FP Premium (D:P Ratio 10:3) using CMC as co-excipient in pH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Diclofenac Potassium-Ethocel (D:P) ratio	$W = k_1t$		$(100-w) = \ln 100-k_2t$		$(100-w)^{1/3}= 100^{1/3}-k_3t$		$W = k_4t^{1/2}$		$M_t / M_{\infty} = k_5 t^n$		
	$k_{1 \pm S D}$	r_1	$k_2 \pm$ SD	r_2	$k_3 \pm$ SD	r_3	$k_4 \pm$ SD	r_4	$k_5 \pm$ SD	r_5	n
Diclofenac Potassium -Ethocel® standard 7 Premium Matrix Tablets											
10:03	11.60 ± 3.33	0.707	0.49 ± 0.64	0.762	0.48 ± 0.56	0.762	9.09 ± 1.55	0.707	0.01 ± 0.03	0.958	0.513
Diclofenac Potassium -Ethocel® standard 7 FP Premium Matrix Tablets											
10:03	10.36 ± 1.73	0.860	0.34 ± 0.53	0.876	0.36 ± 0.49	0.896	8.65 ± 0.52	0.860	0.02 ± 0.05	0.932	0.592
Diclofenac Potassium -Ethocel® standard 10 Premium Matrix Tablets											
10:03	10.71 ± 2.17	0.748	0.45 ± 0.62	0.753	0.44 ± 0.54	0.764	8.78 ± 0.81	0.748	0.01 ± 0.04	0.975	0.579
Diclofenac Potassium -Ethocel® standard 10 FP Premium Matrix Tablets											
10:03	10.47 ± 1.81	0.846	0.36 ± 0.59	0.875	0.38 ± 0.51	0.890	8.72 ± 0.56	0.846	0.01 ± 0.05	0.938	0.588
Diclofenac Potassium -Ethocel® standard 100 Premium Matrix Tablets											
10:03	10.24 ± 1.60	0.820	0.31 ± 0.57	0.820	0.38 ± 0.51	0.837	8.58 ± 0.43	0.820	0.01 ± 0.04	0.958	0.596
Diclofenac Potassium -Ethocel® standard 100 FP Premium Matrix Tablets											
10:03	10.29 ± 1.59	0.870	0.35 ± 0.58	0.863	0.36 ± 0.50	0.895	8.66 ± 0.44	0.870	0.02 ± 0.06	0.932	0.603

Table 6: Parameters of kinetic models applied to release profile of directly compressed CR tablets of Diclofenac Potassium and Ethocel standard 7P; 7FP, 10P, 10FP & 100P, 100FP Premium (D:P Ratio 10:3) using STARCH as co-excipient in pH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Diclofenac Potassium-Ethocel (D:P) ratio	$W = k_1t$		$(100-w) = \ln 100-k_2t$		$(100-w)^{1/3} = 100^{1/3}-k_3t$		$W = k_4t^{1/2}$		$M_t / M_{\infty} = k_5 t^n$		
	$k_1 \pm$ S D	r_1	$k_2 \pm$ SD	r_2	$k_3 \pm$ SD	r_3	$k_4 \pm$ SD	r_4	$k_5 \pm$ SD	r_5	n
Diclofenac Potassium -Ethocel® standard 7 Premium Matrix Tablets											
10:03	12.09 ± 3.59	0.711	0.47 ± 0.61	0.763	0.47 ± 0.54	0.765	9.32 ± 1.63	0.711	0.01 ± 0.03	0.954	0.533
Diclofenac Potassium -Ethocel® standard 7 FP Premium Matrix Tablets											
10:03	11.32 ± 2.69	0.787	0.39 ± 0.58	0.890	0.41 ± 0.52	0.883	9.02 ± 1.07	0.787	0.02 ± 0.04	0.954	0.580
Diclofenac Potassium -Ethocel® standard 10 Premium Matrix Tablets											
10:03	11.15 ± 2.83	0.737	0.46 ± 0.61	0.758	0.46 ± 0.54	0.767	8.91 ± 1.25	0.737	0.01 ± 0.03	0.947	0.530
Diclofenac Potassium -Ethocel® standard 10 FP Premium Matrix Tablets											
10:03	10.71 ± 1.98	0.842	0.36 ± 0.58	0.878	0.38 ± 0.51	0.897	8.83 ± 0.64	0.842	0.02 ± 0.06	0.960	0.599
Diclofenac Potassium -Ethocel® standard 100 Premium Matrix Tablets											
10:03	11.20 ± 2.53	0.769	0.43 ± 0.62	0.833	0.42 ± 0.54	0.834	9.02 ± 0.99	0.769	0.02 ± 0.05	0.972	0.586
Diclofenac Potassium -Ethocel® standard 100 FP Premium Matrix Tablets											
10:03	10.57 ± 1.77	0.887	0.33 ± 0.54	0.852	0.35 ± 0.49	0.889	8.77 ± 0.49	0.887	0.02 ± 0.06	0.933	0.607

Higuchi kinetics

$$W = K_4 t^{1/2} \quad (3)$$

(Higuchi, 1963)

Hixson Crowell kinetics

$$(100 - W)^{1/3} = 100^{1/3} - K_3 t \quad (4)$$

(Xu and Sunada, 1995)

Korsmeyer Peppas equations

$$M_t/M\infty = K_5 t^n \quad (5)$$

(Ritger and Peppas, 1987)

In equation 5, an (n) value which is a diffusion component in the above mentioned kinetic models indicates the drug transport mechanism. When n equals to 0.5 (n = 0.5) indicates that the drug is released from the polymeric tablet with Quasi-Fickian diffusion mechanism, if (n>0.5), then non-Fickian or zero order release exists. The data obtained from the kinetic models applied to the Diclofenac potassium formulations are given below in the tables 3, 4, 5 and 6.

RESULTS

The release profiles of the test preparations (directly compressed Diclofenac potassium CR tablets having different grades of polymers, 7P & 7FP, 10P & 10FP, 100P & 100FP) and that of the reference standard (immediate release) formulation are shown in figure 2.

Influence of Co-excipients on directly compressed Diclofenac Potassium tablets

The use of co-excipients in tablet formulations is done to obtain desirable properties. In this regard, the use of several co-excipients like Carboxy Methyl Cellulose (CMC), Hydroxy Propyl Methyl Cellulose (HPMC) and Starch were examined on the release rate of directly compressed CR tablets of Diclofenac Potassium-Ethocel with both Premium and FP grades. Reference drug was taken from the local market. The comparative studies give the clear data of difference between different release profiles from the tested and the standard reference formulations as shown in figs. 3, 4 and 5.

The Comparative release profiles of Diclofenac Potassium from reference conventional formulation, Ethocel Standard 7 Premium and 7 FP Premium matrices and CMC, HPMC and starch as co-excipients is shown in fig.6.

Applying the Similarity factor f_2 and Dissimilarity factor f_1 to the formulations prepared by direct compression method

F_2 similarity factor is approved by FDA to compare the release profiles of drug from the test with the standard reference formulation and is represented by equation 6. It has a value ranging between 50 and 100. The f_2 values less than 50 indicate the dissimilarity between the release profiles of the drug (CDER, 1997; CPMP, 1990).

$$f_2 = 50\text{Log}\ \{[1+1/n\ W_t \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\} \quad (6)$$

Similarly, the f_1 dissimilarity factor (equation 7) is also used to compare the release profiles of drugs from the test with a standard reference formulation. Its value ranges from 1 to 15, the values smaller than 15 shows the

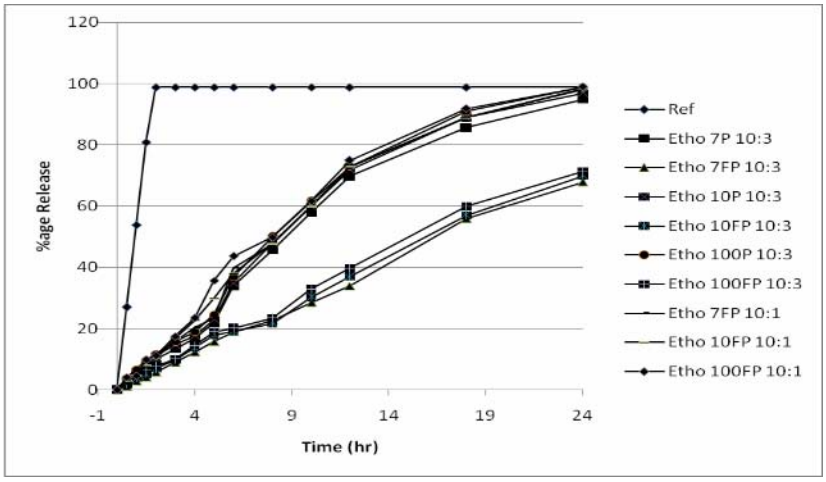

Fig. 2: Release profile of Diclofenac Potassium from Reference conventional formulation, Ethocel® Standard 7, 10 and 100 Premium at (D:P ratio 10:3) and Ethocel® standard 7, 10 and 100 FP Premium matrices at (D:P ratio 10:3 and 10:1) by Direct Compression Method.

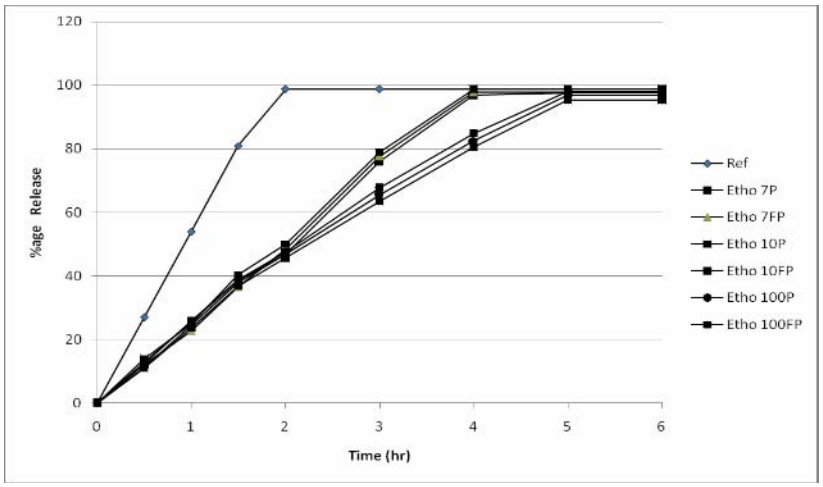

Fig. 3: Release profile of Diclofenac Potassium from Reference conventional formulation, Ethocel Standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium matrices at (D:P ratio 10:3) containing CMC as co-excipient.

similarity between the release profiles and the values greater than 15 shows the dissimilarity (FDA, 1995).

$$f1 = \left\{ \frac{\sum_{t-1}^{n} |R_t - T_t|}{\sum_{t-1}^{n} R_t} \right\} * 100 \qquad (7)$$

In our study f_1 and f_2 factors were applied to the test formulations and were compared with standard Diclofenac Potassium 75 mg immediate release tablets. In comparing the release profiles of drug from the test formulation with a reference standard, the values of f_1 were larger than 15 (Range 0-15) and the values of f_2 were smaller than 50 (range 50-100), which clearly indicates the difference between the release profiles of drug from the test and the reference standard formulation. The values of f_1 and f_2 are given below in table 7.

DISCUSSIONS

It could be observed from figure 2, that as compared to the reference standard, the drug release rate from all of the test preparations was reduced and the release profiles significantly extended. This effect was more prominent in preparations with the Ethocel standard FP Premium fine particles polymer as compared to the Ethocel standard Premium larger particle polymers. Ethocel prolonged the release of Diclofenac Potassium from matrix tablets up to 98% in 24 hours when its Premium grades were used i.e. Ethocel 7P, 10P and 100P but in case of FP grades of

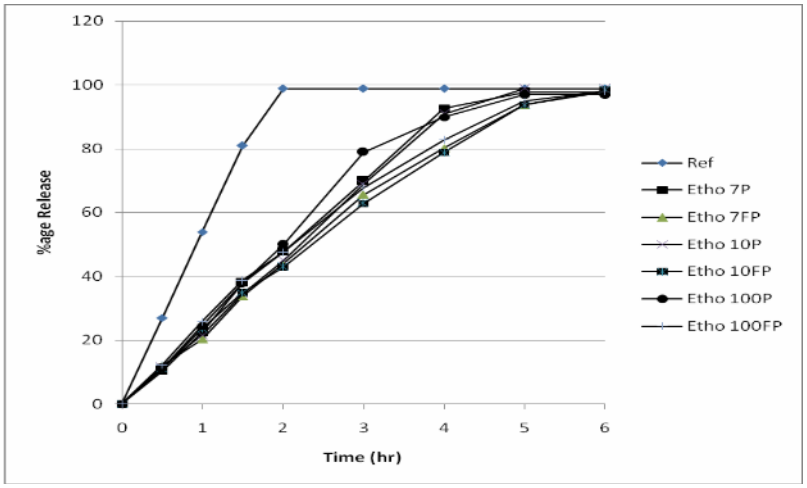

Fig. 4: Release profile of Diclofenac Potassium from Reference conventional formulation, Ethocel Standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium matrices at (D:P ratio 10:3) containing HPMC as co-excipient.

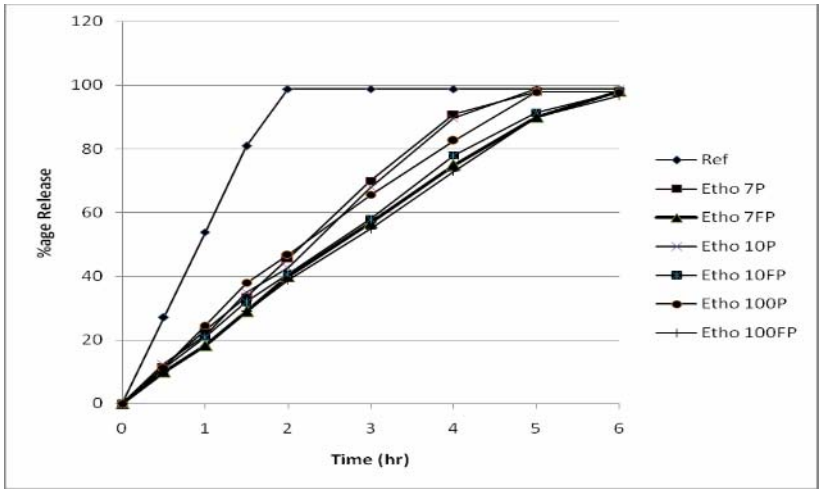

Fig. 5: Release profile of Diclofenac Potassium from Reference conventional formulation, Ethocel Standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium matrices at (D:P ratio 10:3) containing starch as co-excipient.

Ethocel i.e. 7, 10 and 100FP, the prolongation of release time was much more and only up to 70% drug was released in 24 hours. During the process of dissolution the swelling of matrix tablets was observed. This swelling of the tablets might be due to the hydration of the polymer. Tablet swelling causes a rapid decrease in the glass transition temperature of the polymer (*Tg*) to the temperature of the dissolution medium. In the presence of dissolution solvent, the dissolution solvent exerts a stress due to which there occurs a relaxation response in the polymer chains, which produce increased distances among the polymer chains (Ranga-Rao and Devi, 1988). In the hydrated polymer, there occurs an increase in the molecular volume of the polymer, which reduces the free volume because due to the presence of microspores, which itself could manifest as a shift in the drug release mechanism. Several other investigators observed the same results during their investigative studies (Khan and Zhu, 2001).

As shown in fig. 2, in the Ethocel FP formulations with D:P ratio of 10:3, the release profiles were extended desirably, however, the release extent was too small and only 70% of the drug could release in 24 hours. For a maximum amount of the drug (>90%) to be released during 24 hours period, formulations with D:P ratio of 10:1 were tested which gave the expected results with 98% of the drug release during 24 hours. This could be due to the reason that the increase in concentration of polymer and drug to polymer ratio delays the release of the drug, by reducing the amount of polymer in D:P ratio enhance the drug release from the polymeric matrices (Khan and Zhu, 2001).

Effect of CMC

Figure 3 shows Diclofenac Potassium-Ethocel CR tablets containing CMC as co-excipient. *In vitro* dissolution shows that formulations containing CMC exhibit higher release rates. CMC enhances the drug release from the matrix tablets and the formulations which are intended to release the drug in 24 hours, released the drug in only 4-6 hours. Premium grades release the drug in 4 hours while FP grades release in 5 hours. It could be due to the reason that on exposure to water CMC undergoes water absorption and produces osmotic pressure inside the matrix tablets. As a result, the tablet breaks up and thus enhances the release of drug from the matrix tablet (Khan and Zhu, 2001; Ford *et al.*, 1987).

Effect of HPMC

HPMC (Hydroxy Propyl Methyl Cellulose) is also water soluble in nature and influences the drug release form the drug moiety when used as a co-excipient by absorbing water and producing osmotic pressure which leads to its rupture earlier irrespective of the polymers used and thus enhance the release of drug (Khan and Zhu, 2001; Alderman, 1984). As shown in fig.4 the drug was released with in 4-5 hours for Premium grades and the drug was released in 6 hours for FP grades.

Effect of Starch

Starch enhances the release of drug when added to controlled release formulations. Starch is water swellable excipient in nature, so when it combines with other water swellable polymers like Ethocel then it could enhance the swelling of the tablet. As shown in figure 5, starch enhances the release of drug and the drug was released with in 5 hours for formulations containing Premium grades and was released in 6 hours for the drugs having FP grades of Ethocel because of fine particle size of FP grades. Starch enhances the release of drug from polymer which was intended to release the drug in 24 hours because starch absorbs water from the surrounding environment and swallows up and then bursts releasing the drug (Khan and Zhu, 2001).

It was seen that the formulations without co-excipients exhibit the longest dissolution time, while the others with

Table 7: f_1 and f_2 values applied to the CR tablets of Diclofenac Potassium-Ethocel 7, 10 and 100 Premium at (D:P ratio 10:3) and Ethocel 7, 10 and 100FP Premium at (D:P ratio 10:3 and 10:1) by direct compression method.

S.No.	Diclofenac Potassium CR tablets with different grades of Ethocel	D:P Ratio	Co-excipients	F_1 values	F_2 values
1	Ethocel Standard 7Premium	10:3	-	83.68	6.15
2	Ethocel Standard 7 FP	-do-	-	84.15	4.21
3	Ethocel Standard 7Premium	-do-	CMC	38.27	23.45
4	Ethocel Standard 7 FP	-do-	CMC	39.07	19.98
5	Ethocel Standard 7Premium	-do-	HPMC	39.88	22.89
6	Ethocel Standard 7 FP	-do-	HPMC	39.70	19.43
7	Ethocel Standard 7Premium	-do-	STARCH	37.86	23.67
8	Ethocel Standard 7 FP	-do-	STARCH	38.76	19.45
9	Ethocel Standard 10Premium	-do-	-	84.21	6.21
10	Ethocel Standard 10FP	-do-	-	85.15	4.19
11	Ethocel Standard 10Premium	-do-	CMC	39.34	23.66
12	Ethocel Standard 10FP	-do-	CMC	39.41	20.12
13	Ethocel Standard 10Premium	-do-	HPMC	38.35	22.89
14	Ethocel Standard 10FP	-do-	HPMC	38.67	19.05
15	Ethocel Standard 10Premium	-do-	STARCH	38.99	23.77
16	Ethocel Standard 10FP	-do-	STARCH	39.898	19.62
17	Ethocel Standard 100 Premium	-do-	-	84.91	6.98
18	Ethocel Standard 100 FP	-do-	-	86.08	4.71
19	Ethocel Standard 100 Premium	-do-	CMC	39.73	23.55
20	Ethocel Standard 100 FP	-do-	CMC	39.21	19.90
21	Ethocel Standard 100 Premium	-do-	HPMC	38.56	24.71
22	Ethocel Standard 100 FP	-do-	HPMC	38.61	20.78
23	Ethocel Standard 100 Premium	-do-	STARCH	37.20	23.89
24	Ethocel Standard 100 FP	-do-	STARCH	37.94	19.30
25	Ethocel Standard 7 FP	10:1	-	84.96	5.91
26	Ethocel Standard 10FP	-do-	-	86.70	6.36
27	Ethocel Standard 100 FP	-do-	-	87.90	5.80

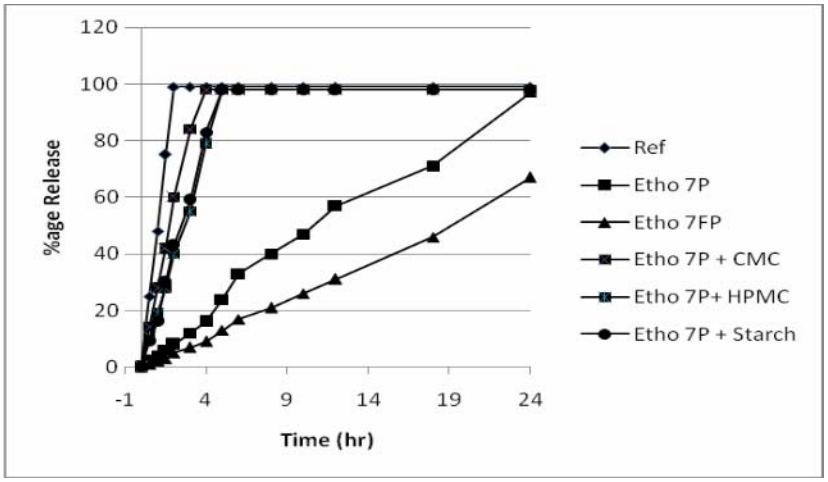

Fig. 6: Comparative Release profiles of Diclofenac Potassium from Reference conventional formulation, Ethocel Standard 7 Premium and 7 FP Premium matrices at (D:P ratio 10:3) and CMC, HPMC and starch as co-excipients.

co-excipients have the shortest dissolution times. Co-excipients used in the formulations enhance the release of drug from the tablets, but the formulations having CMC as co-excipient gives the shortest dissolution time followed by HPMC and Starch and these differences of enhancing the drug release by different co-excipients could be due to the greater permeability and porosity of these excipients. The Comparative release profiles of as co-excipient gives the shortest dissolution time followed by HPMC and Starch and these differences of enhancing the drug release by different co-excipients could be due to the greater permeability and porosity of these excipients.

Clinical Implications

Once-a-day-Controlled release tablets of Diclofenac Potassium may lead to better compliance by the patients. Moreover, in case of prolonged therapy of the drugs, such as in case of rheumatoid arthritis and osteoarthritis; gastric irritation, increased acidity and the stomach ulceration may results which could be avoided by using controlled release formulations containing polymers such as Ethylcellulose ether derivatives (Ethocel Premium and FP premium) which can control and arrest the release of drug in acidic medium of the stomach, hence minimizing the unwanted effects.

CONCLUSIONS

Ethocel can be successfully used to prepare controlled release tablets of Diclofenac Potassium. By increasing the amount of polymer, the drug release could be prolonged and the release rate could be reduced. This study also shows that the drug release can be more extended by using FP grades of Ethocel. In this investigative study all the three co-excipients used showed a real and tangible enhancement in the drug release rates out of which CMC exhibited more substantial enhancement in the release of drug as compared to HPMC and Starch.

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