Development of novel diclofenac potassium controlled release tablets by wet granulation technique and the effect of co-excipients on *in vitro* drug release rates

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Abstract: The aim of the present study was the formulation and evaluation of controlled release polymeric tablets of Diclofenac Potassium by wet granulation method for the release rate, release pattern and the mechanism involved in drug release. Formulations having three grades of polymer Ethocel (7P; 7FP, 10P, 10FP, 100P, 100FP) in several drugs to polymer ratios (10:3 and 10:1) were compressed into tablets using wet granulation method. Co-excipients were added to some selected formulations to investigate their enhancement effect on in vitro drug release patterns. *In vitro* drug release studies were performed using USP Method-1 (Rotating Basket method) and Phosphate buffer (pH 7.4) was used as a dissolution medium. The similarities and dissimilarities of release profiles of test formulations with reference standard were checked using f2 similarity factor and f1 dissimilarity factor. Mathematical/Kinetic models were employed to determine the release mechanism and drug release kinetics.

Keywords: Diclofenac Potassium, Wet granulation, Ethocel Premium and FP Premium, *in vitro* drug release kinetics, effect of co-excipients.

INTRODUCTION

In recent years considerable attention has be attracted by the use of polymeric membranes in the development of controlled-release drug delivery systems. Previously solutions of polymeric materials in organic solvents were used for this purpose, but due to some limitations associated with the use of organic solvents like spiraling cost of solvents, solvent recovery system, high price and potential explosions and toxicity of the solvents, these organic-solvent based polymeric solutions are no more used by the pharmaceutical industries (Khan and Zhu, 1998).In the formulation of solid, liquid and semi-solid dosage forms, polymers have been successfully employed and specifically in the design of modified release drug delivery systems. Both natural and synthetic polymers have been extensively investigated in this regard (Guo *et al*., 1998: Varsoshaz *et al.,* 2006). Among the possible polymers available for multi particulate systems and matrix forming materials such as methacrylic resins, polysaccharide jells and hydrophilic polymers, cellulose derivatives are particularly attractive (Jalal *et al*., 1989: Ford *et al*., 1985). Ethyl cellulose derivatives (Ethocel) are inert and hydrophobic polymers. These are essentially tasteless, colorless, odorless and physiologically inert and is widely used in various formulations (Jan *et al*., 2011). Ethocel is used as a coating material for granules and tablets, as a tablet binder, in the preparation of microcapsules and also matrix forming material for controlled release dosage forms (Donbrow and Friedman, 1974: Bodmeier and Chen, 1989). Diclofenac Potassium belongs to Non Steroidal Anti Inflammatory drugs commonly known as NSAID's. It is a benzene acetic acid derivative and is widely used as analgesic and anti pyretic drug. It is the drug of choice in rheumatoid arthritis and osteoarthritis. The long therapy of Diclofenac Potassium can cause serious GIT problems including ulceration of GIT, obstruction and severe bleeding (Dhikave *et al*., 2002: Anonymous, 2009).

MATERIALS AND METHODS

Mono basic potassium phosphate and NaoH (Merck, Germany), PVP K30 and Diclofenac Potassium (Leeds Pharma, Islamabad, Pakistan), Lactose, Magnesium stearate (BDH Chemical Ltd. Pool, England), Ethocel standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium (Dow Chemical Company, Midland, USA), CMC and HPMC (Merck, Germany), Pharma Test Dissolution Apparatus (D-63512, Hainburg, Germany), 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).

Solubility study of Diclofenac Potassium

Solubility measurements were performed for Diclofenac Potassium in several solvents in order to find out the best soluble solvent for further *in vitro* dissolution studies of

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Table 1: Composition of 200mg wet granulated Diclofenac Potassium controlled-release matrix tablets with Ethocel Standard 7P; FP, 10P, 10FP, 100P, 100FP at (D:P Ratio 10:03 and 10:01)

Drug	D:P Ratio	Polymer		Filler (Lactose)	Lubricant	Co-excipients
Diclofenac Potassium -Ethocel tablets without Co-excipients						
100 mg	10:3	7 Premium	30 mg	69 mg	0.5 %	------
		7 FP Premium			1 mg	
		10 Premium				
		10 FP Premium				
		100 Premium				
		100 FP Premium				
100 mg	10:1	7 FP	10 mg	89 mg	1 mg	------
		10 FP				
		100 FP				
Diclofenac Potassium -Ethocel tablets containing Co-excipients (CMC, HPMC, Starch)						
100 mg	10:3	7 Premium	30 mg	48.4 mg	0.5 %	30 % of filler
		7 FP Premium			1 mg	20.7 mg
		10 Premium				
		10 FP Premium				
		100 Premium				
		100 FP Premium				

Diclofenac Potassium and were performed according to the method described by Higuchi and Connors (Higuchi and Connors, 1965). For solubility studies, 6 different solvents were used including phosphate buffer (pH 6.8, pH 7.2 and pH 7.4), distilled water, 0.1 N HCl and 0.1 N NaoH and were dispensed in 6 conical flasks (100 ml). To each flask 50 mg of the drug was added and were sealed with aluminum foil to prevent evaporation of the solvent. These flasks were kept in shaking incubator at 37°C for 24 hours. After the time period as mentioned, the supernatant were calculated with the help of micropipettes and were filtered through membrane filter. Four different dilutions were prepared of the filtrate and were analyzed through UV Visible spectrophotometer at 276 nm to calculate the concentration of drug in each solvent. These experiments were performed for three different temperatures i.e. 25°C, 37°C and 40°C.

Preparation of tablets

As shown in table 1, Diclofenac Potassium CR tablets were formulated for wet granulation method along with 6 grades and types of polymer Ethocel at a drug to polymer ratio of 10:3 and 10:1. Diclofenac Potassium along with other excipients was mixed and blended geometrically in pestle and mortar and was wetted with 10% PVP solution. The damp mass formed was passed through 8 mm mesh screen to produce granules. These granules were kept in oven until complete drying. The dried granules were again passed through the same 8 mm screen in order to prevent the granules from agglomeration and lump formation. Magnesium stearate was added to the granules at the last stage.

Evaluation of granules

Prior to tablet compression, the granules were physically evaluated for its suitability to be compressed into tablets. For the flowability of the granules, a funnel was used to measure the angle of repose. LBD (Loose Bulk Density) and TBD (Tapped bulk density) were measured by the formulas:

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}}$$

The compressibility of the granules was determined by using the following formula:

$$\text{CI}(\%) = \left[\left(\frac{\text{TBD - LBD}}{\text{TBD}}\right) - \right] \times 100$$

Finally the granules were compressed into tablets using single punch machine (Erweka AR 400, Germany) at a hardness force of 7 kg/cm^2.

In vitro drug release studies

In vitro drug release studies were performed for all the Diclofenac Potassium CR tablets at 276 nm using USP method-1 (Rotating Basket Method). Pharma Test Dissolution Apparatus (D-63512 Hainburg, Germany) was used for the dissolution purpose using phosphate buffer pH 7.4 as dissolution medium. Temperature of the dissolution medium was kept constant at 37 ± 0.1ºC and rotating speed of the baskets was fixed at 100 rpm. Samples of 5 ml each for drug release analysis were

Table 2: Parameters of kinetic models applied to release profile of CR tablets of Diclofenac Potassium and Ethocel standard 7P; 7FP, 10P, 10FP & 100P, 100 FP Premium 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	$W = k_1t$		$(100-w) = \ln 100 - k_2t$		$(100-w)^{1/3} = 100^{1/3} - k_3t$		$W = k_4t^{1/2}$		$M_t / M_{\infty} = k5\ t^n$		
	$k_{1 \pm SD}$	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

withdrawn at specific time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24 hrs) according to the USP limitations and were immediately replaced by fresh buffer. The fresh buffer was also kept constant at the same temperature as a dissolution medium. The samples withdrawn for in vitro drug release analysis were filtered through membrane filter (0.45µm) prior to be analyzed UV-Visible Spectrophotometer for the reason to remove any particles present.

In vitro drug release kinetics

In vitro drug release rate and release mechanism of Diclofenac Potassium was elucidated by several kinetic models including:

1. Zero order kinetics, $W = K_1 t$ (Xu and Sunada, 1995)
2. First order kinetics, $\ln (100 - W) = \ln 100 - K_2 t$ (Xu and Sunada, 1995)
3. Higuchi kinetics, $W = K_4 t^{1/2}$ (Higuchi, 1963)
4. Hixson Crowell kinetics, $(100 - W)^{1/3} = 100^{1/3} - K_3 t$ (Xu and Sunada, 1995)
5. Korsmeyer Pappas equation, $M_t / M\infty = K_5 t^n$ (Ritger and Peppas, 1987)

In equation 5 in Korsmeyer Pappas equation an (n) value is a diffusion component indicating the mechanism involved in drug release. The value of n (n = 0.5) indicates the involvement of Quasi-Fickian release mechanism and if its value is (n>0.5) then non-Fickian or nearly Zero order release exists.

Similarity factor f_2 and Dissimilarity factor f_1

Now a day's Similarity factor f_2 and Dissimilarity factor f_1 are widely used to compare in-vitro dissolution profiles. These simple independent models were adopted by FDA and EMEA committee for proprietary medicinal products (CPMP) as assessment criteria of similarity and dissimilarity of two dissolution profiles (FDA, 1995: CPMP, 1999). The value of f_1 similarity factor is 15 (0-15) and the value of f_2 dissimilarity factor is 50 (50-100).

RESULTS

Solubility study

Prior to tablet formulation and in vitro dissolution studies, solubility studies were performed for Diclofenac Potassium in 6 different solvents to find out maximum solubility of drug in each solvent. The values for solubility's of Diclofenac potassium in different solvents

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

Formulation Diclofenac Potassium-Ethocel	$W = k_1t$		$(100-w) = \ln 100 - k_2t$		$(100-w)^{1/3} = 100^{1/3} - k_3t$		$W = k_4t^{1/2}$		$M_t / M_{\infty} = k5\ t^n$		
	$k_{1 \pm SD}$	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											
10:3	11.78 ± 3.48	0.709	0.48 ± 0.621	0.763	0.48 ± 0.55	0.764	9.17 ± 1.64	0.709	0.01 ± 0.03	0.944	0.512
Diclofenac Potassium-Ethocel standard 7 FP Premium Matrix Tablets											
10:3	11.54 ± 2.83	0.826	0.38 ± 0.59	0.883	0.40 ± 0.52	0.895	9.18 ± 1.16	0.826	0.02 ± 0.07	0.913	0.568
Diclofenac Potassium-Ethocel standard 10 Premium Matrix Tablets											
10:3	11.24 ± 2.76	0.760	0.43 ± 0.61	0.833	0.44 ± 0.54	0.828	8.96 ± 1.15	0.760	0.01 ± 0.03	0.964	0.546
Diclofenac Potassium-Ethocel standard 10 FP Premium Matrix Tablets											
10:3	11.23 ± 2.59	0.838	0.38 ± 0.59	0.878	0.40 ± 0.04	0.895	9.01 ± 1.02	0.838	0.01 ± 0.05	0.922	0.560
Diclofenac Potassium-Ethocel standard 100 Premium Matrix Tablets											
10:3	10.38 ± 1.82	0.776	0.41 ± 0.61	0.829	0.41 ± 0.53	0.828	8.67 ± 0.61	0.776	0.01 ± 0.05	0.974	0.596
Diclofenac Potassium-Ethocel standard 100 FP Premium Matrix Tablets											
10:3	10.04 ± 1.30	0.863	0.34 ± 0.57	0.868	0.36 ± 0.50	0.893	8.52 ± 0.22	0.863	0.01 ± 0.037	0.969	0.613

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

Formulation Diclofenac Potassium-Ethocel	$W = k_1t$		$(100-w) = \ln 100 - k_2t$		$(100-w)^{1/3} = 100^{1/3} - k_3t$		$W = k_4t^{1/2}$		$M_t / M_{\infty} = k5\ t^n$		
	$k_{1 \pm SD}$	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											
10:3	11.66 ± 3.22	0.722	0.47 ± 0.62	0.761	0.46 ± 0.55	0.766	9.17 ± 1.45	0.722	0.01 ± 0.05	0.949	0.545
Diclofenac Potassium-Ethocel standard 7 FP Premium Matrix Tablets											
10:3	10.57 ± 1.89	0.844	0.36 ± 0.58	0.878	0.38 ± 0.51	0.894	8.78 ± 0.62	0.844	0.02 ± 0.06	0.932	0.595
Diclofenac Potassium-Ethocel standard 10 Premium Matrix Tablets											
10:3	11.77 ± 3.35	0.728	0.45 ± 0.58	0.761	0.45 ± 0.53	0.768	9.2 ± 1.53	0.728	0.01 ± 0.051	0.926	0.537
Diclofenac Potassium-Ethocel standard 10 FP Premium Matrix Tablets											
10:3	11.19 ± 2.44	0.836	0.37 ± 0.59	0.879	0.39 ± 0.52	0.895	9.03 ± 0.91	0.836	0.02 ± 0.06	0.936	0.583
Diclofenac Potassium-Ethocel standard 100 Premium Matrix Tablets											
10:3	11.60 ± 2.97	0.744	0.45 ± 0.64	0.833	0.44 ± 0.55	0.824	9.17 ± 1.25	0.744	0.02 ± 0.045	0.968	0.572
Diclofenac Potassium-Ethocel standard 100 FP Premium Matrix Tablets											
10:3	10.87 ± 2.08	0.830	0.37 ± 0.59	0.881	0.38 ± 0.52	0.890	8.90 ± 0.69	0.830	0.02 ± 0.06	0.952	0.605

at various temperatures are shown in table 6 below. From the table it is clear that the minimum solubility of drug was in 0.1 N HCl solutions which mean that Diclofenac Potassium is partially in soluble in acidic solution. The maximum solubility of Diclofenac potassium 0.011 mg/ml was in phosphate buffer pH 7.4 which was therefore selected for further in vitro studies

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

Formulation Diclofenac Potassium-Ethocel	$W = k_1t$		$(100-w) = \ln 100-k_2t$		$(100-w)^{1/3} = 100^{1/3}-k_3t$		$W = k_4t^{1/2}$		$M_t / M_\infty = k5\, t^n$		
	$k_{1 \pm S D}$	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											
10:3	11.73 ± 3.41	0.727	0.45 ± 0.61	0.828	0.46 ± 0.54	0.811	9.18 ± 1.61	0.727	0.01 ± 0.04	0.927	0.520
Diclofenac Potassium-Ethocel standard 7 FP Premium Matrix Tablets											
10:3	11.32 ± 2.71	0.818	0.38 ± 0.57	0.883	0.40 ± 0.52	0.886	9.05 ± 1.11	0.818	0.02 ± 0.06	0.914	0.562
Diclofenac Potassium-Ethocel standard 10 Premium Matrix Tablets											
10:3	10.99 ± 2.56	0.755	0.43 ± 0.61	0.832	0.44 ± 0.54	0.823	8.89 ± 1.07	0.755	0.01 ± 0.04	0.964	0.556
Diclofenac Potassium-Ethocel standard 10 FP Premium Matrix Tablets											
10:3	11.38 ± 2.67	0.833	0.36 ± 0.56	0.884	0.39 ± 0.51	0.900	9.06 ± 1.03	0.833	0.01 ± 0.04	0.951	0.573
Diclofenac Potassium-Ethocel standard 100 Premium Matrix Tablets											
10:3	11.41 ± 3.11	0.720	0.45 ± 0.59	0.762	0.46 ± 0.54	0.764	9.03 ± 1.42	0.720	0.01 ± 0.04	0.946	0.531
Diclofenac Potassium-Ethocel standard 100 FP Premium Matrix Tablets											
10:3	10.91 ± 2.11	0.842	0.36 ± 0.07	0.876	0.38 ± 0.51	0.894	8.92 ± 0.69	0.842	0.02 ± 0.06	0.956	0.601

Table 6: Solubility of Diclofenac Potassium in different solvents

S. No.	Solvent	Temp:	Dilutions made Sample (ml)+Solvent (ml)	Theoretical Conc.	Absorbance of samples	Practical Conc. determined
1	Phosphate Buffer 6.8 PH	25 °C	1ml + 9ml	0.1mg/1ml	0.24	0.009
			1ml + 14ml	0.07mg/ml	0.16	0.006
			1ml + 19ml	0.05mg/ml	0.12	0.004
			1ml + 24ml	0.04mg/ml	0.10	0.003
		37 °C	1ml + 9ml	0.1mg/1ml	0.24	0.009
			1ml + 14ml	0.07mg/ml	0.16	0.006
			1ml + 19ml	0.05mg/ml	0.12	0.004
			1ml + 24ml	0.04mg/ml	0.10	0.003
		40 °C	1ml + 9ml	0.1mg/1ml	0.25	0.009
			1ml + 14ml	0.07mg/ml	0.17	0.006
			1ml + 19ml	0.05mg/ml	0.12	0.004
			1ml + 24ml	0.04mg/ml	0.10	0.003
2	Phosphate Buffer 7.2 PH	25 °C	1ml + 9ml	0.1mg/1ml	0.29	0.010
			1ml + 14ml	0.07mg/ml	0.19	0.007
			1ml + 19ml	0.05mg/ml	0.14	0.005
			1ml + 24ml	0.04mg/ml	0.12	0.004

Continued…

Granules evaluation

The granules were evaluated for physical tests i.e. compressibility index and angle of repose to determine its suitability for compression into tablets. The average angle of repose for all the granules formulations was 26.33 ± 1.51 (Limit <30) which shows good flow property of granules. The average LBD was 0.3751 ± 0.06 and TBD was 0.4211 ± 0.07. The average compressibility index for all the granules formulations was 14.71 ± 0.18.

In vitro drug release kinetics

In-vitro drug release kinetic studies were performed in phosphate buffer pH 7.4 the results of these kinetic models indicate the release of drug from matrix tablets following diffusion or nearly zero order kinetics.

Table continued…

S. No.	Solvent	Temp:	Dilutions made Sample (ml)+Solvent (ml)	Theoretical Conc.	Absorbance of samples	Practical Conc. determined
5	0.1 N NaOH Solution	25 °C	1ml + 9ml	0.1mg/1ml	0.31	0.011
			1ml + 14ml	0.07mg/ml	0.21	0.007
			1ml + 19ml	0.05mg/ml	0.16	0.006
			1ml + 24ml	0.04mg/ml	0.13	0.004
		37 °C	1ml + 9ml	0.1mg/1ml	0.31	0.011
			1ml + 14ml	0.07mg/ml	0.21	0.007
			1ml + 19ml	0.05mg/ml	0.16	0.006
			1ml + 24ml	0.04mg/ml	0.12	0.004
		40 °C	1ml + 9ml	0.1mg/1ml	0.32	0.012
			1ml + 14ml	0.07mg/ml	0.22	0.008
			1ml + 19ml	0.05mg/ml	0.16	0.006
			1ml + 24ml	0.04mg/ml	0.13	0.004
6	0.1 N HCl Solution	25 °C	1ml + 9ml	0.1mg/1ml	0.12	0.004
			1ml + 14ml	0.07mg/ml	0.08	0.002
			1ml + 19ml	0.05mg/ml	0.06	0.002
			1ml + 24ml	0.04mg/ml	0.05	0.001
		37 °C	1ml + 9ml	0.1mg/1ml	0.13	0.004
			1ml + 14ml	0.07mg/ml	0.08	0.002
			1ml + 19ml	0.05mg/ml	0.06	0.002
			1ml + 24ml	0.04mg/ml	0.05	0.001
		40 °C	1ml + 9ml	0.1mg/1ml	0.12	0.004
			1ml + 14ml	0.07mg/ml	0.08	0.002
			1ml + 19ml	0.05mg/ml	0.06	0.002
			1ml + 24ml	0.04mg/ml	0.05	0.001

In vitro dissolution studies

Fig. 1 shows the drug release from Ethocel based Diclofenac Potassium matrix tablets. From the graph it could be seen that in case of Diclofenac Potassium CR tablets with Ethocel Premium the drug release rate was reduced significantly as compared to the reference standard and the drug release profiles were extended. About 96% of the total drug was released from the polymeric tablets in 24 hrs. But this effect was most prominently observed in Diclofenac Potassium CR tablets with Ethocel FP Premium polymer where only 68% of the total drug was released in 24 hrs.

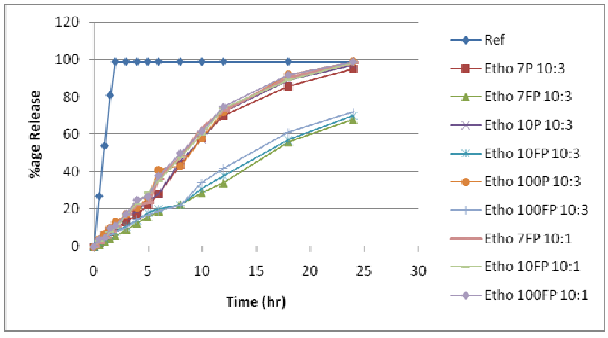

Fig. 1: Release profile of Diclofenac Potassium from Reference (conventional formulation), Ethocel Standard 7, 10 and 100 Premium at (D:P ratio 10:3) and Ethocel standard 7, 10 and 100 FP Premium matrices at (D:P ratio 10:3 and 10:1) by Wet Granulation Method

In order to release a maximum amount of drug in 24 hrs, the D:P ratio for the formulation with Ethocel FP Premium polymer (10:3) was reduced to (10:1) which gave the expected result with 96% of the total drug released in 24 hrs.

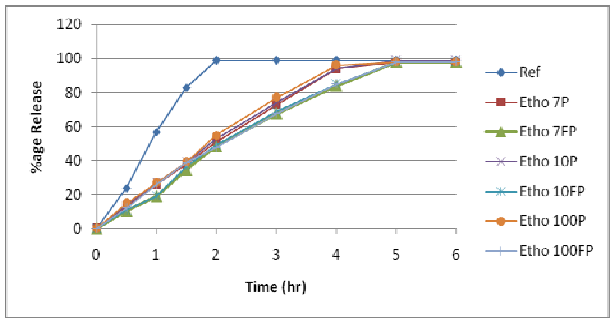

Fig. 2: Release profile of Diclofenac Potassium from Reference (conventional formulation), Ethocel Standard 7, 10 and 100 Premium (D:P ratio 10:3) and Ethocel standard 7, 10 and 100 FP Premium matrices at (D: P ratio 10:3) containing CMC as Co-Excipient

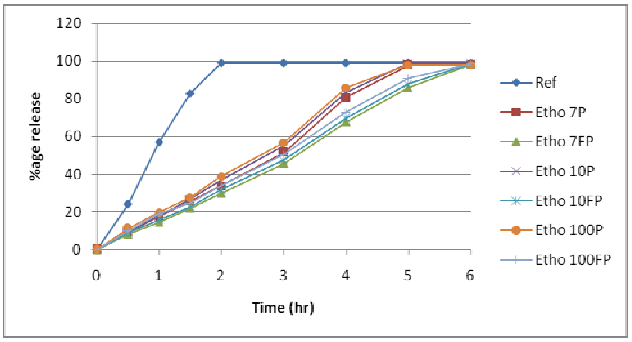

Fig. 3: Release profile of Diclofenac Potassium from Reference (conventional formulation), Ethocel Standard 7, 10 and 100 Premium (D:P ratio 10:3) and Ethocel standard 7, 10 and 100 FP Premium matrices at (D: P ratio 10:3) containing HPMC as Co-Excipient

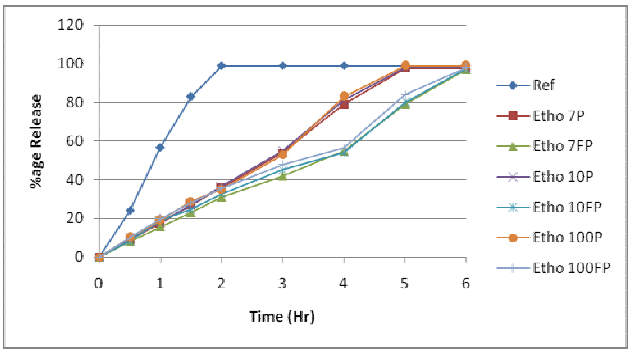

Fig. 4: Release profile of Diclofenac Potassium from Reference (conventional formulation), Ethocel Standard 7, 10 and 100 Premium (D:P ratio 10:3) and Ethocel standard 7, 10 and 100 FP Premium matrices at (D: P ratio 10:3) containing Starch as Co-Excipient

In this investigative study the effect of various co-excipients were studied on in vitro drug release optimization of Diclofenac Potassium and their enhancement effect on drug release profiles were investigated. The co-excipients were found to successfully enhance the drug release profiles of Diclofenac potassium. The figs. 2-4 show the *in vitro* drug release profiles from Diclofenac Potassium CR tablets having co-excipients CMC, HPMC and Starch respectively. It could be seen from the figures that the co-excipients used successfully enhance the release of drug from the Cr formulations and the drug from the formulations was released in 4 hrs and 5 hrs with co-excipients CMC, HPMC and Starch respectively. HPMC and Starch exhibits nearly same enhancement effect while CMC was found to be more efficient by releasing the drug in comparatively shorter time.

Applying f_1 dissimilarity factor and f_2 similarity factor

The f_1 dissimilarity factor and f_2 similarity factors were applied to the test formulations and the results were compared with that of the standard reference (Diclofenac Potassium 75 mg immediate release tablets). While comparing the release profiles of drug from the wet granulated compressed test formulations with a reference standard, the f_1 values were found to be greater than 15 for formulation with Ethocel Premium grade and Ethocel FP Premium grade (Range 0-15) and the $f_2$values were smaller than 50 for formulation with Ethocel Premium grade and with Ethocel FP Premium grade (Range 50-100), which clearly indicate that the release profiles of drug from the test formulations were different than release profile of the reference standard. The reason behind this is that, the release of drug from the test (a CR formulation) was up to 24 hours, while from the reference standard formulation (an immediate release formulation), the drug was released within two hours and there was no resemblance in their release profiles. In another investigative study, while comparing controlled release Carbamazepine matrix granules and tablets from the test with the reference standard CR formulation, the dissimilarity factor f_1 values were smaller than 15, indicating the similarity between the release profiles, because the test CR formulations were compared with another CR reference standard (Nahla *et al.*, 2009).

DISCUSSION

A number of studies have been made to investigate the release mechanism of drug from polymeric tablets. In this study Korsmeyer Peppas equation was used to find out the release mechanism. The (n) value from the equation as mentioned above indicates the way of drug release from drug formulations. For the formulations of Diclofenac Potassium CR tablets with Ethocel standard 7P; 7FP, 10P, 10FP, 100P, 100FP Premium the values for (n) were greater then 0.5 indicating that the release of all the CR formulations exhibited non-Fickian or diffusion mechanism or nearly Zero order release mechanism. In similar investigative studies (Amelia and Vikram, 2007), during the dissolution process of HPMC based Diclofenac Sodium and Chondroitin matrix tablets, the drug releases were found to follow Korsmeyer Pappas model and Zero order kinetics, having (n) values above 0.8 (hence n > 0.5). HPMC was used as a rate controlling polymer. As mentioned above, similar results were observed during investigation of Zidovudine release from guar gum based matrix tablets with (n>0.5), which followed the Korsmeyer Pappas kinetics of drug release. Guar gum was used as a rate controlling material in this study (Amit, 2010). During *in-vitro* dissolution studies was observed that by the increase in concentration of polymer and drug to polymer ratio reduces the drug release; hence, by reducing the ratio of polymer could significantly enhance the drug release from polymer based matrix tablets (Khan and Zhu, 2001). CMC (Carboxy Methyl Cellulose) absorbs water when it is exposed to water and become hydrated and thus the osmotic pressure inside the polymeric tablet is increased which leads to the bursting phenomena of the tablet, thus releasing the drug into

solvent system (Khan and Zhu, 2001). Similarly HPMC (Hydroxy Propyl Methyl Cellulose) also increase osmotic pressure inside tablet by absorbing water thus enhance the release of drug from matrix tablet (Khan and Zhu, 2001). Starch is used as excipients in tablet formulations in two forms, in dry form it is used as disintegrate and in wet form it is used as binder. Starch in dry form when formulated in tablets absorbs water and swallows thus bursts the tablet releasing the drug in solvent (Khan and Zhu, 2001).

CONCLUSIONS

The results obtained from the different parameters of *In vitro* studies showed that Ethocel standard 7 Premium and 7FP Premium could be used successfully to develop wet granulated prolonged release tablets of slightly soluble NSAID's like Diclofenac Potassium. Furthermore, the particle size of the polymer is a determined factor in controlling the release of the drug. This investigative study also shows that the release of drug could be more extended by using FP grades of polymer Ethocel. The co-excipients used in the present study successfully enhanced the release of drug from wet granulated polymeric tablets, CMC being the most efficient by releasing the drug from tablets in much shorter time as compared to HPMC and Starch.

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