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FORMULATION AND EVALUATION OF DIRECTLY COMPRESSED OFLOXACIN-ETHOCEL CONTROLLED RELEASE TABLETS: A KINETIC APPROACH

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ABSTRACT

In this study, Controlled release matrix tablets of Ofloxacin-Ethocel at different drug to polymer ratios were prepared by direct compression method. Main focus of this investigative study was the release patterns and release rates of drug from the matrix tablets, the influence of several co-excipients (CMC, HPMC and Starch) on the drug release rates and the mechanism involved. Different grades of Ethocel were used in this study including (7P, 7FP, 10P, 10FP, 100P and 100FP). *In vitro* dissolution studies in phosphate buffer PH 7.4 showed the prolonged release of drug from the formulations containing Ethocel Premium and FP polymers, but most prominently prolonged release was from the formulations containing FP Premium polymers of Ethocel. All the co-excipients used in Ofloxacin-Ethocel CR tablets enhanced the release rate of Ofloxacin from the matrix tablets but the most rapid release of drug from the tablets was found in the formulations having CMC as co-excipient. The co-excipients enhanced the release rate in the order of CMC > HPMC > Starch. Dissimilarity factor f_1 and similarity factor f_2 were applied to the formulations for the checking of dissimilarities and similarities between the release profiles of drug from the test and the reference standard formulation.

KEY WORDS: Ofloxacin, Ethocel Standard Premium and FP Premium, Direct compression, Controlled release matrix tablets, effect of co-excipients, drug release patterns and kinetics

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INTRODUCTION

In today's medicines different types of polymers are used mainly in tablets and capsules to control the release rate of drug. Controlled delivery occurs when a polymer is combined with a drug or drug moiety in such a way that the drug is released in a constant manner for a long period of time i.e. up to 24 hours. Advantages of maintenance of drug levels in a desired range is to reduce toxicity and to yield a high blood level of the drug for a long period of time which can be achieved by controlled release mechanism[1].

In controlled release drug delivery systems, the release of drug from its polymeric dosage form is enhanced by various factors which directly effects the physiochemical properties and the dosage form of the drug. These factors are associated mostly with those polymers which are being in use in different formulations as rate control excipients and results in a tremendous release of drug from the dosage form. Including these factors are the concentration of polymer used, its molecular weight, its amount in dosage form and its particle size but the factors which are most important are the concentration of the polymer and its drug to polymer ratio which increases the release of drug release from its cellulose based matrix tablets[2,3].

Ethocel or Ethyl cellulose is being used as controlled release excipients since many years. It is mixed with the drug or used in coating of tablets, granules and particles to control the release rate and also to mask the bitter taste of the drug. Ethocel control the release rate by modification in size and length of the diffusion path of the drug. Ethocel standard Premium and Ethocel Standard Fine Premium are two interesting derivatives of Ethyl cellulose and have different grades which are used in different formulations to control the release rate. Ethocel standard Premium is granular while Ethocel Standard FP Premium is in finely milled form[4].

Ofloxacin is considered to be a second generation flouroquinolone antibiotic. Antibiotics of this class are considered to be the drug of last resort in life threatening severe bacterial infections[5,6]. Ofloxacin (Floxin – Floxacin) was first introduced by a European patent Daiichi in 1982 and get FDA approval in December 28, 1990. Ofloxacin is a recemic mixture of which Levofloxacin is biologically active agent which is a mirror image of Ofloxacin[7,8].

MATERIAL AND METHODS

Material

Monobasic potassium phosphate, NaOH, (Merck, Germany), Ofloxacin (Leeds Pharma Islamabad), Lactose, Magnesium Stearate (BDH Chemical Ltd, Pool England), Ethocel standard 7 Premium, 10 Premium and 100 Premium, Ethocel standard 7 FP Premium, 10 FP Premium and 100FP Premium, Methocel K100 M Premium EP (HPMC) (Dow Chemical Co., Midland USA), CMC, and Starch (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 Apparatus (Erweka TA3R, Germany)

Formulation and preparation of matrix tablets

The CR tablets of Ofloxacin were formulated by using different grades of polymer Ethocel (7P, 7FP, 10P, 10FP, 100P, 100FP) at various drugs to polymer ratios i.e. 10:03 and 10:01. Three different co-excipients (CMC, HPMC and Starch) were added to some selected formulations to investigate their effect on drug release rates and patterns from the tablets as given in Table 1. Ofloxacin along with other excipients were taken except magnesium stearate which is used as a lubricant and were blended geometrically with the help of pestle and mortar. Then this material was passed through #08 mesh sieve size for 2-3 times and then magnesium stearate was added. The mixture was again passed through #08 mesh sieve size. After passing through sieves, this mixture was compressed to tablets by single punch machine (Erweka AR 400, Germany) having 8mm diameter punch size.

Physical characteristics of Ofloxacin matrix tablets

After the preparation of matrix tablets by direct compression method, these tablets were further studied for physical properties and appearances which include dimensional tests (thickness and diameter) and QC tests e.g. disintegration, hardness and friability according to USP method. Their dimensional tests i.e. thickness and diameter were checked with the help of screw gauze. Hardness tests of all the tablets were checked by hardness tester machine (Erweka TB24, Germany) on 10 tablets from each batch. For friability tests Friabilator Tester (Erweka TA3R, Germany) was used, and for this purpose 10 tablets from each batch was taken in Friabilator for 4 minutes at 25 rpm.

In vitro drug release study

The in vitro drug release study was carried out in Pharma-test dissolution apparatus (D-63512 Hainburg, Germany) having 6 baskets at 100 rpm speed and 37± 0.1ºC temperature for different CR formulations of Ofloxacin-Ethocel using USP method 1(Rotating basket). Phosphate buffer 7.4 PH was used as dissolution media. At predetermined time intervals samples of 5 ml each were withdrawn from each basket and were replaced with 5 ml fresh buffer solution to keep the volume constant. The samples were filtered through a membrane filter (0.45µm) prior to be analyzed by UV-Spectrophotometer. The absorbance of the drug was checked in the sample by UV-visible spectrophotometer (UVIDEC-1601 Shimadzo, Japan) at 293 nm.

Determination of release kinetics

The data which was obtained from the dissolution study of the different formulations of Ofloxacin-Ethocel CR tablets were fitted in kinetic models in order to obtain the rate and release mechanism of Ofloxacin from the formulations and the different correlation coefficients were calculated in order to find the fitness of the data. The five different kinetic models include Zero Order, First Order, Higuchi kinetics, Hixson Crowell and Korsmeyer Peppas equation[4]. Table 2 shows the kinetic data of Ofloxacin formulations with out co-excipients at (D:P ratio 10:3 and 10:1) while table 3, 4 and 5 shows the kinetic data of Ofloxacin formulations having co-excipients CMC, HPMC and Starch respectively.

RESULTS AND DISCUSSION

Ethocel polymer have granular form having a particle size of greater than 250 microns known as Premium form and is suitable for direct compression but latter it was milled into fine powder form known as FP Premium which have a greater effect on the extension of release profile of the drug which was observed in this study. FP Premium grade of polymer Ethocel can more progressively extend the release of drug then the Premium grades because it can be compressed easily and a harder tablet is formed as compared to granular form of the polymer[4]. The release rates of drugs can be enhanced by reducing the amount of polymer. FP grades gives only up to a maximum 70% release of drug from their formulations at D:P ratio 10:03, so they were formulated at D:P ratio of 10:01 which gives 98 % release because the ratio of polymer was reduced. The results obtained from reference standard were compared with the test

formulations prepared by direct compression method and are discussed with graphs.

The dissolution data of different formulations was fitted in 5 different kinetic models mentioned above. Of all the Kinetic models, Korsmeyer Peppas equation best fitts the dissolution data and clearly describes the drug release mechanism. From Korsmeyer Peppas equation, the (n) value for all the formulations with/without co-excipients, were larger than 0.5 and smaller than 1 i.e. (1<n>0.5), indicating diffusion or nearly Zero order release kinetics[4].

Fig. 1 shows the comparative release profile of reference standard and Ofloxacin-Ethocel controlled release tablets having Ethocel 7, 10 and 100 P at (D:P ratio 10:3) and Ethocel 7, 10 and 100FP Premium at (D:P ratio 10:3 and 10:1) having no co-excipients. The graph shows that in incase of formulations having Ethocel 7, 10 and 100P, the drug was released up to 98% with in 24 hours. However, the release of drug from FP grades was too small and only up to 69% of the drug was released from the tablets, so these formulations with FP grades were formulated at (D:P ratio 10:1) which gave us the expected result and the drug was released with in 24 hours.

Influence of co-excipients on the release rate of Ofloxacin matrix tablets

The effect of several co-excipients was studied on the release rate of Ofloxacin-Ethocel CR tablets for the purpose to obtain desirable properties. For this purpose co-excipients CMC, HPMC and Starch were selected because these are most commonly used excipients in dosage forms.

Influence of CMC

Just as shown in fig. 2, on the addition of CMC to the drug formulation the release time of the drug was enhanced and instead of drug release in 24 hours the whole drug was released with in 4 hours containing Ethocel 7, 10 and 100P, and from Ethocel 7, 10 and 100FP Premium the whole drug was released with in 5 hours because of fine particle size of FP polymer. The reason behind this could be that, Carboxy Methyl Cellulose (CMC) absorbs water when exposed to water and produce osmotic pressure inside the drug moiety or matrix tablets and hence enhance the rupture phenomena of the tablet thus inhibits the extend release process of the polymeric tablet[4].

Influence of HPMC

In fig. 3, on the addition of HPMC to the Ofloxacin-Ethocel CR tablets just like CMC, HPMC also enhance the release of drug and the drug was released up to 98% with in 5 hours for Premium grades and in 6 hours for FP grades and this is also because just like CMC, HPMC also absorbs water on exposure to water and creates osmotic pressure with in the tablet and rupture the tablet in very short time[4,9,2].

Influence of Starch

As shown in fig. 4, the addition of starch also influence the release of drug because starch is water swellable excipients and on exposure to water it absorbs water and swallow up and resulting in the rupturing of the matrix tablet[4], in this case also starch absorbs water and resulting in swallowing and releasing the drug in significantly much lesser time and the drug was released with in 5-6 hours for the formulations with Ethocel Premium and Ethocel FP grades respectively.

Applying the Similarity Factor f_2

Similarity factor f_2 is used to check the similarities between release profiles of reference standard and drug from the test formulations. It is adopted by FDA centre for drug evaluation and research (CDER) as an assessment criterion of similarity between different in vitro profiles, its value is from 50 to 100, the values larger then 50 shows the similarities[10,11].

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

Similarity factor f_2 was used to compare the dissolution profiles of Ofloxacin from different tested formulations with Ethocel 7, 10 and 100P at (D:P ratio 10:3) and Ethocel 7, 10 and 100FP Premium at (D:P ratio 10:3 and 10:1). For this purpose 200 mg Ofloxacin conventional tablets were taken as a reference standard from the local market. The calculated values for f_2 for all the formulations were less than 50 which shows the difference in the release profiles of Ofloxacin reference standard and Ofloxacin-Ethocel tested formulations, the following Table 6 presents the relevant data.

Applying the Dissimilarity Factor f_1

Dissimilarity factor f_1 is also used to compare the dissimilarity of release profiles between reference standard and tested formulations and is approved by FDA[7], its value is lower than 15 (0-15). In studying the release profiles of Ofloxacin reference standard and the tested formulations, the similarity value f_1 was greater then 15 which shows the dissimilarity between the standard formulation and tested formulation. F1 values are shown in table 7.

$$f_1 = \{\sum^{n}_{t-1}[Rt - T] + \sum^{n}_{t-1} Rt\} \times 100$$

CONCLUSION

It was concluded from this investigative study that Ethocel polymers could effectively control the release of Ofloxacin from controlled release matrix tablets. The use of FP grades of Ethocel could more significantly extend the drug release rates. The statistical/Mathematical modeling suggests that all the formulations exhibit

Quasi-Fickian diffusion mechanism but can also be occurred by swelling-controlled mechanism. All the co-excipients used in the formulations successfully enhance the release rate of drug from polymer but CMC cause more substantial enhancement of drug release from controlled release tablets followed by HPMC and Starch.

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Table 1 Composition of 200mg CR tablets of Ofloxacin and Ethocel Standard 7, 10 and 100 Premium at (D:P ratio 10:3) and Ethocel Standard 7, 10 and 100 FP Premium at (D:P Ratio 10:3 and 10:01)

Drug	D:P Ratio	Polymer		Filler (Lactose)	Lubricant	Co-excipients
Ofloxacin-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				
Ofloxacin-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				

Table 2 Parameters of kinetic models applied to release profile of Directly compressed CR tablets of Ofloxacin and Ethocel® standard 7P, 10P and 100P at (D:P ratio 10:3) and Ethocel® standard 7, 10 and 100 FP Premium at (D:P ratio 10:3 and 10:1) in PH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Formulation Ofloxacin-Ethocel	$W = k_1 t$		$(100-w) = \ln 100 - k_2 t$		$(100-w)^{1/3} = 100^{1/3} - k_3 t$		$W = k_4 t^{1/2}$		$M_t / M_{\infty} = k_5 t^n$		
	$k_{1 \pm SD}$	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
Ofloxacin-Ethocel® standard 7 Premium Directly compressed Matrix Tablets											
10:03	4.619 ± 1.686	0.910	0.083 ± 0.180	0.654	0.115 ± 0.213	0.763	5.40 ± 1.134	0.910	0.224 ± 0.429	0.987	0.755
Ofloxacin-Ethocel® standard 7 FP Premium Directly compressed Matrix Tablets											
10:03	3.58 ± 0.943	0.948	0.058 ± 0.09	0.880	0.085 ± 0.131	0.906	3.92 ± 0.705	0.948	0.599 ± 1.145	0.985	0.722
10:01	5.619 ± 1.78	0.922	0.083 ± 0.182	0.674	0.115 ± 0.253	0.763	5.40 ± 1.234	0.922	0.234 ± 0.429	0.981	0.775
Ofloxacin-Ethocel® standard 10 Premium Directly compressed Matrix Tablets											
10:03	4.519 ± 1.46	0.880	0.080 ± 0.17	0.615	0.113 ± 0.20	0.724	5.287 ± 0.92	0.880	0.170 ± 0.32	0.934	0.714
Ofloxacin-Ethocel® standard 10 FP Premium Directly compressed Matrix Tablets											
10:03	4.007± 0.96	0.971	0.065 ± 0.11	0.932	0.095 ± 0.15	0.948	4.24 ± 0.80	0.971	0.47 ± 0.91	0.989	0.736
10:01	4.58 ± 0.943	0.949	0.058 ± 0.10	0.887	0.085 ± 0.231	0.906	3.82 ± 0.705	0.949	0.599 ± 1.115	0.981	0.753
Ofloxacin-Ethocel® standard 100 Premium Directly compressed Matrix Tablets											
10:03	5.05 ± 1.77	0.942	0.097 ± 0.23	0.604	0.129 ± 0.25	0.769	5.774 ± 1.26	0.942	0.173 ± 0.99	0.989	0.767
Ofloxacin-Ethocel® standard 100 FP Premium Directly compressed Matrix Tablets											
10:03	3.87 ± 1.05	0.959	0.070 ± 0.11	0.893	0.102 ± 0.15	0.919	4.198 ± 0.82	0.959	0.243 ± 0.98	0.979	0.683
10:01	4.321 ± 1.57	0.889	0.080 ± 0.16	0.605	0.113 ± 0.21	0.734	5.287 ± 0.92	0.889	0.170 ± 0.32	0.937	0.721

Table 3 Parameters of kinetic models applied to release profile of directly compressed CR tablets of Ofloxacin and Ethocel® standard 7P; 7FP, 10P, 10FP & 100P, 100FP Premium (D:P Ratio 10:03) containing CMC as co-excipient in PH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Formulation Ofloxacin-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
Ofloxacin-Ethocel® standard 7 Premium Directly compressed Matrix Tablets											
10:3	10.62 ±2.95	0.755	0.38 ±0.47	0.837	0.43 ±0.48	0.824	8.38 ± 1.35	0.755	0.002±0.007	0.948	0.451
Ofloxacin-Ethocel® standard 7 FP Premium Directly compressed Matrix Tablets											
10:3	10.20 ±2.16	0.8.7	0.34 ±0.46	0.853	0.39 ±0.47	0.851	8.3 ±0.82	0.807	0.004 ±0.01	0.951	0.514
Ofloxacin-Ethocel® standard 10 Premium Directly compressed Matrix Tablets											
10:3	10.92 ±3.10	0.753	0.36 ±0.45	0.840	0.42 ±0.47	0.826	8.57 ±1.44	0.753	0.004 ±0.02	0.937	0.480
Ofloxacin-Ethocel® standard 10 FP Premium Directly compressed Matrix Tablets											
10:3	10.53 ±2.33	0.822	0.35 ±0.50	0.893	0.39 ±0.49	0.890	8.5 ±0.91	0.822	0.004 ±0.01	0.955	0.513
Ofloxacin-Ethocel® standard 100 Premium Directly compressed Matrix Tablets											
10:3	10.69 ±2.52	0.780	0.404 ±0.56	0.835	0.43 ±0.51	0.836	8.6 ±1.06	0.780	0.004 ±0.01	0.950	0.505
Ofloxacin-Ethocel® standard 100 FP Premium Directly compressed Matrix Tablets											
10:3	11.21 ±2.49	0.819	0.34 ±0.51	0.893	0.37 ±0.49	0.894	9.02 ±0.94	0.819	0.02 ±0.05	0.955	0.604

Table 4 Parameters of kinetic models applied to release profile of directly compressed CR tablets of Ofloxacin and Ethocel® standard 7P; 7FP, 10P, 10FP & 100P, 100FP Premium (D:P Ratio 10:03) containing HPMC as co-excipient in PH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Formulation Ofloxacin-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
Ofloxacin-Ethocel® standard 7 Premium Directly compressed Matrix Tablets											
10:3	11.01 ±2.96	0.744	0.36 ±0.46	0.830	0.41 ±0.47	0.814	8.65 ±1.28	0.744	0.006 ±0.02	0.969	0.513
Ofloxacin-Ethocel® standard 7 FP Premium Directly compressed Matrix Tablets											
10:3	9.21 ±0.97	0.893	0.26 ±0.40	0.916	0.31 ±0.42	0.923	7.87 ±0.03	0.893	0.008 ±0.02	0.983	0.583
Ofloxacin-Ethocel® standard 10 Premium Directly compressed Matrix Tablets											
10:3	10.26 ±2.09	0.792	0.36 ±0.5	0.835	0.4 ±0.49	0.837	8.36 ±0.75	0.792	0.004 ±0.01	0.980	0.522
Ofloxacin-Ethocel® standard 10 FP Premium Directly compressed Matrix Tablets											
10:3	9.76 ± 1.58	0.897	0.29 ±0.46	0.916	0.35 ±0.46	0.933	8.14 ±0.44	0.897	0.004 ±0.01	0.946	0.528
Ofloxacin-Ethocel® standard 100 Premium Directly compressed Matrix Tablets											
10:3	9.71 ±1.29	0.844	0.33 ±0.51	0.878	0.36 ±0.48	0.884	8.23 ±0.24	0.844	0.007 ±0.02	0.975	0.574
Ofloxacin-Ethocel® standard 100 FP Premium Directly compressed Matrix Tablets											
10:3	9.71 ±1.12	0.904	0.29 ±0.48	0.903	0.32 ±0.46	0.926	8.3 ±0.13	0.904	0.01 ±0.04	0.921	0.602

Table 5 Parameters of kinetic models applied to release profile of directly compressed CR tablets of Ofloxacin and Ethocel® standard 7P; 7FP, 10P, 10FP & 100P, 100FP Premium (D:P Ratio 10:03) containing STARCH as co-excipient in PH 7.4 Phosphate Buffer solution (mean ± SD of three determinations)

Formulation Ofloxacin-Ethocel	$W = k_1t$		$(100-w) = \ln 100-k_2t$		$(100-w)^{1/3} = 100^{1/3}-k_3t$		$W = k_4t^{1/2}$		$M_t / M_\infty = k_5 t^n$		
	$k_{1 \pm SD}$	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
Ofloxacin-Ethocel® standard 7 Premium Directly compressed Matrix Tablets											
10:3	10.56 ±2.80	0.755	0.36 ±0.45	0.824	0.42 ±0.47	0.812	8.41 ±1.27	0.755	0.004 ±0.01	0.933	0.479
Ofloxacin-Ethocel® standard 7 FP Premium Directly compressed Matrix Tablets											
10:3	9.52 ±1.05	0.916	0.27 ±0.45	0.896	0.35 ±0.44	0.922	8.15 ±0.08	0.916	0.009 ±0.03	0.944	0.587
Ofloxacin-Ethocel® standard 10 Premium Directly compressed Matrix Tablets											
10:3	9.44 ±1.02	0.849	0.31±0.47	0.873	0.35 ±0.46	0.877	8.07 ±0.06	0.849	0.005 ±0.02	0.989	0.580
Ofloxacin-Ethocel® standard 10 FP Premium Directly compressed Matrix Tablets											
10:3	8.99 ±0.80	0.908	0.29 ±0.48	0.901	0.34 ±0.46	0.929	7.82 ±0.04	0.908	0.003 ±0.01	0.931	0.544
Ofloxacin-Ethocel® standard 100 Premium Directly compressed Matrix Tablets											
10:3	10.25 ±1.85	0.863	0.33 ±0.51	0.878	0.37 ±0.48	0.895	8.45 ±0.57	0.863	0.005 ±0.02	0.939	0.542
Ofloxacin-Ethocel® standard 100 FP Premium Directly compressed Matrix Tablets											
10:3	9.49 ±0.87	0.900	0.28 ±0.46	0.909	0.31 ±0.49	0.928	8.20 ±0.04	0.900	0.02 ±0.04	0.982	0.629

Table 6 f_2-Metric Values for the Determination of Equivalency between the Release profile from Ofloxacin 200mg reference standard and CR tablets of Ofloxacin with Ethocel® 7, 10 and 100Premium at (D:P ratio 10:3) and Ethocel® 7, 10 and 100FP Premium at (D:P ratio 10:3 and 10:1)

S/No	Ofloxacin CR tablets with different grades of Ethocel	D:P Ratio	Co-Excipients	f_2-metric values
1	Ethocel® Standard 7Premium	10:3	-	5.90
2	Ethocel® Standard 7 FP	-Do-	-	5.4
3	Ethocel® Standard 7Premium	-Do-	CMC	23.65
4	Ethocel® Standard 7 FP	-Do-	CMC	15.05
5	Ethocel® Standard 7Premium	-Do-	HPMC	22.96
6	Ethocel® Standard 7 FP	-Do-	HPMC	14.12
7	Ethocel® Standard 7Premium	-Do-	STARCH	23.70
8	Ethocel® Standard 7 FP	-Do-	STARCH	14.82
9	Ethocel® Standard 10Premium	-Do-	-	6.24
10	Ethocel® Standard 10 FP	-Do-	-	5.55
11	Ethocel® Standard 10Premium	-Do-	CMC	23.90
12	Ethocel® Standard 10FP	-Do-	CMC	15.34
13	Ethocel® Standard 10Premium	-Do-	HPMC	22.99
14	Ethocel® Standard 10FP	-Do-	HPMC	15.91
15	Ethocel® Standard 10Premium	-Do-	STARCH	23.67
16	Ethocel® Standard 10FP	-Do-	STARCH	16.01
17	Ethocel® Standard 100 Premium	-Do-	-	6.07
18	Ethocel® Standard 100 FP	-Do-	-	5.95
19	Ethocel® Standard 100 Premium	-Do-	CMC	23.89
20	Ethocel® Standard 100 FP	-Do-	CMC	14.98
21	Ethocel® Standard 100 Premium	-Do-	HPMC	22.78
22	Ethocel® Standard 100 FP	-Do-	HPMC	14.89
23	Ethocel® Standard 100 Premium	-Do-	STARCH	23.33
24	Ethocel® Standard 100 FP	-Do-	STARCH	15.29
25	Ethocel® Standard 7 FP	10:1	-	6.27
26	Ethocel® Standard 10FP	-Do-	-	6.99
27	Ethocel® Standard 100 FP	-Do-	-	5.79

Table 7 F_1-Metric Values for the Determination of Dissimilarity between the release Profile from Ofloxacin 200mg reference standard and CR tablets of Ofloxacin-Ethocel® 7, 10 and 100 Premium at (D:P ratio 10:3) and Ethocel® 7, 10 and 100 FP Premium at (D:P ratio 10:3 and 10:1)

S/NO	Ofloxacin CR tablets with different grades of Ethocel	D:P Ratio	Co-Excipients	F_1-metric values
1	Ethocel® Standard 7Premium	10:3	-	85.56
2	Ethocel® Standard 7 FP	-Do-	-	87.68
3	Ethocel® Standard 7Premium	-Do-	CMC	38.34
4	Ethocel® Standard 7 FP	-Do-	CMC	37.99
5	Ethocel® Standard 7Premium	-Do-	HPMC	39.77
6	Ethocel® Standard 7 FP	-Do-	HPMC	39.89
7	Ethocel® Standard 7Premium	-Do-	STARCH	41.86
8	Ethocel® Standard 7 FP	-Do-	STARCH	40.56
9	Ethocel® Standard 10Premium	-Do-	-	84.12
10	Ethocel® Standard 10FP	-Do-	-	87.06
11	Ethocel® Standard 10Premium	-Do-	CMC	38.75
12	Ethocel® Standard 10FP	-Do-	CMC	37.91
13	Ethocel® Standard 10Premium	-Do-	HPMC	39.08
14	Ethocel® Standard 10FP	-Do-	HPMC	38.73
15	Ethocel® Standard 10Premium	-Do-	STARCH	39.78
16	Ethocel® Standard 10FP	-Do-	STARCH	40.43
17	Ethocel® Standard 100 Premium	-Do-	-	84.86
18	Ethocel® Standard 100 FP	-Do-	-	85.40
19	Ethocel® Standard 100 Premium	-Do-	CMC	38.76
20	Ethocel® Standard 100 FP	-Do-	CMC	38.46
21	Ethocel® Standard 100 Premium	-Do-	HPMC	38.97
22	Ethocel® Standard 100 FP	-Do-	HPMC	39.96
23	Ethocel® Standard 100 Premium	-Do-	STARCH	41.98
24	Ethocel® Standard 100 FP	-Do-	STARCH	41.57
25	Ethocel® Standard 7 FP	10:1	-	84.99
26	Ethocel® Standard 10FP	-Do-	-	84.78
27	Ethocel® Standard 100 FP	-Do-	-	85.79

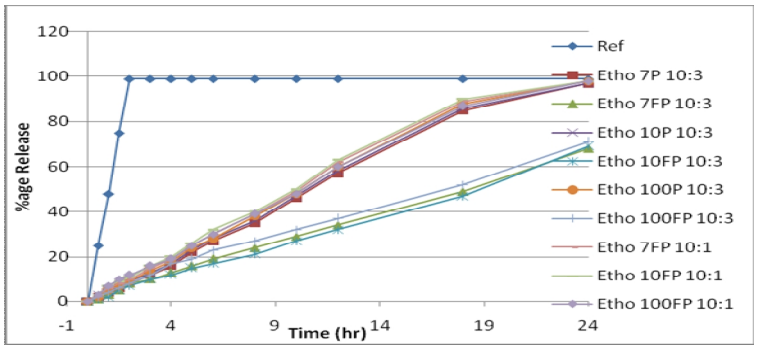

Fig. 1 Release profile of Ofloxacin from Reference conventional formulation, Ethocel Standard 7, 10 and 100 Premium at (D:P ratio 10:3) and Ethocel standard 7, 10 and 100 FP Premium matrices at (D: P ratio of 10:03 and 10:1) by Direct Compression Method

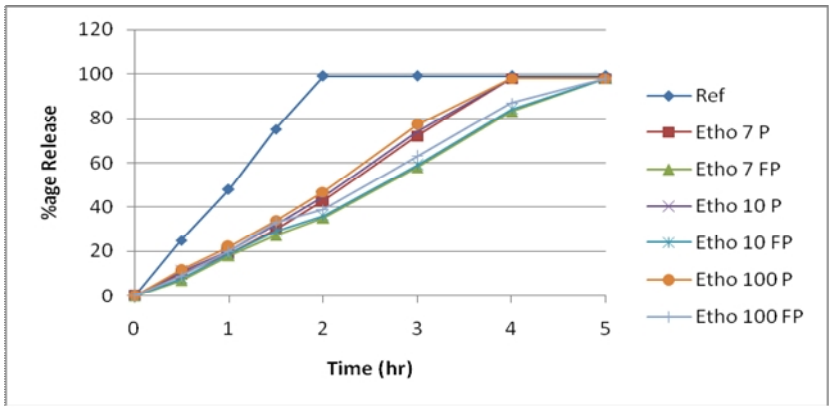

Fig. 2 Release profile of Ofloxacin from Reference conventional formulation, Ethocel Standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium matrices at (D: P ratio 10:03) containing CMC as Co-excipient

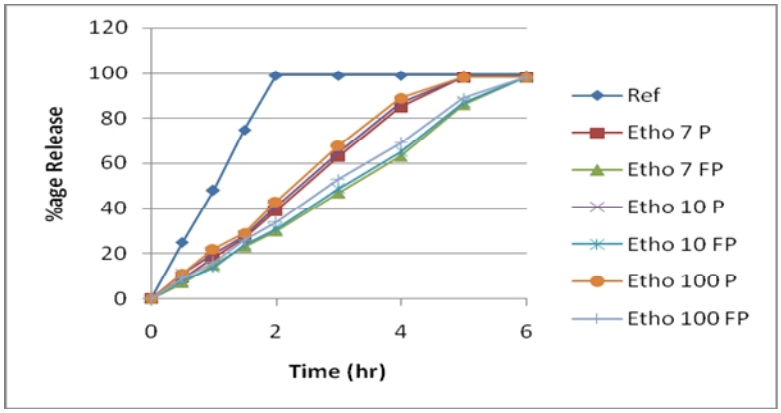

Fig. 3 Release profile of Ofloxacin from Reference conventional formulation, Ethocel Standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium matrices at (D: P ratio 10:03) containing HPMC as Co-excipient

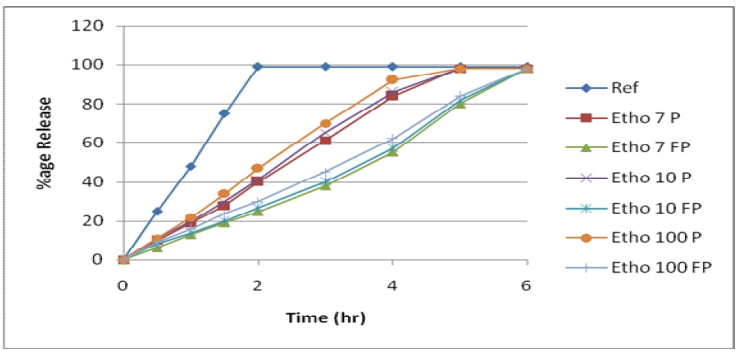

Fig. 4 Release profile of Ofloxacin from Reference conventional formulation, Ethocel Standard 7, 10 and 100 Premium and Ethocel standard 7, 10 and 100 FP Premium matrices at (D: P ratio of 10:03) containing Starch as Co-excipient

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