

Formulation development and investigation of ibuprofen controlled release tablets with hydrophilic polymers and the effect of co-excipients on drug release patterns

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Abstract: The aim and objective of the present study was to formulate and evaluate controlled release polymeric tablets of Ibuprofen with determinations of formulation factors using various grades and types of polymer Ethocel i.e. Ethocel Standard 10P; 10FP, 100P and 100FP for their release rates and release patterns in suitable media and also the mechanism involved in the release of drug from the matrices. The effect of several co-excipients was also studied on the drug release rates and patterns of Ibuprofen from the polymeric matrices. Ibuprofen-Ethocel CR tablets were prepared at three different D: P ratios i.e. 10:1, 10:2 and 10:3. The effects of co-excipients were studied only in formulations having D: P ratio of 10:3. In vitro drug release studies of Ibuprofen-Ethocel controlled release matrix tablets were carried out in phosphate buffer pH 6.8 using Pharma Test Dissolution Apparatus adopting Rotating Basket Method according to USP. Different kinetic models were applied to the release data of test formulations in order to investigate the release mechanism of drug from the controlled release matrix tablets. The release patterns of Ibuprofen-Ethocel CR matrices were compared with reference conventional Ibuprofen tablets and Ibuprofen SR tablets. F₂ similarity factor was applied to the test formulations and reference standard to compare their similarities. The drug formulations studied exhibited satisfactory release results.

Keywords: Ibuprofen, ethocel premium and fp premium polymers, direct compression, controlled release tablets, release kinetics, co-excipients.

INTRODUCTION

Sustained release and controlled release drug delivery systems have gained great advancement in the world of medicine in the recent years. The release rate of drug from the site of absorption into the systemic circulation is controlled by the use of polymers in controlled delivery systems and is used mainly in oral preparations such as tablets and capsules. The particulate form of these polymers combines with the particles of the drug and thus controls the release rate of the drug from its moiety or matrix tablets in a constant manner and for specific time period either preferably up to 24 hours. The drug plasma level is maintained to an optimum range in controlled drug delivery systems so as to reduce the toxicities (Vert *et al.*, 1991).

The drug release rate is directly influenced by several factors in controlled drug delivery systems that are directly related to both physical and chemical properties of the drugs and its dosage form. These factors are mainly polymers associated and show a tremendous influence in drug release from the polymeric tablets. These factors include polymer's amount used, its molecular weight, particle size and concentration. The most important amongst these is the concentration of polymer and the

drug to polymer ratio that increases the drug's release rate from the cellulose matrices (Ford *et al.*, 1985, Mitchell *et al.*, 1993, Shekar *et al.*, 2010).

Ibuprofen is a propionic acid derivative and belongs to non-steroidal anti-inflammatory drugs commonly known as (NSAIDS). Ibuprofen is used for various chronic inflammatory diseases like arthritis, primary dysmenorrhea and fever etc. Generally Ibuprofen acts as vasodilator, causing dilation of coronary arteries and some other blood vessels. Ibuprofen is a core medicine in WHO's "Essential Drugs List" that serves as a list of minimum medical needs for a basic health care system (WHO Essential Drugs List, 2006).

MATERIALS AND METHODS

Ibuprofen (BDH Chemical Ltd., Pool, England), monobasic potassium phosphate, NaOH, CMC, HPMC, Starch (Merk, Germany), Ethocel Standard 10 and 100 P and FP premium, Methocel KM100 Premium EP (Dow Chemical Co., Midland, USA), Pharma Test Dissolution Apparatus (D 63512, Hainburg, Germany), UV-Visible Spectrophotometer (Shimadzu, Japan), Hardness Tester (TB24, Germany), Friability Tester (Erweka TA3R, Germany).

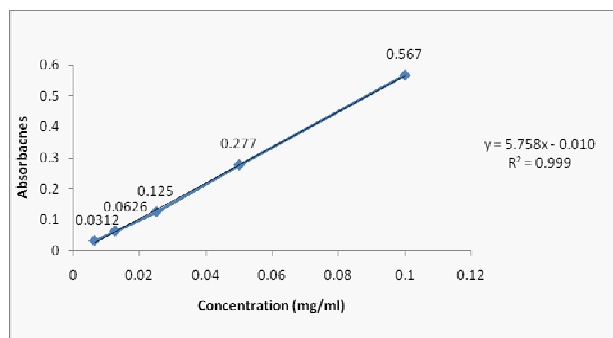
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Standard calibration curve of Ibuprofen

For standard curve of Ibuprofen, first of all stock solution was prepared by taking 20 mg of Ibuprofen in 100 ml solvent (phosphate buffer pH 6.8) in a volumetric flask. The drug was dissolved in the solvent by ultra sonifier. Four different dilutions were prepared of the stock solution (0.1 mg/ml) having concentrations, 0.05 mg/ml, 0.025 mg/ml, 0.0125 mg/ml and 0.0062 mg/ml respectively. These prepared dilutions were then analyzed by UV-Visible Spectrophotometer (Shimadzu, Japan) at 264 nm. The values of absorbance are given in table 1 below. The values of absorbance were plotted against concentrations and a slope was developed as given in fig. 1.

Table 1: Concentration vs Absorbance of Ibuprofen

S. No.	Concentration	Absorbance
1.	0.1 mg/ml	0.567
2.	0.05 mg/ml	0.277
3.	0.025 mg/ml	0.125
4.	0.0125 mg/ml	0.0626
5.	0.00625 mg/ml	0.0312

**Fig. 1:** Standard curve of Ibuprofen.**Table 2:** Formulation of 200 mg CR tablets of Ibuprofen

D:P Ratio	Drug	Polymer	Filler (Lactose)	Lubricant	Co-excipients	
200 mg Ibuprofen -Ethocel matrices						
10:1	100mg	10 Premium	10 mg	89 mg	0.5 %	-----
		10 FP Premium				
		100 Premium		1 mg		
		100 FP Premium				
10:2	100mg	10 Premium	20 mg	79 mg	1 mg	-----
		10 FP Premium				
		100 Premium				
		100 FP Premium				
10:3	100 mg	10 Premium	30 mg	69 mg	1 mg	-----
		10 FP Premium				
		100 Premium				
		100 FP Premium				
200 mg Ibuprofen -Ethocel matrices having Co-excipients (CMC, HPMC, Starch)						
10:3	100mg	10 Premium	30 mg	48.3 mg	0.5 %	30 % of filler
		10 FP Premium			1 mg	20.7 mg
		100 Premium & FP				

Development of Ibuprofen CR tablets

As given in Table 2, 200 mg of Ibuprofen tablets with several types and grades of Ethocel (Ethocel Standard 10 and 100 Premium and FP Premium) were developed at several drugs to polymer ratios i.e. 10:1, 10:2 and 10:3. In this formulation Lactose was used as a filler and magnesium stearate was used a lubricant. Co-excipients were added to several formulations to see their effect on drug release rates from polymeric tablets. The formulations having co-excipients, 30% of the filler was replaced by three co-excipients CMC, HPMC and Starch. To develop CR tablets of Ibuprofen, the polymer and drug were mixed using pestle and mortar and filler was added to this mixture. The mixture was passed through 30 mm sieve. After sieving lubricant was added to the sieved mixture and was again passed through the same mesh screen twice. The final mixture was compressed to tablets by single punch machine (Erweka AR100, Germany).

Physical characterization

After the compression of Ibuprofen CR tablets, they were evaluated for physical tests including hardness, friability, dimensional and disintegration tests. The hardness tests were performed by Hardness tester (TB24, Germany). Friability of the tablets was performed by Friability Tester (Erweka TA3R, Germany). All the tablets were evaluated for disintegration tests by using Disintegration Apparatus (Hainburg, Germany). The dimensional tests were performed with the help of vernier caliper.

In vitro release studies and the drug release kinetics

Pharma Test Dissolution Apparatus (D 63512, Hainburg Germany) was used for the in vitro drug release studies of Ibuprofen. The method adopted for in vitro release studies was USP Method-1 (Rotating Basket Method), using

phosphate buffer pH 6.8 as a dissolution solvent. Temperature of the dissolution solvent was maintained at a constant temperature of $37 \pm 0.1^\circ\text{C}$ and rotating speed of the baskets was kept constant at 100 rpm. At specific time intervals, samples were withdrawn from the dissolution solvent and were immediately replaced by fresh solvent which was already stored at the same temperature. The samples were filtered through membrane filters and were analyzed by using UV spectrophotometer at 264 nm to calculate their absorbances. These absorbances were fitted in regression line equation obtained from the standard calibration curve and the concentration of drug dissolved in the solvent was calculated.

Drug release kinetics for matrix tablets of each formulation was calculated by the following five kinetic models.

$$\text{Zero-order Kinetics} \quad W = K_1 t \quad (\text{Xu and Sunada, 1995}) \quad (1)$$

$$\text{First-Order Kinetics} \quad \ln(100-W) = \ln 100 - K_2 t \quad (2) \\ (\text{Xu and Sunada, 1995})$$

$$\text{Higuchi-Kinetics} \quad W = K_4 t^{1/2} \quad (\text{Higuchi T, 1963}) \quad (3)$$

$$\text{Hixson-Crowell Kinetics} \quad (100-W)^{1/3} = 100^{1/3} - K_3 t \quad (\text{Xu and Sunada, 1995}) \quad (4)$$

$$\text{Korsmeyer-Peppas Equation} \quad M_t/M_\infty = K_5 t^n \quad (\text{Ritger and Peppas, 1987}) \quad (5)$$

Where k_1 - k_4 = drug release constant, W = percent release of drug at time t , M_t/M_∞ = fractional release of drug into dissolution solvent and N = diffusion exponent which shows the mechanism of drug release from the matrix tablets.

Similarity factor f_2

Similarity factor f_2 was adopted by FDA Center for Drug Evaluation and Research (CDER, 1997) to compare different dissolution profiles. Its value ranges between 50 and 100, the values smaller than 50 shows dissimilarity between the different dissolution profiles.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$$

Where n = number of pull points, W_t = optional weight factor, R_t = reference profile at time (t) and T_t = test profile at same time t .

RESULTS

All the tablets were evaluated for physical appearance and tests and were found to be within the USP limits. The physical appearance was smooth and fair and was shiny. The average hardness of all the test formulations was 6.63

$\pm 0.19 \text{ kg/cm}^2$ which were within the USP range ($5\text{--}10 \text{ kg/cm}^2$). The average thickness of the tablets was $2.595 \pm 0.002 \text{ mm}$ which was also within the USP limits ($2\text{--}4 \text{ mm}$). The average friability of all the formulations were $0.133\% \pm 0.016$ which was also within the USP limits ($< 0.8\%$). In order to find out the release mechanism of drug from the CR tablets, the *in vitro* release profiles were fitted in five different kinetic models as mentioned above. In these kinetic models the Korsmeyer Pappas equation best fits the dissolution data. In Korsmeyer Pappas equation an (n) value demonstrates the way by which the drug is released from the matrix tablets. The value of (n) greater than 0.5 shows that the drug is released from the matrix tablets by non-Fickian, diffusion or nearly Zero order release mechanism. The *in vitro* study results of all the Ibuprofen CR formulations with/without co-excipients showed that the (n) value was greater than 0.5 which clearly indicate the diffusion a non-Fickian or nearly Zero order release mechanism.

As shown in fig 2, the release of drug from the test formulations were significantly reduced thus extends the release profiles of the drug. The time of drug release was extended up to 16 hours of Ibuprofen with Ethocel standard Premium polymers i.e. Ethocel standard 10 and 100 Premium at a drug to polymer ratio of 10:1, but in case of Ibuprofen with FP Premium grades of Ethocel (Ethocel standard 10 and 100 FP Premium) the effect was more prominent and a cumulative release was up to 80%. This could be due to the fine particle size of FP grades of Ethocel which delays the release of drug from polymeric tablets which confirms the findings of (Khan and Zhu, 2001 and Jan *et al.*, 2011 and 2012) in which similar results were found. Similarly when Ibuprofen was formulated with various grades and types of Ethocel at a drug to polymer ratio of 10:2, the release of drug was more reduced as compared to formulations with D: P ratio of 10:1 and more than 90% of the drug was released in 19 hours for Ibuprofen formulations with Premium grades of Ethocel and 75% drug was released from Ibuprofen formulations with FP grades of polymer. This effect could be due to the reason that increasing the concentration/amount of polymer in drug to polymer ratios reduces the drug release and extends the time of drug release. Similar extension of drug release time was found in Ibuprofen-polymer CR formulations prepared at D:P ratio of 10:3 in which the commutative drug release from Ethocel Premium matrices were found to be 98% in 24 hours of time duration and 64% drug release was found in formulations with FP Premium matrices. The comparative release profiles of Ibuprofen-Ethocel matrices prepared at D: P ratio 10:2, release profiles of reference standard (conventional Ibuprofen immediate release tablets) and Ibuprofen SR tablets are given in fig 5 below.

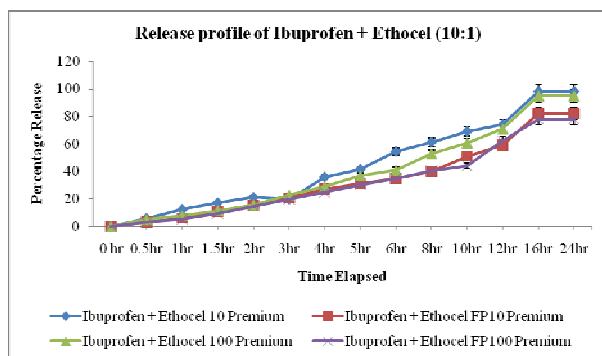


Fig. 2: Release profile of Ibuprofen from Ethocel standard 10P;10FP,100P,100FP at D:P ratio of 10:1.

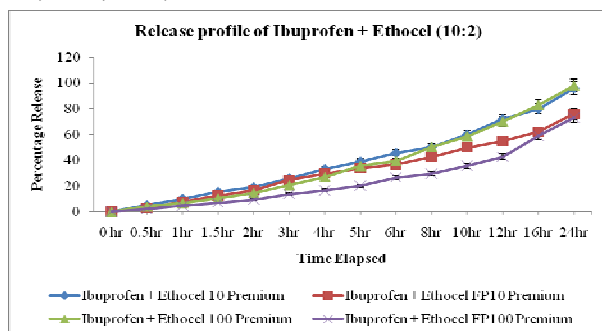


Fig. 3: Release profile of Ibuprofen from Ethocel standard 10P;10FP,100P,100FP at D:P ratio of 10:2.

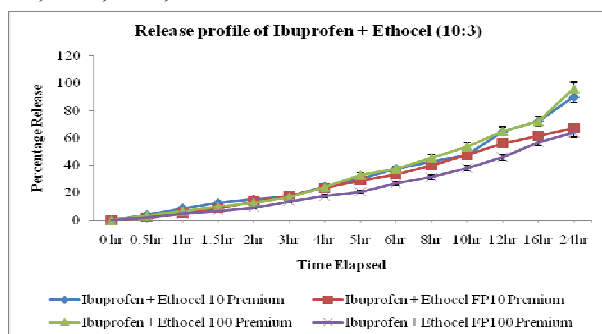


Fig. 4: Release profile of Ibuprofen from Ethocel standard 10P;10FP,100P,100FP at D:P ratio of 10:3.

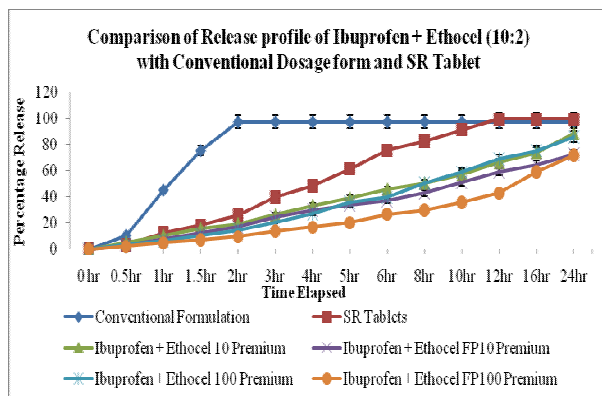


Fig. 5: Comparative release profiles of Ibuprofen from Conventional formulation, Ibuprofen SR tablet and Ethocel standard 10P;10FP,100P,100FP at D:P ratio of 10:2.

DISCUSSION

Effect of co-excipients on drug release profiles

The effect of several co-excipients was elucidated on Ibuprofen-Ethocel CR formulations with D:P ratio of 10:3 in order to obtain desirable properties and release profiles. These co-excipients include CMC, HPMC and Starch. Fig 6 shows the effect of CMC on the release profiles of Ibuprofen from controlled release matrix tablets. It could be observed that the addition of CMC to CR formulations enhances the release of drug from the formulations irrespective whether the formulation is with Premium grade of Ethocel or FP grade of Ethocel. The drug from CR formulations with Ethocel Premium polymer was released in 8 hrs instead of 24 hrs and following the same patterns the release of drug from Ethocel FP formulations was in 10 hrs. This effect could be due to the reason that when formulations with CMC are exposed to water then the CMC absorbs water from the external surroundings and become swollen and the internal osmotic pressure is increased due to which the tablets burst and release the drug into the surroundings. The addition of HPMC and Starch to the CR formulations also enhances the release of drug from the CR formulations which could be observed from the figs. 6, 7, 8 and 9. Starch and HPMC are also water swell able excipients in nature thus leads to the rupturing of dosage form on exposure to water and releasing the drug loaded on them (Khan and Zhu, 2001 and Shefaat Ullah Shah *et al.*, 2011 and 2012).

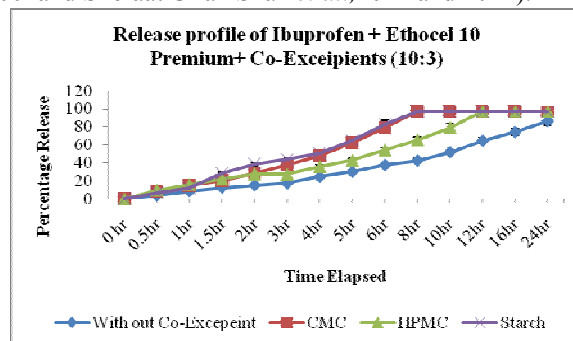


Fig. 6: Release profile of Ibuprofen from Ethocel standard 10 Premium at D:P ratio of 10:3 containing co-excipients CMC, HPMC and Starch.

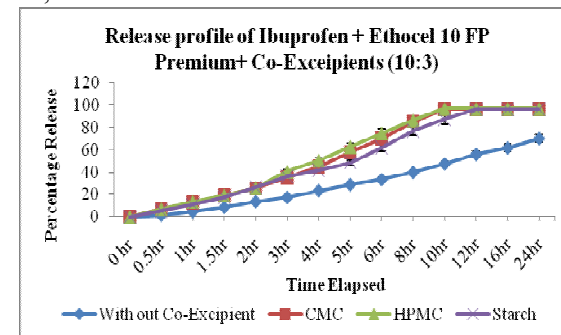


Fig. 7: Release profile of Ibuprofen from Ethocel standard 10FP Premium at D:P ratio of 10:3 containing co-excipients CMC, HPMC and Starch.

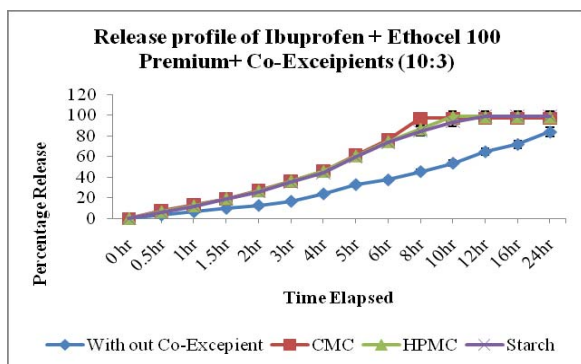


Fig. 8: Release profile of Ibuprofen from Ethocel standard 100 Premium at D:P ratio of 10:3 containing co-excipients CMC, HPMC and Starch.

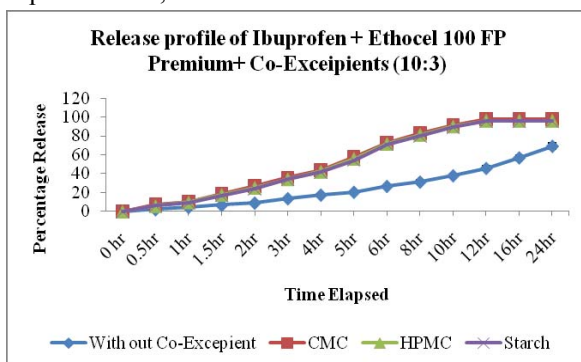


Fig. 9: Release profile of Ibuprofen from Ethocel standard 100FP Premium at D:P ratio of 10:3 containing co-excipients CMC, HPMC and Starch.

Similarity factor f_2

The f_2 similarity factor was applied to all the test preparations and was compared with reference standard formulation which was obtained from the local market as Ibuprofen SR tablet. In comparing the release profiles of test formulations with reference standard, the values of CR formulations without co-excipients were less than 50 (range 50-100) which clearly indicates the difference in the release profiles of test with that of reference standard formulations, while the values for the formulations with co-excipients were larger than 50 which indicates that the release profiles of test formulations have resemblance with that of reference standard because the reference standard was an SR formulation. The values of f_2 similarity factor are given in table 3.

Table 3: F_2 values applied to CR tablets of Ibuprofen-Ethocel.

S. No	Ibuprofen CR tablets with different grades of Ethocel	D:P Ratio	Co-excipients	F_2 values
1	Ethocel 10 Premium	10:1	-	45.07
2	Ethocel 10FP Premium	-do-	-	46.12
3	Ethocel 100 Premium	-do-	-	43.56
4	Ethocel 100FP Premium	-do-	-	45.55

S. No	Ibuprofen CR tablets with different grades of Ethocel	D:P Ratio	Co-excipients	F_2 values
5	Ethocel 10 Premium	10:2	-	44.76
6	Ethocel 10FP Premium	-do-	-	46.99
7	Ethocel 100 Premium	-do-	-	44.58
8	Ethocel 100FP Premium	-do-	-	45.78
9	Ethocel 10 Premium	10:3	-	44.78
10	Ethocel 10FP Premium	-do-	-	43.99
11	Ethocel 100 Premium	-do-	-	43.71
12	Ethocel 100FP Premium	-do-	-	46.65
13	Ethocel 10P Premium	-do-	CMC	59.08
14	Ethocel 10FP Premium	-do-	CMC	58.98
15	Ethocel 100P Premium	-do-	CMC	59.45
16	Ethocel 100FP Premium	-do-	CMC	58.19
17	Ethocel 10P Premium	-do-	HPMC	66.66
18	Ethocel 10FP Premium	-do-	HPMC	66.88
19	Ethocel 100P Premium	-do-	HPMC	66.91
20	Ethocel 100FP Premium	-do-	HPMC	64.90
21	Ethocel 10P Premium	-do-	Starch	64.98
22	Ethocel 10FP Premium	-do-	Starch	65.67
23	Ethocel 100P Premium	-do-	Starch	65.35
24	Ethocel 100FP Premium	-do-	Starch	64.96

CONCLUSION

The results obtained from the different parameters of Ibuprofen-Ethocel controlled release matrix tablets showed that the investigated types and grades of polymer Ethocel could be successfully used to prepare rate controlled matrix tablets of Ibuprofen. This investigative study also showed that the FP Premium grades of polymer Ethocel could more efficiently extend the drug release profiles as compared to Premium grades of Ethocel. The three co-excipients successfully enhanced the drug release profiles with CMC being the more efficient co-excipient in nature.

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