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Drug Release Kinetics from Tablet Matrices Based Upon Ethylcellulose Ether-Derivatives: A Comparison Between Different Formulations

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ABSTRACT The present study involved the preparation of ibuprofen-containing controlled release tablets formulated from either the established granular product, Ethocel®Standard Premium, or the novel finely-milled product, Ethocel®Standard FP Premium. The tablets were prepared by either direct compression or wet granulation. The aim was to explore the influence of different parameters on the kinetics and mechanisms of ibuprofen release from the tablets. These parameters were; polymer particle size, polymer molecular weight, drug:polymer ratio, preparation methodology and partial replacement of lactose with the coexcipient–hydroxypropyl methylcellulose (HPMC). The derived drug release data were analyzed with reference to various established mathematical models while the f_2-metric technique was used in order to determine profile equivalency. It was found that drug release was mostly modulated by several interactive factors apparently exhibiting crosstalk. Nevertheless, it was possible to identify some simple rules. Incorporation of Ethocel® FP polymers and application of the wet granulation technique facilitated greater efficiency in controlling ibuprofen release behavior from the matrices. Furthermore, drug release profiles could be modulated by partial substitution of the primary excipient with HPMC. Polymer concentrations and particle sizes, rather than viscosity grade, were found to be decisive factors in controlling drug release rates.

KEYWORDS Ibuprofen, Ethocel® polymers, Controlled-release matrices, Kinetic models, Release mechanisms

INTRODUCTION

Recent years have witnessed growing pharmaceutical interest in the use of biofunctional polymers for formulating prolonged-release dosage forms. In particular, the inert hydrophobic polymer, ethylcellulose, has attracted considerable attention (Kumar et al., 1993; Huang et al., 2006; Mohammad &

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Dashevsky, 2006). This material has found applications in various dosage forms as a binder (Desai et al., 2001), film forming agent (Rowe, 1986), coating material (Palmieri & Wehrle, 1997) as well as a matrix material (Shlieout & Zessin, 1996; Shaikh et al., 1987a,b; Khan & Zhu, 2001).

The Ethocel®Premium ethylcellulose ethers represent an interesting class of ethylcellulose derivatives. Until recently, these long-established organosoluble thermoplastics were available only in varying viscosity grades, physically granular in nature, with average particle size greater than 250 μm (Dow Chem. Co., 1996). Such properties meant incorporation of these polymers into dosage forms required their dissolution in organic solvents. However, mounting environmental concerns are making this step progressively more problematic and more expensive. To avoid such issues, the Dow Chemical Company recently introduced Ethocel®Standard FP Premium polymers (Ethocel® Standard 7 FP, 10 FP, and 100 FP Premium). In these novel products, the material exists in a very finely milled form, thus allowing the use of direct compression to incorporate the polymer into the controlled-release matrix (Khan & Zhu, 2001).

The present study involved the preparation of ibuprofen-containing controlled release tablets formulated from either the conventional granular product Ethocel®Standard Premium or the newer product, Ethocel®Standard FP Premium. Table 1 presents a comparison between these two products in terms of some of their physical properties. The objective was to investigate the influence of different variables on the kinetics and mechanisms of ibuprofen release from the tablets. The investigated parameters were polymer particle size, polymer molecular weight, drug:polymer (D:P) ratio, matrix preparation methodology and partial replacement of the primary excipient (lactose) with hydroxypropyl methylcellulose (HPMC).

TABLE 1 **Physical Properties of Ethocel®Standard Premium and Ethocel®Standard FP Premium Polymers**

Ethocel®Premium	Average particle size (μm)	Viscosity* (cps)	Ethylcellulose content (% w/w)
Standard 7 cp	310	7	48.0–49.5
Standard 7 FP	9.7	7	48.0–49.5
Standard 10 cp	375	10	48.0–49.5
Standard 10 FP	6.1	10	48.0–49.5
Standard 20 cp	--------	20	48.0–49.5
Standard 45 cp	--------	45	48.0–49.5
Standard 100 cp	465	100	48.0–49.5
Standard 100 FP	41	100	48.0–49.5

*Solution viscosity of a 5 % (w/w) polymer in 80/20 toluene/alcohol at 25°C.

The derived drug release data was characterized with reference to various established kinetic-mechanistic models. These were the zero-order, first-order, Hixon-Crowell cube root, Higuchi and Power Law equations. The zero-order model represents an ideal sustained release system in which drug dissolution occurs at a constant rate from beginning to end. Conversely, the first order model better fits the typical drug release pattern of conventional tablets. The popular Higuchi model assumes that very small drug particles are dispersed in an insoluble, nonswelling matrix in which release is limited by the rate of drug diffusion. The Power Law represents a broader, more comprehensive interpretation of the Higuchi model. The Hixon-Crowell model describes the behavior of systems in which there is progressive erosion and dissolution of the polymer matrix. In addition to these kinetic models, the f_2-metric technique was used to identify dissolution profile equivalency.

MATERIALS AND METHODS

Materials

Ibuprofen was purchased from the Xin Hua Pharmaceutical Factory (Shandong, China). Conventional granular Ethocel®Standard Premium (hereafter referred to as Ethocel®) and various viscosity grades of Ethocel®Standard FP Premium were obtained as gift from the Dow Chemical Co. (Midland, MI). MEthocel® E50-LV HPMC (Mean. MW of 20,000 Da; hydroxypropyl content 7–12% (w/w); methoxy content 19–24 % (w/w); viscosity in 2% aqueous solution 50 cps; and particle size < 590 μm) was also obtained as a gift from the Dow Chemical Co. Magnesium stearate and lactose were purchased from Agent Factory No. 2 (Shanghai, China). All the other reagents were of analytical grade.

Preparation of the Tablets

Ibuprofen-Ethocel®tablets, each weighing 300 mg and containing 200 mg ibuprofen, were formulated

at D:P ratios of 10:1, 10:2, and 10:3. Lactose was the primary excipient while HPMC was used as a coexcipient, replacing lactose at concentrations of 10 and 20% (w/w). Incorporated magnesium stearate (0.5% w/w) acted as a lubricating agent. The batch size was 200 tablets. The tablets were prepared by two distinct methods; direct compression and wet granulation.

In the direct compression approach, ibuprofen and the respective polymer were mixed together at the selected D:P ratio with the excipients. Initially, this involved adding and mixing geometrically using a mortar and pestle. Each powder mixture was then passed three times through a #30-mesh screen in order to achieve thorough mixing of the constituents. Subsequently, 0.5% (w/w) magnesium stearate was added and each of the resulting mixtures was again passed twice through the same mesh screen. Finally, each powder mixture was directly compressed into tablets using a single punch tableting machine (Shanghai Mechanical Equipment Factory, Shanghai, China) equipped with flat-faced beveled-edges tooling of 11 mm diameter. The target tablet weight was 300 mg. The compression force was modulated in order to yield tablets exhibiting a hardness ranging between 6 and 7 kg. In our previous study (Khan & Zhu, 2001), we showed that lower viscosity grades of granular Ethocel® formed harder tablets than those of higher viscosity grades. It was desirable in the current study to separate the hardness effect from the composition effect.

The wet granulation methodology involved physical mixing of the components as described above. However, magnesium stearate was not added at this stage. Instead, each mixture was moistened by aspersion with an ethanol:water (30:70) v/v solution and kneaded continuously until the subjective end point of suitable consistency was achieved. Wet milling was performed by manually passing the wet masses through a #8-mesh screen. The wet granulations were placed in Teflon-coated trays in beds with a thickness of ~0.5 cm. These were dried in a conventional hot air oven at 45°C until a moisture content varying between 0.5–1.0% was achieved. The dry granulations were dry milled using a #18-mesh sieve and finally lubricated with 0.5% w/w magnesium stearate. The granulations were compressed into tablets in the same manner as described above.

In Vitro Drug Release Studies

Measurements of drug release from the tablets were performed using the USP method 1, otherwise known as the rotating basket method. To this end, we used a PharmaTest Dissolution Tester (Hainburg, Germany). The dissolution medium, consisting of phosphate buffer solution at pH 6.8, was stirred at 100 rpm and maintained at 37 ± 0.1°C by a thermally-modulated water bath. At predetermined time intervals, 5 mL aliquots of medium were withdrawn, filtered (0.45 μm) and analyzed spectrophotometrically (Jesco UV Dec-610) at a detection wavelength of 264 nm. After each sampling, equal volumes of the dissolution medium (maintained at 37 ± 0.1°C) were added as replacement solution. From the UV absorbance values and a standard ibuprofen calibration curve, cumulative percentages of released ibuprofen were calculated. Mathematical adjustments were made for the loss of active drug during sampling. All experiments were performed in triplicate.

Testing Dissolution Equivalency

Recently a simple model independent approach that uses a similarity factor (f_2) was proposed to compare dissolution profiles and was adopted by FDA Center for Drug Evaluation and Research (CDER) and also by the European Medicines Evaluation Agency (EMEA) Committee for Proprietary Medicinal Products (CPMP) as an assessment criterion of similarity between two *in-vitro* dissolution profiles. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the curves (US FDA, 1997; EMEA, 1999). This equation is given by:

$$f_2 = 50\,\mathrm{Log}\{[1+\frac{1}{n}W_t\Sigma_{t=1}^{n}(R_t - T_t)^2]^{-0.5}\times 100\}$$

Where n is the number of pull points, w_t is an optional weight factor, R_t is the reference profile at time point t and T_t is the test profile at the same time point. An f_2 value of 100 suggests that the test and reference profiles are identical. However, as the f_2 value becomes smaller, the dissimilarity between release profiles increases (Gohel & Panchal, 2002). The FDA has proposed that two dissolution profiles should be considered similar when f_2 ranges between 50 and 100. In our studies, we used linear regression

to compute f_2-metric values, using the IBM-compatible software 'True Basic-Version 2.03' (True Basic Inc., Hartford, VT).

Fitting Kinetic Models to the Drug Release Data

In order to analyze drug release kinetics from each of the prepared matrices, the following mathematical models were fitted to the release data:

(i) Zero-order Kinetics (Xu & Sunada, 1995; Singla & Medirata, 1988)

$$W = k_1 t \quad (1)$$

(ii) First-order Kinetics (Xu & Sunada, 1995; Singla & Medirata, 1988)

$$\ln(100 - W) = \ln 100 - k_2 t \quad (2)$$

(iii) Hixon Crowel's Cube-root Equation (erosion model) (Xu & Sunada, 1995; Singla & Medirata, 1988)

$$(100 - W)^{1/3} = 100^{1/3} - k_3 t \quad (3)$$

(iv) Higuchi's Square Root of Time Equation (diffusion model) (Higuchi, 1963)

$$W = k_4 t^{1/2} \quad (4)$$

(v) Power Law Equation (diffusion/relaxation model) (Ritger & Peppas, 1987)

$$Mt / M_\infty = k_5 t^n \quad (5)$$

Where W is percent drug release at time t, k_1– k_4 are release rate constants, depending on the kinetic model used. Mt/M_∞ is the fractional drug release into the dissolution medium and k_5 is a constant incorporating structural and geometric characteristic of the tablet. The parameter, *n,* is a diffusion exponent that characterizes the drug release transport mechanism. When n=0.5, the drug diffuses through and is released from the polymeric matrix with a quasi-Fickian diffusion mechanism. When $n > 0.5$, anomalous, non-Fickian drug diffusion occurs. When n=1, a non-Fickian, Case II or zero-order release kinetics occurs. All this analysis was performed by applying multiple linear regression analysis using suitable IBM-compatible software (SAS Institute Inc., Cary, NC).

RESULTS AND DISCUSSION

Ibuprofen Release from Ethocel® Formulations

Ibuprofen release profiles from directly compressed Ethocel®matrices exhibiting different viscosity grades and various D:P ratios are given in Fig. 1. It can be seen that Ethocel®7 cp demonstrated the slowest drug release rate and Ethocel® 100 cp demonstrated the fastest drug release rate. This is explainable by the fact that tablets containing Ethocel® of lower viscosity grades were more compressible

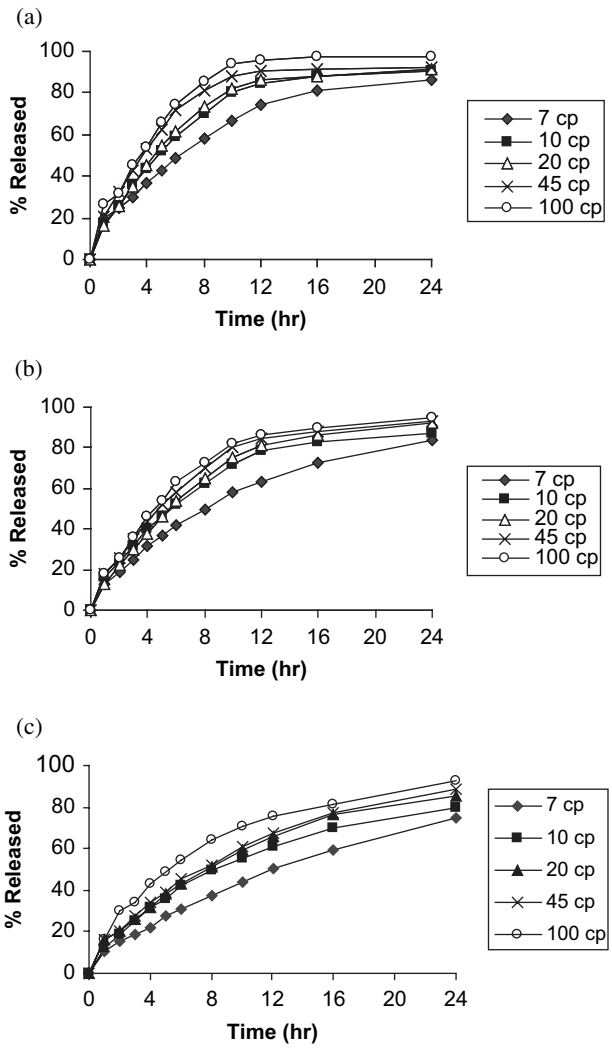

FIGURE 1 **Release Profiles of IBF from Ethocel Matrices with Different Viscosity Grades Containing D:P 10:1 (a), 10:2 (b), and 10:3 (c).**

and hence exhibited less porosity. On the other hand, Ethocel®of higher viscosity grades (granular polymer with larger particle size and thus higher porosity) may not have produced a matrix containing pores sufficiently small to trap the drug and retard its release. Interestingly, for formulations containing granular Ethocel® with intermediate viscosity grades, the influence of viscosity grade on drug release rates was relatively insignificant. Since Ethocel® is water insoluble there is no ethylcellulose hydration occurring during dissolution. Consequently, the polymer viscosity grade had little effect on the drug release rates. This result is similar to those documented by others (Shlieout & Zessin, 1996; Upadrashta et al., 1993) who reported that lower viscosity grades of ethylcellulose yielded slower drug release rates. Interestingly, two reports (Sheikh et al., 1987a,b) stated that the higher the viscosity grade of ethylcellulose the slower the release of water soluble and sparingly soluble drugs. Since ibuprofen is practically water insoluble, our findings do not contradict those studies.

It is important to consider the influence of the D:P ratios on ibuprofen release rates. It can be seen that increased Ethocel® levels reduced the drug release rates. This might be attributable to the strength of the matrix because the matrices formed at higher Ethocel® concentrations would be expected to be stronger. This kind of matrix would cause a decrease in the size, and an increase in the diffusional path length. This will be associated with reduced water penetration through the micropores and decreased drug diffusion, resulting in slower release rates.

The f_2-metric technique was used to compare the different ibuprofen release profiles obtained from Ethocel®matrices. For this purpose, the release profile associated with Ethocel®7 cp functioned as a reference profile. Table 2 presents the relevant data. It can be seen that at a D:P ratio of 10:1, the drug release profile from Ethocel®10 cp was not significantly different from that of Ethocel®7 cp (f_2=53.25). However, drug release from Ethocel® 20cp, Ethocel® 45cp and Ethocel® 100cp matrices did differ significantly from that of the reference matrix (f_2=49.95; 39.87; 35.67, respectively). Similarly, at D:P ratios of 10:2 and 10:3, the computed f_2 values in all but one case were < 50 indicating that the performance of these tablets was significantly different from that of the reference tablet. The exception was the 20 cp dosage form exhibiting a D:P ratio of 10:3.

Table 3 shows dissolution data relating to drug release from directly compressed ibuprofen-Ethocel®CR tablets and its fitness to various established kinetic models. For Ethocel® 7 cp polymers, a reasonable good fit was obtained with all five kinetic models although Eq. (5) was generally more suitable than the others. Ibuprofen release from Ethocel®10 cp polymers best fitted Eq. (5) and to a lesser extent Eq. (4). Eq. (1) yielded the poorest fit. The kinetics of release from Ethocel® 20 cp were best modeled by Eq. (5) while Eqs. (2–4) still provided a reasonable match. Again, Eq. (1) was the least suitable. For Ethocel® 45 cp and Ethocel® 100 cp, the extent of fit to the various models was highly dependent upon D:P ratios. Generally speaking, Eq. (5) was the best kinetic model overall while suitability of the other equations varied considerably with D:P ratio. Interestingly, dissolution testing of Ethocel® 45 cp and Ethocel® 100 cp showed

TABLE 2 **f_2-Metric Values for the Determination of Equivalency Between the Release Profiles from Ethocel® and Ethocel® FP Polymer Matrices. Other Variables are D:P Ratio and Viscosity Grade**

No.	D:P ratio	Ethocel® viscosity grade using Ethocel®7cp as reference	f_2-metric values	Ethocel®vs. Ethocel® FP Reference / Test	f_2-metric values
1.	10:1	Ethocel®7cp/	53.2503	Ethocel® 7cp/	41.5345
2.	10:2	Ethocel®10cp	49.3385	Ethocel®7 FP	40.5641
3.	10:3		35.8490		45.4498
4.	10:1	Ethocel®7cp/	49.9490	Ethocel® 10cp/	28.2113
5.	10:2	Ethocel®20cp	45.4243	Ethocel®10 FP	26.3842
6.	10:3		52.4309		27.3842
7.	10:1	Ethocel®7cp/	39.8738	Ethocel®100cp/	42.5796
8.	10:2	Ethocel®45cp	37.7040	Ethocel®100FP	24.7618
9.	10:3		46.2485		23.8480
10.	10:1	Ethocel®7cp/	35.6744	----------	--------
11.	10:2	Ethocel®100cp	38.2114		
12.	10:3		43.7651		

TABLE 3 **Kinetic Model Parameters Applied to Ibuprofen Release Profiles of Directly Compressed CR Tablets Using Ethocel® Polymers of Different Viscosity Grades (Mean SD of Three Determinations)**

Formulation	$W = k_1 t$		$(100-W) = \ln 100 - k_2 t$		$(100-W)^{1/3} = 100^{1/3} - k_3 t$		$W = k_4 t^{1/2}$		$M_t/M_\infty = k_5 t^n$		
IBF:Ethocel	$k_1 \pm SD$	$r_1 \pm SD$	$k_2 \pm SD$	$r_2 \pm SD$	$k_3 \pm SD$	$r_3 \pm SD$	$k_4 \pm SD$	$r_4 \pm SD$	$k_5 \pm SD$	$r_5 \pm SD$	$n \pm SD$
IBF- Ethocel® Standard 7 cp Premium											
10:1	3.289±.226	0.939±.046	0.101±.023	0.979±.026	0.103±.015	0.972±.034	20.3581±.258	0.979±.024	0.219±.063	0.985±.015	0.625±.122
10:2	3.203±.409	0.959±.024	0.085±.033	0.993±.007	0.096±.021	0.988±.008	19.6762±.816	0.990±.008	0.167±.013	0.995±.003	0.637±.115
10:3	2.657±.204	0.986±.005	0.059±.010	0.999±.006	0.068±.008	0.998±.0006	15.5734±.866	0.995±.005	0.098±.051	0.994±.004	0.684±.241
IBF- Ethocel® Standard 10 cp Premium											
10:1	3.409±.201	0.883±.029	0.124±.031	0.958±.036	0.119±.019	0.941±.038	21.9161±.187	0.957±.018	0.251±.049	0.970±.022	0.564±.046
10:2	3.188±.155	0.891±.019	0.086±.004	0.936±.016	0.094±.004	0.930±.018	20.388±.788	0.960±.011	0.216±.031	0.977±.008	0.590±.038
10:3	2.474±.233	0.823±.029	0.056±.008	0.868±.027	0.065±.008	0.855±.027	16.383±.382	0.918±.020	0.199±.030	0.977±.012	0.511±.048
IBF- Ethocel® Standard 20 cp Premium											
10:1	3.231±.107	0.849±.021	0.102±.005	0.921±.021	0.104±.005	0.901±.022	21.127±.591	0.947±.033	0.215±.012	0.966±.002	0.578±.018
10:2	3.649±.231	0.900±.031	0.116±.012	0.964±.016	0.118±.004	0.949±.022	23.200±.064	0.964±.016	0.159±.058	0.980±.008	0.686±.134
10:3	2.896±.874	0.975±.041	0.0739±.039	0.984±.025	0.081±.037	0.977±.024	18.014±.321	0.988±.005	0.167±.009	0.989±.007	0.614±.026
IBF- Ethocel® Standard 45 cp Premium											
10:1	3.024±.126	0.815±.013	0.114±.006	0.899±.015	0.109±.005	0.875±.016	20.1170±.835	0.913±.010	0.269±.028	0.955±.007	0.506±.043
10:2	3.238±.225	0.870±.021	0.102±.008	0.936±.025	0.104±.008	0.918±.024	20.941±.217	0.948±.014	0.219±.035	0.974±.006	0.565±.052
10:3	3.190±.189	0.959±.006	0.560±.041	0.997±.003	0.089±.007	0.990±.001	19.584±.280	0.991±.001	0.175±.028	0.989±.004	0.580±.071
IBF- Ethocel® Standard 100 cp Premium											
10:1	3.231±.133	0.825±.019	0.183±.010	0.938±.003	0.145±.002	0.906±.005	21.343±.696	0.915±.018	0.279±.023	0.958±.010	0.452±.017
10:2	3.302±.063	0.862±.009	0.111±.002	0.940±.011	0.110±.002	0.919±.010	21.465±.314	0.944±.006	0.216±.009	0.917±.003	0.571±.012
10:3	3.284±.016	0.960±.025	0.088±.001	0.994±.001	0.960±.001	0.991±.012	20.167±.449	0.992±.009	0.171±.011	0.993±.005	0.584±.006

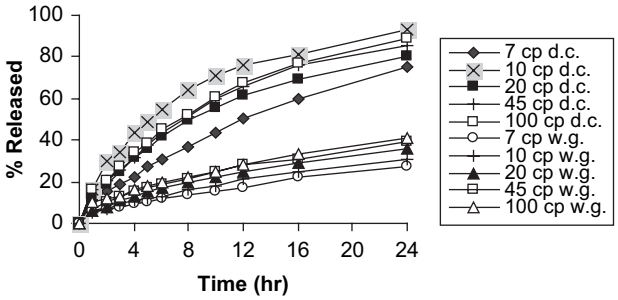

FIGURE 2 **Release Profiles of IBF-Ethocel (10:3) Directly Compressed (d.c.) and Wet-Granulated (w.g.) Matrix Tablets.**

that the *r*-values increased as the D:P ratio increased in all formulations except one.

It is noteworthy that when wet granulation was used as opposed to direct compression, all the Ethocel® polymeric formulations demonstrated drastically reduced drug release rates (Fig. 2). This effect is attributable to the excellent compressibility of the granulations, resulting in harder tablets with lower porosity. This may lead to greater interparticle cohesion, which decreases the water penetration rate through the matrix micropores, yielding slower drug release rates from the tablets. In this respect, our results contradict those of Shlieout and Zessin (1996) who reported increased dissolution rates with wet granulation. That group proposed a probable increase in the erosion rates of the drug from ethyl cellulose matrices. Table 4 represents the release kinetics parameters for IBF-Ethocel® (10:3) tablets produced by wet granulation. It can be seen that the ibuprofen release data could be easily fitted with all five kinetic models. However, as can be seen from the linearity of the release curves in Fig. 2, the '*n*' values were underestimated by Eq. (5).

Ethocel®Formulations versus Ethocel®Standard FP Premium Formulations

Fig. 3 shows the drug release profiles from directly compressed tablets containing Ethocel® 7, 10, 100 cp and 7, 10, 100 Ethocel®FP Premium polymers, each at different D P ratios are shown in Fig. 3. The relevant f_2-metric values are presented in Table 2. It is noteworthy that use of Ethocel® FP Premium polymers extended the ibuprofen release rates more efficiently than the conventional granular form of the polymer.

TABLE 4 **Kinetic Model Parameters Applied to Ibuprofen Release Profiles of Ethocel® (10:3) Wet-Granulated CR Matrix Tablets Using Ethocel® Polymers with Different Viscosity Grades (Mean SD of Three Determinations)**

	$W = k_1 t$		$(100\text{-}W) = \ln 100\text{-}k_2 t$		$(100\text{-}W)^{1/3} = 100^{1/3}\text{-}k_3 t$		$W = k_4 t^{1/2}$		$M_t/M_\infty = k_5 t^n$		
Viscosity grade	$k_1 \pm SD$	$r_1 \pm SD$	$k_2 \pm SD$	$r_2 \pm SD$	$k_3 \pm SD$	$r_3 \pm SD$	$k_4 \pm SD$	$r_4 \pm SD$	$k_5 \pm SD$	$r_5 \pm SD$	$n \pm SD$
IBF-Ethocel® Standard cp Polymers											
7 cp	0.956±.034	0.986±.006	0.012±.001	0.990±.004	0.014±.003	0.989±.005	5.682±.243	0.987±.001	0.180±.015	0.978±.007	0.523±.039
10 cp	1.095±.067	0.988±.001	0.016±.003	0.994±.008	0.020±.001	0.992±.001	6.563±.395	0.998±.00	0.160±.025	0.999±.00	0.572±.026
20 cp	1.390±.080	0.992±.003	0.019±.003	0.998±.001	0.026±.002	0.997±.002	8.270±.429	0.993±.001	0.211±.102	0.991±.002	0.469±.053
45 cp	1.482±.102	0.983±.006	0.020±.010	0.994±.003	0.028±.009	0.991±.003	8.945±.689	0.999±.00	0.192±.003	0.999±.003	0.516±.021
100 cp	1.520±.027	0.985±.038	0.021±.026	0.995±.001	0.029±.003	0.992±.001	9.154±.095	0.999±.010	0.188±.021	0.998±.276	0.520±.033
IBF-Ethocel® Standard FP Polymers											
7 FP	1.132±.096	0.975±.026	0.015±.002	0.985±.001	0.021±.012	0.982±.001	6.895±.542	0.999±.001	0.363±.004	0.998±.003	0.973±.028
10 FP	1.286±.082	0.984±.004	0.017±.003	0.993±.003	0.024±.022	0.990±.003	7.755±.432	0.999±.003	0.481±.025	0.998±.001	0.481±.066
100 FP	1.190±.008	0.975±.025	0.015±.001	0.985±.010	0.022±.003	0.982±.002	7.239±.380	0.999±.001	0.210±.020	0.998±.001	0.493±.032

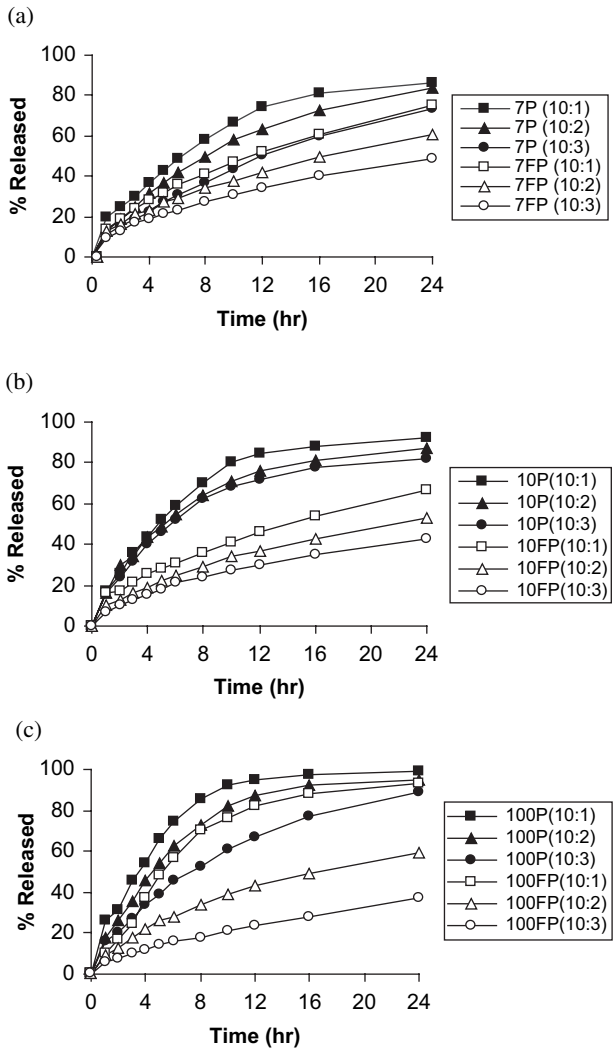

FIGURE 3 **Release Profiles of Ibuprofen from Ethocel Premium and Ethocel FP Premium Matrices with Different Viscosity Grades and D:P ratios. (a) 7cp; (b) 10cp; (c) 100cp.**

This is probably due to the small particle size of the Ethocel® FP polymers. As seen in Fig. 3, Ethocel® 7 cp tablets released 87, 84, and 73% of ibuprofen after 24 hr at D:P ratios of 10:1, 10:2, and 10:3, respectively. In contrast, Ethocel® 7 FP Premium with similar D:P ratios released, respectively, 75, 61, and 49% of ibuprofen after 24 hr. The cumulative percentage of drug released from Ethocel® 10 cp and 10 FP Premium polymers at the above D:P ratios were 92, 87, 82.0% and 67, 53, 43%, respectively. Similarly, Ethocel® 100 cp and Ethocel® 100 FP Premium polymers released 99, 95, 89% and 93, 59, 37%, respectively, at the above-mentioned D:P ratios. Hence, it seems that polymer concentration and polymer particle size, rather than viscosity grade, are the key parameters modulating drug release in this system. Table 5 shows that in case of

TABLE 5 **Kinetic Model Parameters Applied to Ibuprofen Release Profiles of Directly Compressed CR Tablets Using Ethocel® FP Polymers of Different Viscosity Grades (Mean SD of Three Determinations)**

Formulation	$W = k_1 t$		$(100-W) = \ln 100 - k_2 t$		$(100-W)^{1/3} = 100^{1/3} - k_3 t$		$W = k_4 t^{1/2}$		$M_t/M_\infty = k_5 t^n$		
IBF:Ethocel	$k_1 \pm SD$	$r_1 \pm SD$	$k_2 \pm SD$	$r_2 \pm SD$	$k_3 \pm SD$	$r_3 \pm SD$	$k_4 \pm SD$	$r_4 \pm SD$	$k_5 \pm SD$	$r_5 \pm SD$	$n \pm SD$
IBF- Ethocel® Standard 7 FP Premium											
10:1	2.584±.165	0.977±.003	0.295±.350	0.999±.001	0.062±.005	0.995±.003	15.684±.969	0.999±.001	0.188±.014	0.998±.001	0.530±.023
10:2	2.067±.103	0.990±.013	0.034±.003	0.998±.001	0.045±.003	0.996±.004	12.440±.689	0.998±.0	0.198±.001	0.996±.001	0.500±.008
10:3	1.707±.069	0.98±.009	0.025±.003	0.995±.005	0.034±.003	0.992±.007	10.290±.304	0.999±.001	0.188±.008	0.999±.001	0.505±.025
IBF- Ethocel® Standard 10 FP Premium											
10:1	2.291±.033	0.989±.00	0.041±.001	0.999±.00	0.052±.001	0.999±.001	13.695±.170	0.996±.00	0.272±.102	0.981±.011	0.450±.053
10:2	1.799±.012	0.992±.007	0.027±.004	0.997±.00	0.037±.001	0.995±.00	10.794±.046	0.997±.001	0.196±.002	0.996±.003	0.504±.004
10:3	1.464±.037	0.979±.001	0.020±.00	0.990±.001	0.280±.001	0.988±.001	8.881±.220	0.999±.0	0.174±.025	0.998±.00	0.548±.033
IBF- Ethocel® Standard 100 FP Premium											
10:1	3.886±.760	0.850±.038	0.128±.026	0.937±.033	0.127±.017	0.917±.038	25.085±.144	0.938±.022	0.131±.095	0.958±.007	0.819±.276
10:2	1.432±.200	0.975±.027	0.039±.028	0.995±.001	0.050±.031	0.989±.004	13.2756±.071	0.995±.00	0.150±.018	0.991±.006	0.626±.021
10:3	0.017±.001	0.998±.00	0.017±.003	0.995±.001	0.025±.025	0.994±.001	8.1180±.439	0.990±.0	0.141±.020	0.995±.002	0.613±.050

directly compressed Ethocel® 7 FP polymer matrices, all the kinetic models suitably fitted the drug release data. Yet Eqs. (4, 5) yielded the greatest reproducibility (SD ≤ 0.001). In the case of Ethocel® 10 FP Premium polymers, good fits were again obtained for all five kinetic models. However, for Eqs. (2, 3), *r*-values were inversely related to polymer concentrations whilst for Eqs. (4, 5), *r*-values increased with rising polymer concentrations. For Ethocel® 100 FP Premium polymers, D:P ratios determined the degree of fit to the different kinetic models. At a D:P ratio of 10:1, Eqs. (2–4) were the most appropriate. At D:P ratios of 10:2 and 10:3, all five Eqs. provided a good fit. Intriguingly, use of Eq. (5) for modeling drug release from Ethocel® 7 FP and Ethocel® 10 FP matrices, again yielded underestimated '*n*' values.

Progressive Replacement of Lactose with HPMC

For Ethocel® tablets produced by direct compression (Fig. 4) and those produced by wet granulation (Fig. 5), lactose substitution with 10% HPMC resulted in somewhat higher release rates. Substitution with 20% HPMC produced even higher release rates from all the formulations studied. The release profiles obtained from

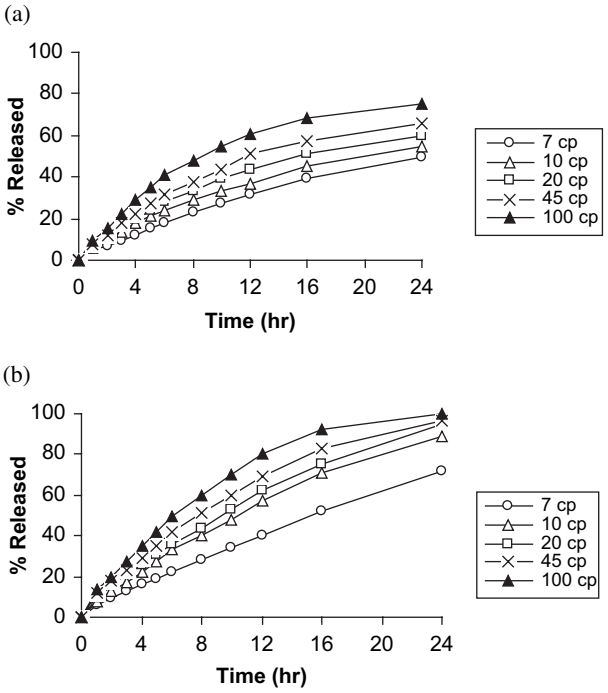

FIGURE 5 **Release Profiles from IBF-Ethocel (10:3) Wet-Granulated Matrix Tablets Containing 10% (a) and 20% (b) HPMC as Lactose Replacement.**

directly compressed (a) and wet granulated (b) Ethocel® FP tablets that contained HPMC are shown in Fig. 6. It is apparent that for tablets of Ethocel®7 FP and 10 FP,

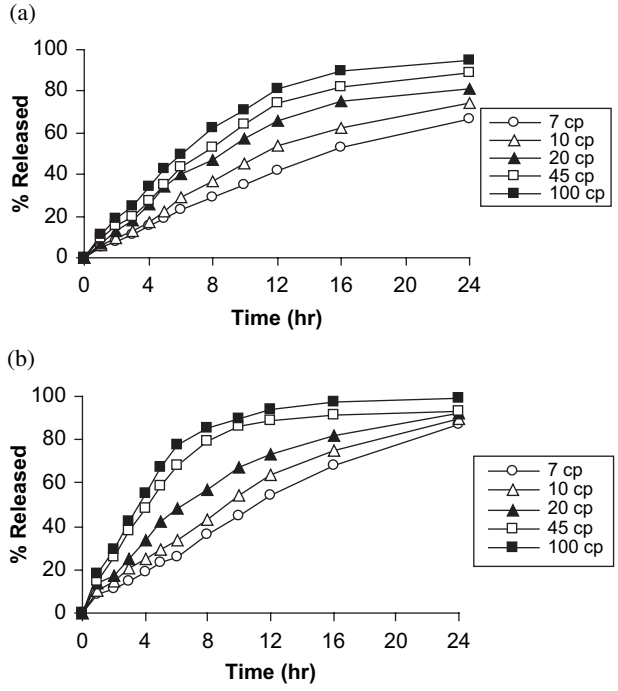

FIGURE 4 **Release Profiles from IBF-Ethocel (10:3) Directly Compressed (d.c.) Matrix Tablets Containing 10% (a) and 20% (b) HPMC as Lactose Replacement.**

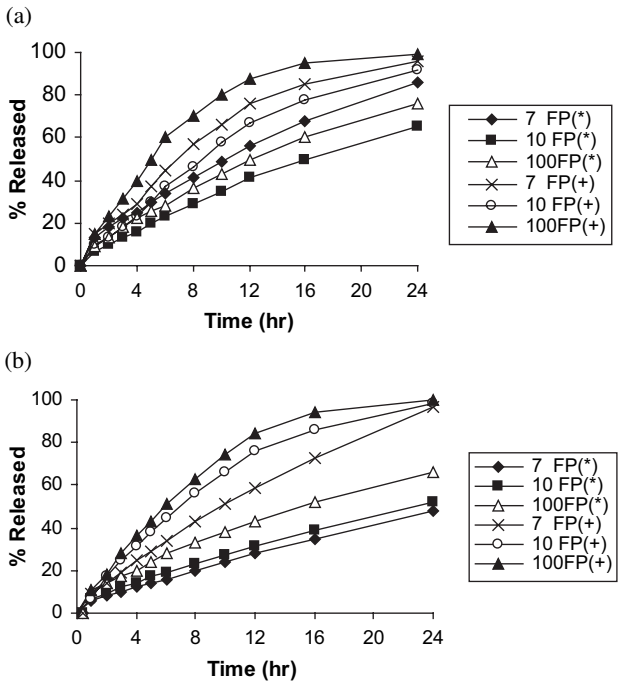

FIGURE 6 **Release Profiles of IBF-Ethanol FP Premium (10:2) Directly Compressed (a) and Wet-Granulated (b) Matrix Tablets Containing 10% (*) or 20% (+) HPMC as Lactose Replacement.**

TABLE 6 Kinetic Model Parameters Applied to Ibuprofen Release Profiles of Directly Compressed Ethocel® (10:3) CR Tablets Containing HPMC as a Coexcipient (Mean SD of Three Determinations)

Ethocel®	$W = k_1 t$		$(100-W) = \ln 100 - k_2 t$		$(100-W)^{1/3} = 100^{1/3} - k_3 t$		$W = k_4 t^{1/2}$		$M_t/M_\infty = k_5 t^n$		
(% HPMC)	$k_1 \pm$ SD	$r_1 \pm$ SD	$k_2 \pm$ SD	$r_2 \pm$ SD	$k_3 \pm$ SD	$r_3 \pm$ SD	$k_4 \pm$ SD	$r_4 \pm$ SD	$k_5 \pm$ SD	$r_5 \pm$ SD	$n \pm$ SD
IBF- Ethocel® Standard Premium Directly Compressed Matrix Tablets											
7 cp (10)	2.484±.029	0.971±.020	0.040±.012	0.992±.004	0.052±.022	0.986±.001	15.1084±.20	0.995±.003	0.096±.024	0.992±.003	0.789±.021
(20)	4.119±.044	0.960±.010	0.126±.032	0.994±.003	0.127±.012	0.996±.003	25.2566±.11	0.992±.012	0.069±.020	0.986±.006	0.935±.016
10 cp (10)	3.707±.050	0.976±.008	0.094±.003	0.994±.001	0.103±.008	0.995±.003	22.3344±.32	0.990±.008	0.101±.014	0.997±.001	0.755±.008
(20)	4.160±.028	0.929±.022	0.174±.026	0995±.003	0.152±.003	0990±.001	25.9235±.00	0975±.010	0.116±.010	0986±.010	0.754±.010
20 cp (10)	3.356±.010	0.936±.014	0.937±.054	0.994±.008	0.100±.001	0.981±.00	20.985±.088	0.985±.024	0.132±.008	0.995±.008	0.679±.004
(20)	3.800±.022	0.895±.031	0.196±.010	0.998±.014	0.157±.006	0.982±.003	24.251±.56	0.962±.006	0.176±.018	0.980±.003	0.626±.003
45 cp (10)	4.104±.046	0.979±.008	0.103±.032	0.987±.006	0.113±.012	0.992±.004	24.4622±.10	0.983±.003	0.052±.012	0.996±.002	0.983±.016
(20)	4.295±.014	0.930±.016	0.191±.016	0.989±.003	0.159±.020	0.996±.003	26.816±.096	0.977±.003	0.092±.008	0.983±.001	0.847±.022
100 cp (10)	3.248±.033	0.825±.024	0.112±.009	0.909±.001	0.110±.006	0.885±.006	21.517±.08	0.920±.001	0.237±.008	0.911±.012	0.522±.008
(20)	3.636±.018	0.837±.022	4.318±.014	0.851±.001	0.215±.003	0.963±.013	23.954±.00	0.928±.003	0.202±.003	0.957±.008	0.610±.003
IBF- Ethocel® Standard FP Premium Directly Compressed Matrix Tablets											
7 FP (10)	1.730±.120	0.976±.003	0.025±.024	0.991±.004	0.034±.010	0.987±.014	10.5131±.25	0.999±.010	0.166±.010	0.998±.002	0.575±.010
(20)	3.352±.056	0.978±.008	0.070±.008	0.996±.001	0.083±.009	0.994±.008	20.2063±.06	0.992±.014	0.099±.001	0.996±.003	0.759±.008
10 FP (10)	1.481±.038	0.971±.019	0.020±.040	0.985±.016	0.028±.003	0.981±.012	9.039±.078	0.998±.022	0.158±.003	0.997±.00	0.602±.003
(20)	2.528±.040	0.967±.008	0.041±.028	0.987±.008	0.054±.001	0.982±.001	15.398±.36	0.992±.008	0.109±.008	0.995±.003	0.740±.001
100 FP (10)	2.254±.020	0.977±.014	0.037±.008	0.996±.00	0.049±.007	0.992±.006	13.6674±.12	0.998±.012	0.164±.001	0.997±.008	0.576±.004
(20)	4.197±.064	0.950±.003	0.266±.012	0.936±.003	0.175±.013	0.997±.003	25.8443±.62	0.985±.008	0.114±.003	0.989±.022	0.7410±.00

TABLE 7 Kinetic Model Parameters Applied to the Release Profiles of Wet Granulated Ethocel® (10:3) CR Tablets Containing HPMC as a Coexcipient (Mean SD of Three Determinations)

Ethocel®	$W = k_1 t$		$(100-W) = \ln 100 - k_2 t$		$(100-W)^{1/3} = 100^{1/3} - k_3 t$		$W = k_4 t^{1/2}$		$M_t/M_\infty = k_5 t^n$		
(% HPMC)	$k_1 \pm SD$	$r_1 \pm SD$	$k_2 \pm SD$	$r_2 \pm SD$	$k_3 \pm SD$	$r_3 \pm SD$	$k_4 \pm SD$	$r_4 \pm SD$	$k_5 \pm SD$	$r_5 \pm SD$	$n \pm SD$
IBF- Ethocel® Standard Premium Wet Granulated Matrix Tablets											
7 cp (10)	1.335±.006	0.985±.003	0.018±.012	0.993±.003	0.025±.021	0.991±.001	8.0292±.56	0.998±.003	0.312±.012	0.993±.003	0.512±.012
(20)	2.885±.003	0.965±.006	0.053±.030	0.990±.001	0.067±.016	0.983±.003	17.527±4.10	0.998±.001	0.131±.008	0.985±.002	0.664±.008
10 cp (10)	1.420±.012	0.975±.001	0.019±.008	0.988±.002	0.026±.012	0.984±.003	8.6482±.56	0.999±.005	0.151±.010	0.997±.000	0.615±.008
(20)	3.135±.008	0.967±.003	0.059±.024	0.996±.003	0.073±.008	0.990±.005	19.1923±.12	0.993±.002	0.088±.014	0.993±.008	0.819±.012
20 cp (10)	1.422±.003	0.979±.010	0.019±.014	0.990±.001	0.027±.008	0.987±.008	8.6173±.58	0.999±.004	0.205±.020	0.999±.010	0.499±.015
(20)	3.331±.001	0.961±.006	0.073±.016	0.986±.006	0.086±.032	0.982±.002	20.3182±.92	0.987±.003	0.115±.016	0.986±.006	0.739±.008
45 cp (10)	1.720±.001	0.992±.003	0.025±.002	0.998±.001	0.034±.010	0.997±.004	10.2544±.06	0.996±.008	0.183±.014	0.996±.002	0.522±.006
(20)	3.619±.006	0.956±.001	0.094±.003	0.992±.008	0.103±.027	0.986±.001	22.2172±.00	0.988±.006	0.123±.008	0.994±.003	0.710±.014
100 cp (10)	1.499±.014	0.982±.009	0.020±.008	0.993±.003	0.028±.016	0.990±.003	8.8781±.54	0.999±.010	0.312±.018	0.999±.002	0.531±.020
(20)	4.223±.008	0.931±.006	0.193±.008	0.988±.006	0.159±.012	0.995±.001	26.3422±.24	0.978±.003	0.106±.008	0.984±.008	0.790±.012
IBF- Ethocel® Standard FP Premium Wet Granulated Matrix Tablets											
7 FP (10)	1.173±.003	0.986±.003	0.151±.005	0.993±.003	0.022±.014	0.992±.008	7.0531±.22	0.998±.002	0.217±.012	0.995±.001	0.468±.008
(20)	2.305±.001	0.989±.002	0.036±.008	0.999±.003	0.047±.012	0.997±.004	13.734±.086	0.992±.003	0.112±.010	0.990±.003	0.680±.012
10 FP (10)	1.345±.002	0.983±.002	0.018±.003	0.992±.008	0.025±.003	0.989±.010	8.115±.110	0.999±.006	0.192±.020	0.996±.006	0.515±.003
(20)	2.675±.003	0.978±.001	0.046±.003	0.996±.001	0.059±.001	0.992±.008	16.105±.078	0.992±.004	0.126±.016	0.988±.003	0.662±.008
100 FP (10)	1.439±.008	0.981±.006	0.019±.006	0.992±.003	0.027±.020	0.989±.008	8.701±.084	0.999±.008	0.173±.003	0.999±.005	0.555±.010
(20)	2.985±.006	0.983±.010	0.054±.010	0.996±.002	0.068±.016	0.994±.012	17.796±.104	0.987±.001	0.099±.008	0.985±.001	0.734±.004

TABLE 8 Cumulative (%) Ibuprofen Released and Determination of Equivalency Between Release-Profiles of Ethocel® and Ethocel® FP Polymer Matrix Tablets at D:P ratio of 10:3

Ethocel®polymer (viscosity grade)		7 cp	10 cp	20 cp	45 cp	100 cp	7 FP	10 FP	100 FP
Cumulative (%) released (24 hr)[1]	D.C.*	74.83	73.99	77.70	85.31	88.67	49.40	42.52	36.82
	W.G.@	26.33	31.78	39.82	38.64	43.79	35.49	38.41	35.15
f_2-metric values[1]	Ref/Test	29.5722	22.4945	29.7843	26.5805	24.2268	59.4796	80.76578	81.4149
Cumulative % released (24 hr)[2]	D.C.[2]	60.69	89.98	89.13	90.24	91.11	49.07	40.49	62.15
	D.C.[3]	94.60	98.21	99.13	98.94	100	80.20	61.09	99.90
f_2-metric values[2]	Ref/Test	53.5604	42.1605	53.7019	46.0310	34.5881	91.5963	86.1481	40.2543
f_2-metric values[3]	Ref/Test	43.3196	45.6391	36.0671	47.5563	30.0617	39.6292	48.4751	20.2755
Cumulative % released (24 hr)[4]	W.G.[4]	38.36	38.98	41.88	48.40	43.04	35.12	38.84	40.26
	W.G.[5]	71.32	74.65	81.20	88.19	98.99	58.31	67.29	71.64
f_2-metric values[4]	Ref/Test	56.6945	63.2688	86.8278	64.8695	94.5934	87.2794	96.0120	80.7125
f_2-metric values[5]	Ref/Test	29.0704	31.0345	30.9399	26.2331	22.2429	49.9907	41.2653	37.9166

*direct compression and @wet granulation (also used as references).
[1]direct compression (Reference) vs. wet granulation (Test) without co-excipient,
[2]direct compression without co-excipient (Reference) vs. direct compression with 10 % co-excipient (Test),
[3]direct compression without co-excipient (Reference) vs. direct compression with 20 % co-excipient (Test),
[4]wet granulation without co-excipient (Reference) vs. wet granulation with 10 % co-excipient (Test), and
[5]wet granulation without co-excipient (Reference) vs. wet granulation with 20 % co-excipient (Test).

prepared by either of the two methods, 10% HPMC substitution had little influence on the drug release behavior. Contrastingly, Ethocel®100 FP matrices with 10% HPMC substitution and all the formulations with 20% HPMC exhibited considerable enhancement in their release rates. A probable reason for this is that the water soluble HPMC dissolves following water absorption, creating osmotic forces within the matrices. Alternatively or additionally, small amounts of HPMC can act as a channeling agent, causing higher release rates (Alderman, 1984; Ford et al., 1987; Khan & Zhu, 1998a,b; Gohel et al., 2003). Table 8 shows the influence of partial substitution of HPMC in terms of f_2-metric values. Interestingly, for all tested tablet types, incorporating 20% HPMC significantly changed the dissolution rate profile. Yet the incorporation of just 10% HPMC had a variable effect that depended upon the precise tablet formulation.

With respect to drug release kinetic models, the directly compressed, HPMC-containing tablets released ibuprofen in a manner that was modeled well by all five equations (Table 6).

Table 7 shows results relating to wet granulation tablets formulated from Ethocel®and Ethocel® FP polymers at a D:P ratio of 10:3. Again, a general observation was that all the investigated kinetic models represented well the experimental data. Moreover, Eq. (5) underestimated '*n*' values for tablets containing 10% HPMC and overestimated the '*n*' values for tablets containing 20% HPMC.

CONCLUSIONS

Generally speaking, this study has shown that the ibuprofen release kinetics from these ethylcellulose ether derived polymers are somewhat complex in nature. Drug release profiles were determined by more than formulation parameter with crosstalk occurring between parameters in most circumstances. Nevertheless, it was possible to identify some general principles. First, the use of Ethocel® FP polymers and wet granulation facilitated more precise control of the release kinetics. Furthermore, polymer level and particle size, rather than the viscosity grade, modulated release behavior from the matrices. In terms of modeling ibuprofen release profiles, the first-order kinetics, Higuchi's square root of time and the power law equations were found to be generally more accurate than the zero-order kinetics and Hixon Crowel's cube root

equation. This indicates that diffusional processes rather than erosion of the matrix were the key dissolution mechanism in most cases (Costa et al., 2001; Sepmann & Peppas, 2001). The generally poor fit of the zero-order model means the test formulations do not yet perform as ideal sustained release systems. Importantly, the Power Law equation failed to provide a precise estimation of '*n*' values with respect to wet granulated matrices, especially when smaller particle sized polymers was used. Partial substitution of the primary excipient, lactose, with HPMC at 10% levels increased drug release rates from all the matrices without altering their release mechanisms. However, increasing HPMC levels to 20% markedly changed both the release rates as well as the kinetics.

We are now extending these studies in our laboratories, specifically researching drug release from ethylcellulose ether derived polymeric tablets within the in vivo context. We also aim to develop and model more accurate kinetic interpretations of the observed drug release paradigms.

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