Wet Granulation Fine Particle Ethylcellulose Tablets: Effect of Production Variables and Mathematical Modeling of Drug Release

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ABSTRACT

In the present study, the applicability of fine particle ethylcellulose (FPEC) to produce matrix tablets by a wet granulation technique was evaluated. The effect of various formulation and process variables, such as FPEC content, hardness of the tablet, and solubility of the drug, on the release of drug from these tablets was examined. Tablets were prepared by wet granulation of drug and FPEC in an appropriate mass ratio. Theophylline, caffeine, and dyphylline were selected as nonionizable model drugs with solubilities from 8.3 to 330 mg/mL at 25°C. Ibuprofen, phenylpropanolamine hydrochloride, and pseudoephedrine hydrochloride were selected as ionizable drugs with solubilities from 0.1 to 2000 mg/mL at 25°C. Drug release studies were conducted in 37°C water with UV detection. As the FPEC content and the hardness of the tablets increased, the release rate of the drug decreased. The drug release rate increased with an increase in the solubility of the drug. Model equations, intended to elucidate the drug release mechanism, were fitted to the release data. Parameters were generated and data presented by SAS software. The Akaike Information Criterion was also considered to ascertain the best-fit equation. Fickian diffusion and polymer relaxation were the release mechanisms for nonionizable and ionizable drugs.

KEYWORDS: fine particle ethylcellulose, wet granulation, ionizable drugs, nonionizable drugs, Fickian diffusion, polymer relaxation

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INTRODUCTION

Ethylcellulose is an inert, hydrophobic polymer and is essentially tasteless, odorless, colorless, noncaloric, and physiologically inert. It has been extensively used as a pharmaceutical vehicle in a number of dosage forms. It has been used as a coating material for tablets and granules,¹ as a tablet binder,² in preparing microcapsules and microspheres,^{3,4} and also as film- and matrix-forming material for sustained-release dosage forms.⁵⁻¹¹ Preparation of these dosage forms in some cases required several unit operations. Especially noteworthy is that many of these processes required solubilization of all or part of the ethylcellulose using an organic solvent. Environmental issues are making these processes less tolerable and more expensive.

The manufacture by direct compression of matrix-type tablets using ethylcellulose as the matrix-forming polymer has been studied,^{5,6,8,11,12} and the effect of various formulation and process variables on such tablets has been studied in depth.^{5,6,8-10,12} The drug release mechanism from directly compressed ethylcellulose tablets has also been elucidated.¹³ Preparation of matrix-type tablets by an aqueous wet granulation method using commercially available coarse ethylcellulose has not been successful. Nevertheless, the wet granulation process offers several advantages. For example, high dose drugs that experience poor flow and/or poor compactibility can be granulated to obtain suitable flow and cohesion for compaction. With low dose drugs, content uniformity in the tablets can be increased.¹⁴ This study examines whether or not ethylcellulose matrix tablets could be produced by an aqueous wet granulation method, providing an alternative manufacturing method to the formulator.

Recently, fine particle ethylcellulose (FPEC) has become available to the pharmaceutical industry.¹² These polymers range in average particle size from 6 to 50 μm and are chemically equivalent to the existing standard ethoxyl grade of coarse ethylcellulose materials. It is well established in the industry that the particle size of an excipient

can have a dramatic effect on the characteristics of the final product.^{4,15} Thus, these smaller ethylcellulose particle sizes may offer the formulator new options for addressing problems in the areas of tablet physical properties, active release profiles, and manufacturing limitations.

The use of ethylcellulose to prepare matrix tablets by a wet granulation method has not been investigated so far because of the general contention that ethylcellulose is a hydrophobic polymer. However, the new fine particle version offers the potential to improve the characteristics of wetted powder blends because of its overall tremendous surface area, which allows water binding. If ethylcellulose tablets can be manufactured as proposed in this study, then it is important to examine the effects of various formulation and process variables on tablet characteristics. Drug release profiles were studied to determine the release mechanisms. Ionizable and non-ionizable drugs of varying aqueous solubility were selected to examine the differences in the resulting release mechanisms. Xanthine derivatives were chosen as model nonionizable drugs to minimize differences caused by the effects of size and shape of drug molecules. The average particle sizes of the model drugs were similar, so that only the drug solubility would affect the release rate.

The objectives of this study were to use a wet granulation method to prepare matrix tablets using a low viscosity grade of fine particle ethylcellulose; to observe the effect of drug solubility, hardness of the tablet, and FPEC content on release of drug from the tablet; and to analyze the drug release profiles for nonionizable and ionizable model drugs to determine which of several release equations provides the best fit to the data.

MATERIALS AND METHODS

Materials

Ethylcellulose (Ethocel*FP Premium, 7 cps viscosity grade with ethoxy content of 48%-49.5%) of average particle size 9.7 μm was a gift from the Dow Chemical Company (Midland, MI). Magnesium stearate (Fisher Scientific, Fair Lawn, NJ) was used as a lubricant. Dipyhylline, caffeine, and theophylline (Sigma Chemical Co, St Louis, MO) were used as the model nonionizable drugs, with solubilities of 330, 20, and 8.3 mg/mL in water, respectively, at 25°C.¹⁵ Pseudoephedrine hydrochloride (PSE.HCl) and phenylpropanolamine hydrochloride (PPA.HCl) from Sandoz Research Ltd (Lincoln, NE) and ibuprofen from ICN Biomedical Inc (Aurora, OH) were used as the model ionizable

drugs, with solubilities of 2000, 909, and less than 0.1 mg/mL in water, respectively, at 25°C.¹⁶

Methods

Drug and FPEC were mixed in the desired mass ratio in a Hobart Model N-501 planetary mixer (Hobart Corporation, Troy, OH) for 10 minutes. The batch size was 500 g. In the FPEC content study, the formulations consisted of FPEC ranging from 49.5% to 89.5% wt/wt and caffeine ranging from 49.5% to 9.5% wt/wt. For the hardness study, the formulation consisted of 9.5% wt/wt caffeine and 89.5% wt/wt FPEC. For the study to examine the effect of drug solubility, tablets consisting of 9.5% wt/wt model drug and 89.5% wt/wt FPEC were prepared. Deionized, distilled water was used as the granulating fluid to form the wetted mass. The amount of water added for the FPEC content study and for the hardness study was 60% of the powder mass. In the solubility study, the water content ranged from 60% to 62.5% of the powder mass depending on the active involved. Water was added with a 60-cc syringe over a period of 5 minutes while mixing the powder blend in the Hobart mixer; then wet mixing was carried out for an additional 5 minutes. The wetted mass was granulated manually by passing it through a 12-mesh screen. The granules were dried in a vacuum oven at 40°C for 24 hours. The dried granules (moisture content below 2%) were manually passed through a 20-mesh screen and collected on a 120-mesh screen. The granules were then lubricated with 1% wt/wt magnesium stearate in a V-blender (model LB-1348, Patterson-Kelley Co, East Stroudsburg, PA) for 2 minutes. Tablets of 200 mg mass were compacted using a 4-station Colton press (model 204-76, Vector Corp, Marion, IA) with 11-mm flat-faced circular punch and die sets. The compaction force was varied to obtain the desired hardness.

Release studies, in 37°C purified water, were conducted with 6 replicates using an automated dissolution apparatus (model 2000, Distek Inc, North Brunswick, NJ) with a paddle stirring rate of 100 rpm and UV detection at 290 nm for dipyhylline, caffeine, and theophylline, and at 214 nm for PSE.HCl and PPA.HCl. Ibuprofen is insoluble in water; therefore, the release study for ibuprofen was conducted in 37°C simulated intestinal fluid without enzymes, which was prepared as per the United States Pharmacopeia 23, with UV detection at 221 nm.

Tablet hardness was measured using a Pfizer hardness tester (model 1463, Pfizer Inc, Groton, CT), and 5 determinations were averaged. Friability studies were conducted using a Vanderkamp friabilator (model 10805, Vankel Industries, Edison, NJ) along with 25 glass beads

of 3 mm diameter. The percentage loss in weight was determined for 20 tablets subjected to 100 revolutions at 25 rpm.

The suitability of several equations, which are reported to define the release mechanism(s), was tested with respect to the release data. Drug diffusion and polymer relaxation were the mechanisms considered relevant (polymer hydration and swelling are sometimes referred to as polymer relaxation¹⁷). Tablets with $\geq 70\%$ FPEC content remained intact during the release studies; therefore erosion was not considered one of the release mechanisms.

Data Analysis

The diffusion models are expected to be valid only up to approximately 60% cumulative drug released,¹⁸ and the data for analysis was therefore restricted to that range. Data obtained from each set of 6 experiments were pooled for nonlinear least-squares regression analysis using SAS software version 1.05 (SAS Institute Inc, Cary, NC). The model that best fit the data was chosen by the following criteria:

1. examination of the fit of the predicted curve to the data and the sum of the squared residuals (SSR) that resulted;
2. comparison of the Akaike information criterion (AIC) determined for each model fit; and
3. examination of the validity of the final parameter estimates (including magnitude and confidence intervals)

The AIC is defined by $n[\ln(\text{SSR})] + 2p$, where n is the number of experimental data points, SSR is the sum of the squared residuals, and p is the number of parameters to be estimated.¹⁹ The more negative the value of the AIC, the better the model describes the data. Since the AIC is based on both the fit to the data and the number of estimated parameters, if 2 models each fit the data well, the AIC will be lower for the model with fewer estimated parameters.

Empirical and Semi-Empirical Mathematical Models for Release Kinetics

The following models were considered. Time in each case was measured in minutes. Model 1 is based on drug diffusion through the matrix²⁰:

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} \quad (1)$$

Where M_t/M_∞ is the cumulative fraction of drug released, k_1 is the kinetic constant reflecting design variables of the system, and t is the release time. Model 2 is similar to Model 1 except that the exponent is not fixed¹⁸ at 0.5:

$$\frac{M_t}{M_\infty} = k_1 t^m \quad (2)$$

Here, k_1 is a constant incorporating structural and geometric characteristics of the device, and m is the release exponent characteristic of the release mechanism. The magnitude of the exponent m allows the general indication of Fickian diffusion, case II transport, or anomalous transport as the release mechanism. Ritger and Peppas have defined the exponent m as a function of the aspect ratio for 1-dimensional to 3-dimensional systems (slabs, cylinders, and discs). The aspect ratio is defined as the ratio of diameter to thickness. For tablets, depending on the aspect ratio, an m value between 0.43 and 0.5 indicates Fickian diffusion-controlled drug release, and an m value ≥ 0.89 indicates a swelling controlled drug release (zero-order release or case II transport). Values of m between 0.5 and 0.89 can be regarded as an indicator of the superimposition of both phenomena, commonly called anomalous transport.^{18,21}

Peppas and Sahlin²² noted that contributions to drug release could be considered additive, and this allowed the development of several other models for drug release from matrix tablets. In Model 3, the first term on the right-hand side represents the Fickian diffusional contribution, whereas the second term represents the case-II relaxation contribution²³:

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} + k_2 t \quad (3)$$

Model 4 is based on Model 3 without exponents fixed²² at $m = 0.5$:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (4)$$

Table 1. Size Distribution Data for FPEC- or Coarse Ethylcellulose-Containing Particles Obtained After Wet Screening Through the 12-Mesh Screen*

Sieve Number (Aperture in mm)	Percent Mass Retained on Each Sieve	
	FPEC	Coarse Ethylcellulose
10 (2.00)	-	-
12 (1.68)	32.0	-
14 (1.41)	23.1	4.22
16 (1.19)	8.23	4.22
18 (1.00)	6.17	5.49
20 (0.840)	6.58	5.06
25 (0.710)	5.35	6.75
30 (0.590)	3.70	10.9
35 (0.500)	4.12	13.5
50 (0.297)	5.81	32.9
60 (0.250)	2.06	7.17
70 (0.210)	1.24	2.95
80 (0.177)	0.820	4.26
100 (0.149)	0.820	1.72
120 (0.125)	0.410	0.430
Through 120	-	0.430

*FPEC indicates fine particle ethylcellulose. The formulation of each batch is 69.5% wt/wt polymer and 29.5% wt/wt caffeine.

RESULTS AND DISCUSSION

Coarse Ethylcellulose Versus Fine Particle Ethylcellulose

To compare 2 types of ethylcellulose products, 2 batches were taken with coarse ethylcellulose (Ethocel Premium, viscosity grade 7 cps with ethoxy content of 48%-49.5%). The formula of the first batch was 29.5% wt/wt caffeine and 69.5% wt/wt coarse ethylcellulose and that of the second batch was 9.5% wt/wt caffeine and 89.5% wt/wt coarse ethylcellulose. Magnesium stearate accounts for the remaining 1% wt/wt in each formulation. No coherent mass was obtained during the wet massing step. The agglomerated mass was passed through the 12-mesh screen and the particles thus obtained were dried in a vacuum oven at 40°C for 24 hours. Sieve analysis of the dried particles was conducted to determine the average particle size and the particle size distribution. In the case of the second batch with 89.5% wt/wt coarse ethylcellulose content,

all of the particles passed through the 50-mesh screen (0.297 mm aperture) during the sieve analysis, indicating that the granulation process was marginally successful. The sieve analysis results of the first batch with 69.5% wt/wt coarse ethylcellulose content and the batch produced using FPEC with the same formulation were compared and are presented in **Table 1**. The average particle size of the coarse ethylcellulose batch was 0.593 mm and that of the FPEC batch was 1.32 mm. The particle size distribution results (**Table 1**) show that, in the case of the coarse ethylcellulose batch, 65% of the particles passed through the 35-mesh screen (0.500 mm aperture) and mostly fine particles were obtained. In the case of the FPEC batch with the same formulation, 90% of the particles were retained above the 35-mesh screen. Thus, based on the average particle size and the particle size distribution results, the granulation process was far more successful with fine particle ethylcellulose.

The average particle size of 7 cps viscosity grade coarse ethylcellulose is 310 μ m and that of the same viscosity

Figure 1. Release profile of ibuprofen in simulated intestinal fluid without enzymes from tablets compressed at 13 kp hardness.

Table 2. Effect of FPEC Content on the Release of Caffeine from Tablets of 13 kp Hardness*

% FPEC	Dissolution Rate Constant, k ($\text{mg}/\text{cm}^2\text{min}^{1/2}$) (mean $\pm$ SD)
70	5.065 ± 0.540
80	1.422 ± 0.047
90	0.498 ± 0.027

*FPEC indicates fine particle ethylcellulose. Data were analyzed using Equation 5.

grade FPEC is 9.7 μm . These ethylcellulose products are chemically equivalent and differ only in particle size. Because of its reduced particle size, FPEC might result in far greater opportunities for bonding surfaces, which might make it possible to manufacture wet granulated tablets using FPEC as opposed to coarse ethylcellulose. FPEC tablets also resulted in sustained release of drug over an extended period of time. Release of drug over 24 hours was obtained for theophylline and for ibuprofen. See **Figure 1** for ibuprofen data that is essentially superimposable on theophylline data.

Effect of FPEC Content

At a hardness of 13 kp, tablets possessed a friability <1%. Thus, tablets for the FPEC content study were compressed to a consistent hardness of 13 kp by appropriately varying the compression force. The release

profiles for caffeine tablets with an FPEC content ranging from 49.5% to 89.5% were compared. Caffeine tablets prepared with FPEC content below 69.5% behaved as immediate release tablets, and complete release of the drug was obtained within 30 minutes. Tablets obtained from formulations containing 69.5%, 79.5%, and 89.5% FPEC remained intact over the drug release period, suggesting that 69.5% FPEC batch is a transition formulation leading to sustained release products.

As the FPEC content was increased, the release rate decreased (**Table 2**), suggesting that the matrix that is established with higher FPEC content provides a more tortuous pathway and/or a less porous tablet was formed (**Figure 2**). Drug release profiles for caffeine tablets of varying FPEC content and hardness were characterized using the Higuchi square root of time relationship²⁰:

Figure 2. Release profiles of various FPEC and caffeine formulation tablets compressed to a 13 kp hardness. Symbols ($\diamond$), ($\square$), ($\triangle$) represent data for 69.5% wt/wt, 79.5% wt/wt, and 89.5% wt/wt FPEC formulation, respectively. Data were analyzed using Equation 5.

$$Q = \left[\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right]^{1/2} = kt^{1/2} \quad (5)$$

where Q is the cumulative amount of drug released in time t (min) per unit surface area (mg/cm^2); D denotes the drug diffusion coefficient in the matrix phase (cm^2/min); C_s is the drug solubility in the dissolution medium (mg/cm^3); A represents the drug concentration in the matrix (mg/cm^3); ε is the porosity; τ denotes the tortuosity of the matrix; and k is the dissolution rate constant. According to the equation, the cumulative amount of drug released is a linear function of the square root of time. The data, as presented in **Figure 1**, confirm that the linear relationship exists as the R^2 value is greater than 0.97 in each case.

Effect of Hardness

As the hardness of the tablet was increased, the release rate decreased (**Figure 3**). At higher compression force, porosity should decrease, resulting in an increase in binding surfaces and thus a harder tablet. The decrease in porosity also results in a more tortuous path-

way, and, according to Equation 5, these both reduce the release rate.

Effect of Solubility

Tablets for the solubility study were compressed to a hardness of 13 kp. Drug release data was analyzed using Model 1. The release rate increased with the solubility of the drug (**Table 3**) as predicted by Equation 5. Converting the left-hand side of Equation 5 to the fraction of drug released gives¹³:

$$\frac{M_t}{M_\infty} = \left[\frac{S^2 D \varepsilon}{\tau V^2 A^2} (2A - \varepsilon C_s) C_s t \right]^{1/2} \quad (6)$$

where S is the exposed surface area of the tablet (cm^2), and V is the volume of the tablet (cm^3). According to this equation, if the drug loading is assumed to be much greater than the drug solubility in the release medium ($A \gg C_s$), the release rate constant in Model 1, k_1 , should be directly proportional to the square root of the drug solubility, if all other factors are constant.

Figure 3. Effect of the tablet hardness on the release rate constant from Equation 5 for tablets containing 9.5% wt/wt caffeine and 89.5% wt/wt FPEC.

Table 3. Effect of the Solubility of Ionizable and Nonionizable Drugs on the Release Rate Constant from Model 1 for Tablets of 13 kp Hardness Containing 9.5% wt/wt drug and 89.5% wt/wt FPEC*

Drug Name	Solubility in Water (mg/mL)	Release Rate Constant, k_1 (mg/cm ² /min ^{-1/2})
Theophylline	8.3	0.0219
Caffeine	20	0.0407
Dyphylline	330	0.0561
Phenylpropanolamine. HCl	909	0.0594
Pseudoephedrine. HCl	2000	0.0749

*FPEC indicates fine particle ethylcellulose; HCl, hydrochloride.

$$k_1 = \left(\frac{2S^2 D \varepsilon}{\tau V^2 A} C_s \right)^{1/2} \quad (7)$$

The drug loading does not dramatically exceed the solubility of drugs that have a high solubility. Thus the increase in release rate is not proportional to the solubility of drug with high solubility values (**Table 3**). Nevertheless an increase in the release rate with an increase in the solubility of the drug confirms that the solubility of a drug is indeed an important factor in the release of drug from an inert, hydrophobic matrix.

Ibuprofen data are not included in **Table 3** because the release study for ibuprofen was carried out in simulated intestinal fluid without enzymes as it is insoluble in water. The solubility of ibuprofen was determined by the shake flask method to be 4.13 mg/mL (n = 3) in

simulated intestinal fluid without enzymes, and k_1 is 0.0229 min⁻¹ as determined by Model 1. The low k_1 of ibuprofen again confirms that a drug with low solubility is released slowly.

Release Mechanisms

The aspect ratio ($2a/l$, where a is the radius and l is the thickness of the tablet) of the flat-faced, disc-shaped tablets was determined to be 4.0, so the m value was predicted to be 0.46 according to the figure presented by Peppas and Sahlin.²² Thus, when Model 2 is fitted to the present release data, and the m value is 0.46, it indicates a Fickian diffusion release mechanism. If the m value is above 0.46, it indicates that polymer relaxation also contributes to the release mechanism in addition to the diffu

Figure 4. Release profiles for tablets containing nonionizable drugs predicted using Model 2. Symbols (Δ), ($\square$), ($+$) represent data for theophylline, caffeine, and dyphylline FPEC tablets, respectively.

sion mechanism, and the fit of Model 3 or 4 to the data should be considered.

Nonionizable Drugs

The release mechanisms in the case of nonionizable drugs are drug diffusion and polymer relaxation, as shown by the excellent fit of Model 2 to the data (Figure 4) and the confirmation by the value of exponent m in the range of 0.46-0.89 (Table 4). Forcing the time exponent to 0.5 (Model 1) did not allow as good a fit as Model 2 (Figure 5). Model 3 also provides a good fit to the data (Figure 6) as indicated by the low SSR and low AIC values that are close to Model 2 values (Table 4). Model 3 takes into account both release mechanisms, which again confirms that, in the case of nonionizable drugs, Fickian diffusion and polymer relaxation both are contributing to the drug release mechanism. Based on the values of the release rate constants and the time period over which the release study was conducted,²² Fickian diffusion was the primary release mechanism, and polymer relaxation was a secondary release mechanism. Model 4 was ruled out because the AIC and SSR values were very high compared with other models (for example, in the case of dyphylline, the SSR was 4400 and the AIC was 81.51). The contribution of polymer relaxation to the drug release mechanism increased as the solubility of the non-

ionizable drug increased as evident by the magnitude of k_2 values obtained for Model 3 (Table 4).

Ionizable Drugs

Model 2 and Model 3 each provide a good fit to the release data for ionizable drugs compared with Model 1 (Figures 7, 8, 9), as indicated by the AIC and SSR shown in Table 4. Since the AIC and SSR values are low for Model 2, it is considered the best-fit model to describe release of ionizable drugs from FPEC tablets (Table 4, Figure 7). The value of m in each case is again greater than 0.46, indicating that there is a mechanism other than diffusion, which contributes to drug release.²² Model 4 was again ruled out because the AIC and SSR values were very high compared with other models (for example, in the case of PSE.HCl, the SSR was 423.4 and the AIC was 42.29). The contribution of polymer relaxation to the drug release mechanism increased as the solubility of the ionizable drugs increased, as evident by the magnitude of k_2 values obtained for Model 3 (Table 4). Nevertheless the percentage contribution of polymer relaxation was always found to be less than that of Fickian diffusion, thereby indicating that, for ionizable drugs, Fickian diffusion was the primary release mechanism and polymer relaxation was a secondary release mechanism.

Table 4. Parameter and Statistical Estimates for Nonionizable and Ionizable Drug Release From Wet Granulated FPEC Tablets*

Model No.	$k_1 \times 10^2$ (Mean $\pm$ SEM)	$k_2 \times 10^3$ (Mean $\pm$ SEM)	R^2	m (Mean $\pm$ SEM)	AIC	SSR $\times 10^2$
Nonionizable Drugs						
Dyphylline						
1	5.61 $\pm$ 0.199	-	0.989	-	-36.2	1.43
2	2.28 $\pm$ 0.182	-	-	0.723 $\pm$ 0.019	-62.7	0.061
3	2.91 $\pm$ 0.242	3.52 $\pm$ 0.30	0.999	-	-61.3	0.071
Caffeine						
1	4.07 $\pm$ 0.138	-	0.982	-	-49.9	3.90
2	1.00 $\pm$ 0.051	-	-	0.801 $\pm$ 0.011	-116	0.055
3	1.45 $\pm$ 0.100	2.55 $\pm$ 0.09	0.999	-	-111	0.076
Theophylline						
1	2.19 $\pm$ 0.027	-	0.994	-	-136	3.18
2	1.20 $\pm$ 0.082	-	-	0.601 $\pm$ 0.011	-183	0.934
3	1.72 $\pm$ 0.070	0.235 $\pm$ 0.033	0.997	-	-167	1.38
Ionizable Drugs						
Pseudoephedrine.HCl						
1	7.49 $\pm$ 0.127	-	0.998	-	-36.3	0.169
2	5.63 $\pm$ 0.383	-	-	0.577 $\pm$ 0.018	-44.8	0.029
3	6.22 $\pm$ 0.356	1.97 $\pm$ 0.54	0.999	-	-43.1	0.039
Phenylpropanolamine.HCl						
1	5.94 $\pm$ 0.105	-	0.997	-	-50.1	0.544
2	3.86 $\pm$ 0.288	-	-	0.603 $\pm$ 0.018	-65.6	0.095
3	4.58 $\pm$ 0.283	1.65 $\pm$ 0.34	0.999	-	-62.1	0.136
Ibuprofen						
1	2.29 $\pm$ 0.032	-	0.993	-	-124	3.60
2	1.20 $\pm$ 0.091	-	-	0.612 $\pm$ 0.013	-169	1.04
3	1.75 $\pm$ 0.080	0.285 $\pm$ 0.041	0.997	-	-155	1.52

*FPEC indicates fine particle ethylcellulose; AIC, Akaike information criterion; SSR, sum of the squared residuals; HCl, hydrochloride.

CONCLUSION

A wet granulation technique can be successfully employed to manufacture matrix-type tablets containing FPEC. Tablets could not be manufactured using this wet granulation method when using the same viscosity grade of coarse ethylcellulose. FPEC content, as a formulation variable, affects the release of drug from the tablets. An increase in FPEC content decreases the re-

lease rate constant. Other variables, such as tablet hardness and the solubility of the drug, also affect the release of drugs from the tablet. Drug release rates decreased with an increase in tablet hardness and increased with an increase in the solubility of both ionizable and nonionizable drugs. The mathematical modeling suggests that Fickian diffusion was the primary release mechanism, and polymer relaxation was a secondary release mechanism for release of both nonionizable and ionizable

Figure 5. Release profiles for tablets containing nonionizable drugs predicted using Model 1. Symbols (-Δ-), (-□-), (-+ -) represent data for theophylline, caffeine, and dyphylline FPEC tablets, respectively.

Figure 6. Release profiles for tablets containing nonionizable drugs predicted using Model 3. Symbols (-Δ-), (-□-), (-+ -) represent data for theophylline, caffeine, and dyphylline FPEC tablets, respectively.

Figure 7. Release profiles for tablets containing ionizable drugs predicted using Model 2. Symbols (-+-), (-□-), (-Δ-) represent data for ibuprofen, PPA.HCl, and PSE.HCl FPEC tablets, respectively.

Figure 8. Release profiles for tablets containing ionizable drugs predicted using Model 1. Symbols (-+-), (-□-), (-Δ-) represent data for ibuprofen, PPA.HCl, and PSE.HCl FPEC tablets, respectively.

Figure 9. Release profiles for tablets containing ionizable drugs predicted using Model 3. Symbols (-+-), (-□-), (-Δ-) represent data for ibuprofen, PPA.HCl, and PSE.HCl FPEC tablets, respectively.

drugs. This study proposes the applicability of FPEC for the preparation of tablets by an aqueous wet granulation technique.

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