Drug Development and Industrial Pharmacy, 25(9), 1045–1050 (1999)

COMMUNICATION

Kinetic Release of Theophylline from Hydrophilic Swellable Matrices

Clara I. Vargas and Evone S. Ghaly*

School of Pharmacy, University of Puerto Rico, P.O. Box 365067, San Juan, Puerto Rico 00936-5067

ABSTRACT

The objective of this research was to evaluate the effect of hydroxypropylmethylcellulose (HPMC; Methocel K4M Premium) level and type of excipient on theophylline release and to attempt to predict the drug release from hydrophilic swellable matrices. Formulations containing theophylline anhydrous (10% w/w), Methocel K4M Premium (10%, 30%, and 40% w/w), different diluents (Lactose Fast Flo, Avicel PH-101, and Emcompress), and magnesium stearate (0.75% w/w) were prepared by direct compression at a target weight of 450 mg ± 5% and target hardness of 7 kp to 10 kp. It was found that, as the percentage of polymer in all formulations increased from 10% to 30% or 40%, the drug release decreased. However, there was no significant difference in drug release between formulations containing 30% polymer and formulations containing 40% polymer. At low levels of polymer, the drug release is controlled by the type of diluent used. Avicel PH-101 formulation gave the highest release, while its corresponding Emcompress formulation gave the lowest release. Formulations containing 30% or 40% polymer gave the same release profiles irrespective of the type of diluent used. In all cases, replacement of a portion of Methocel K4M Premium with any diluent resulted in increase of theophylline release. In addition, this investigation demonstrated that the drug release from hydrophilic swellable matrices can be predicted using only a minimum number of experiments.

* To whom correspondence should be addressed.

INTRODUCTION

The design and development of sustained-release systems has been and continues to be of great importance in the pharmaceutical industry. Sustained drug therapy offers may potential advantages, such as avoiding patient compliance problems, employing less total drug, minimizing side effects, improving control of condition by reducing fluctuation in blood, and providing cost-effectiveness (1).

In tablet matrix systems, the tablet is in the form of a compressed compact containing an active ingredient, excipient, binder, or polymer and lubricant. The matrix may be tableted from wet massed granules or by direct compression (1). The process used to prepare formulations for compression depends on the polymer and drug: polymer ratio (2).

Hydroxypropylmethylcellulose (HPMC) is one of a number of cellulose ethers commonly used in the formulation of controlled-release dosage forms. It is available in grades containing 16.5–30% methoxy and 4–32% hydroxypropoxy groups.

The mechanism of drug release from polymer matrices may be described by a swelling phenomenon. The solvent molecules move into the glassy polymer matrix with a well-defined front at a particular velocity; simultaneously, the thickness of the swollen region increases with time in the opposite direction (3). The mechanism of drug release may be described by a second phenomenon that involves the disentanglement and erosion of the rubbery polymer (4).

Korsmeyer et al. (5) derived a simple relationship that describes drug release from polymeric systems in which release deviates from Fickian diffusion and follows a non-Fickian diffusion or anomalous behavior. Ford et al. (6) examined the dissolution of seven drugs from HPMC matrices, and Nakano et al. (7) showed that the release of theophylline from HPMC matrices decreased as the viscosity grade and polymer content increased.

Peppas and Sahlin (8) showed that it is possible to calculate the approximate contributions of the diffusional and relaxational mechanisms by fitting the data to a heuristic model containing both phenomena. Colombo et al. (9) modulated drug release by imposing physical restriction of matrix swelling in tablets prepared with HPMC and diliatiazem hydrochloride. Vigoreaux and Ghaly (10) also showed that it is possible to modify the kinetics of drug release by imposing a physical restriction on matrix swelling.

Lapidus and Lordi (11) showed that addition of lactose increased the release rate of chlorpheniramine more than the addition of an equivalent amount of calcium phosphate because lactose reduces the tortuosity of the diffusion pattern of the drug, whereas the calcium phosphate only reduces the polymer concentration.

The objective of this work was to investigate the effect of polymer level and diluent type on theophylline release from matrices containing HPMC (Methocel K4M Premium) and prepared by direct compression. A second objective was to predict drug release from theophylline matrices containing different polymer levels and different diluents.

MATERIALS AND METHODS

Materials

Except where noted, all chemicals were analytical grade and were used as received. The chemicals were theophylline anhydrous (Behringer Inggleheim, Germany); HPMC (Methocel K4M Premium) supplied by Dow Chemical Company (Midland, MI); microcrystalline cellulose (Avicel PH-101) (FMC Corp., Philadelphia, PA); Lactose Fast Flo (Foremost Ingredient Group); dibasic calcium phosphate dihydrate (Emcompress), supplied by Mendell Company (NY); and magnesium stearate (Amend Drug and Chemical Co., NJ).

Theoretical Considerations

Shah et al. (12) developed a working equation to predict the drug release from HPMC matrices containing different polymer concentrations and release of the drug according to Higuchi's square-root-of-time equation:

$$Q = K\sqrt{t} \tag{1}$$

where Q is the amount of drug released at time t, and K is the kinetic constant.

Equation 1 can be modified to the following:

$$Q = \alpha\sqrt{1/C_p} \tag{2}$$

where α is a kinetic constant, and C_p is the polymer concentration.

If the plot of the amount of drug released at different given times versus the reciprocal of the square root of polymer concentration in the matrix gave a linear relationship, it would be possible to predict drug release from HPMC matrices at different polymer concentrations.

The regression equations for the amount of drug released (Q_1, Q_2, Q_3, . . . Q_n) in relation to the polymer concentration are as follows:

$$Q_I = a_I + b_I \cdot 1/\sqrt{C_p} \quad (3)$$

A plot of the amount of Q_i versus $1/\sqrt{C_p}$ will give a_i and b_i. It is possible that both a_i and b_i are a function of the square root of time if C_p is constant; therefore,

$$a_i = c + K_a\sqrt{t_i}$$

$$b_i = d + K_b\sqrt{t_I}$$

Equation 3 is derived further to obtain the working equation for prediction of drug release from a hydrophilic swellable matrix:

$$\begin{aligned} Q_I &= (c + K_a\sqrt{t_i}) + (d + K_b\sqrt{t_i})1/\sqrt{C_p} \\ &= (c + d/\sqrt{C_p}) + (K_a + K_b \cdot 1/\sqrt{C_p})\sqrt{t_I} \end{aligned} \quad (4)$$

where c, d, K_a, and K_b are regressional constants.

Preparation of Blends

Twelve formulations were prepared by direct compression. The batch size for each formulation was 1 kg. A 10% w/w anhydrous theophylline was used as a model drug. HPMC (Methocel K4M Premium) was used as a hydrophilic polymer at 10%, 30%, or 40% w/w. The diluents used were Lactose Fast Flo, microcrystalline cellulose (Avicel PH-101), and dibasic calcium phosphate (Emcompress). Magnesium stearate was used as a lubricant at the 1% w/w level. All materials were passed manually through a number 12 screen, except the lubricant, which was passed through a number 30 screen.

Blending of theophylline anhydrous was performed in a Turbula mixer (Willy A. Bachafen, model T2C, Switzerland) at a speed of 90 rpm for 5 min. The drug and polymer mixture was transferred to a V blender (PK processor, Patterson Kelly, model LB 5322), diluent was added, and the blend was mixed by geometrical dilution for an additional 10 min. Finally, the lubricant was added, and the blend was mixed for another 5 min.

Matrices Preparation

The matrices were made by direct compression of the mixture in a Manesty B3B rotating machine equipped with a 12/32-inch round flat-face tooling. Target tablet weight was 450 mg (±5%), and the target hardness was 7 kp to 10 kp.

Drug Content

Four tablets were pulverized, and three samples of 450 mg each were transferred to a 1000-ml volumetric flask and brought to volume with distilled water. Samples were stirred for 3 hr with a magnetic stirrer. An aliquot was filtered and analyzed for drug content by measuring absorbance in an ultraviolet (UV) spectrophotometer at a wavelength of 270 nm.

Dissolution Testing

The dissolution from the matrices was measured in 900 ml of distilled water at 37°C ± 0.5°C using a rotating basket apparatus (Hanson Research, model SR2) at a speed of 50 rpm. Filtered samples were withdrawn and assayed using a UV spectrophotometer (Beckman Instruments, model DU 65) at 270 nm. These replicates were tested, and their mean percentage release was calculated.

RESULTS AND DISCUSSIONS

The composition of the different theophylline formulations and the controls are shown in Table 1. The effect of polymer levels on the drug release from matrices prepared with Lactose Fast Flo is shown in Fig. 1. The drug release at 6 hr of testing dissolution from matrices prepared with Lactose Fast Flo and 10% Methocel K4m Premium was 95.3%, while the drug release from matrices of the same composition but prepared with 30% or 40% polymer level was 49.9% and 47.6%, respectively. For the Avicel PH-101 formulation, the percentage of drug release from matrices containing 10% polymer was 97.2%, while the drug release at 6 hr of testing dissolu-

Table 1

Theophylline Formulations Prepared with Hydroxypropylmethylcellulose K4M Premium and Different Diluents

Batch No.	Polymer (%)	Theophylline (%)	Diluent
1	10	10	79% Lactose Fast Flo
2	30	10	59% Lactose Fast Flo
3	40	10	49% Lactose Fast Flo
4	10	10	79% Avicel PH 101
5	30	10	59% Avicel PH-101
6	40	10	49% Avicel PH-101
7	10	10	79% Emcompress
8	30	10	59% Emcompress
9	40	10	49% Emcompress
10	0	10	89% Lactose Fast Flo
11	0	10	89% Avicel PH-101
12	0	10	89% Emcompress

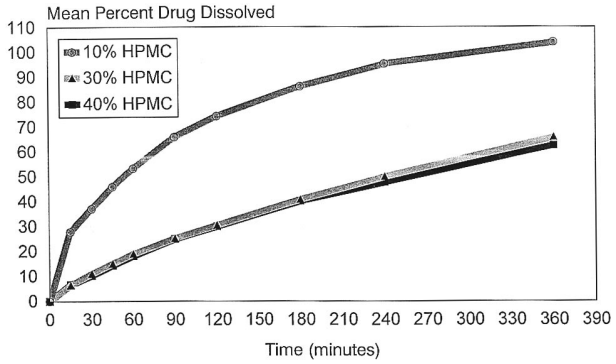

Figure 1. Effect of polymer levels on drug release from matrices prepared with Lactose Fast Flo.

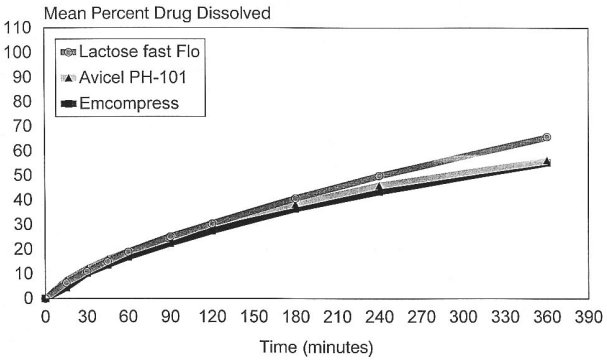

Figure 3. Effect of diluent type on drug release from matrices containing 30% hydroxypropylmethylcellulose K4M Premium.

tion from matrices of the same composition but prepared with 30% or 40% polymer was 56.3% and 56.1%, respectively. For the Emcompress formulation, the percentage of drug released at 6 hr of testing dissolution from matrices prepared with 10% polymer was 68.1%, while the percentage drug release from matrices of the same composition but prepared with 30% polymer or 40% polymer was 55.3% and 55.1%, respectively.

For the three diluents used, as the percentage of polymer increased from 10% to 30% or 40%, the drug release decreased. Analysis of variance (ANOVA) supported these data and showed a significant difference ($p < .01$). The Bonferroni T test showed no significant difference between formulations containing 30% polymer, formulations containing 30% polymer, and formulations containing 40% polymer ($p > .01$) and showed a significant difference between formulations containing 10% and 30% and formulations containing 10% and 40%.

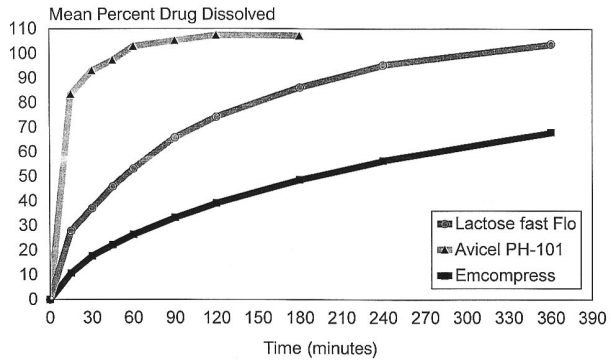

Figure 2. Effect of diluent type on drug release from matrices containing 10% hydroxypropylmethylcellulose K4M Premium.

The effect of diluent type on drug release from matrices containing 10% polymer was investigated. As depicted in Fig. 2, at the 10% polymer level, Avicel PH-101 matrices could not maintain integrity, and all drug was released at 1 hr of dissolution testing. Lactose Fast Flo released all drug at 6 hr of dissolution testing, while Emcompress matrices released only 68.1%.

Figure 3 shows the percentage of drug release from matrices containing 30% polymer and different diluents. At 6 hr of dissolution testing, the percentage drug released from lactose matrix was 65.5%, while the percentage drug released from Avicel PH-101 and Emcompress matrices was 56.3% and 55.3%, respectively. The data showed no significant difference between the three diluents up to 3 hr of dissolution testing. At 4 hr and 6 hr, there was a slight difference in drug release between matrices prepared with Lactose Fast Flo and matrices prepared with Avicel PH-101 or Emcompress. No difference in drug release was observed between Avicel PH-101 and Emcompress matrices up to 6 hr. The same trend was true for matrices prepared with 40% polymer.

The divergence between dissolution profiles of the different diluent formulations may be explained by the difference in solubility of the diluents and their subsequent effects on the tortuosity factor. In addition, the results show that at low polymer level (high diluent content), differences are more apparent between soluble and insoluble diluent. Less difference can be seen in tablet formulations containing 30% Methocel K4M and 40% Methocel K4M.

To determine the mechanism of drug release and to predict the drug release from Methocel K4M Premium matrices, the working equation of Peppas and Sahlin (8)

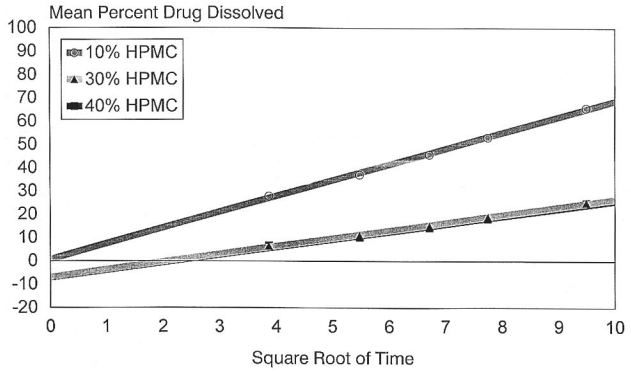

Figure 4. Square-root-of-time plots for matrices prepared with Lactose Fast Flo and different polymer levels.

was used. As depicted in Fig. 4, plots of the square root of time versus mean percentage drug dissolved for matrices prepared with Lactose Fast Flo and different polymer levels gave a linear relationship for up to 90 min.

The plot of the amount of drug released at different given times versus the reciprocal square root of polymer concentration in the matrix showed good linearity. The plots of square root of time versus slopes or intercepts obtained from the plots of the reciprocal square root of polymer concentration versus percentage drug release at different time intervals showed a straight line (Figs. 5 and 6). The regressional constants (obtained from the plots of Figs. 5 and 6) used to establish the working equation for Lactose Fast Flo formulations are shown in Table 2.

Using the model described by Peppas and Sahlin (8), the working equation to predict drug release from matrices containing different levels of polymer and Lactose Fast Flo diluent is

$$Q = (-15.818 + 5.161/\sqrt{C_p}) + (-0.668 + 2.354/C_p)\sqrt{t}$$

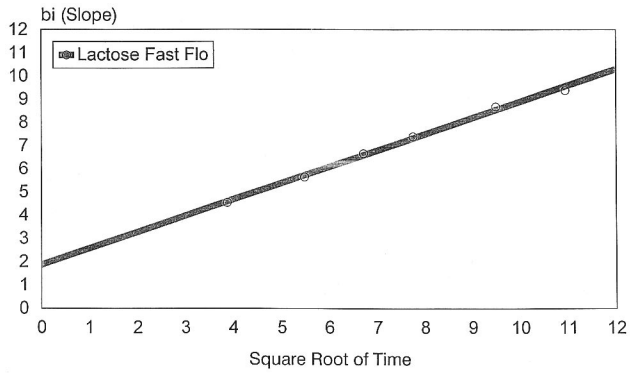

Figure 5. Square root of time versus slopes (b) for formulations containing Lactose Fast Flo.

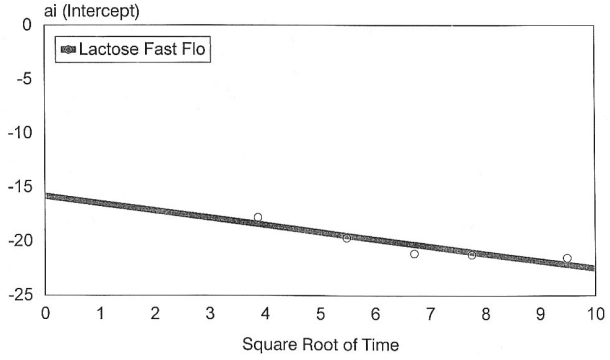

Figure 6. Square root of time versus intercepts (a) for formulations containing Lactose Fast Flo.

Figure 7 shows the theoretical predicted value versus experimental data for matrices prepared with Lactose Fast Flo and different polymer levels. The experimental data from dissolution testing matched the predicted data.

The same trend was true for Avicel PH-101 and Emcompress. Tables 3 and 4 show the regressional constants used to establish the working equation for Avicel PH-101 and Emcompress, respectively.

The working equations to predict drug release from Avicel PH-101 and Emcompress containing different levels of Methocel K4M Premium are given next. For Avicel PH-101,

$$Q = (-82.133 + 46.213/\sqrt{C_p}) + (0.660 + 1.331/\sqrt{C_p})\sqrt{t}$$

For Emcompress,

$$Q = (-7.126 + 1.858/\sqrt{C_p}) + (1.647 + 1.858/\sqrt{C_p})\sqrt{t}$$

Table 2

Regressional Constants Used to Establish a Working Equation for Lactose Fast Flo Formulations

$K_a = -0.668$	$c = -15.818$
$K_b = 2.354$	$d = 5.161$

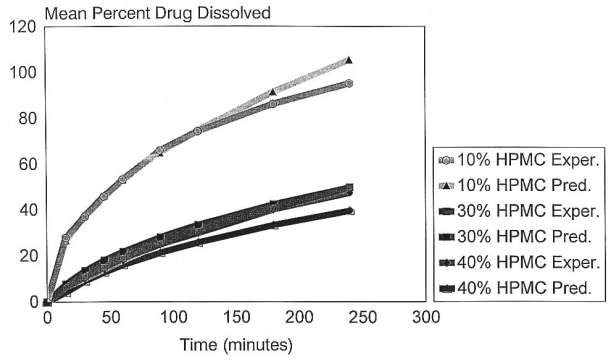

Figure 7. Theoretical predicted data versus experimental data for matrices prepared with Lactose Fast Flo and different polymer levels.

Table 3

Regressional Constants Used to Establish a Working Equation for Avicel PH-101 Formulations

$K_a = 0.660$	$c = -82.133$
$K_b = 1.331$	$d = 46.213$

Table 4

Regressional Constants Used to Establish a Working Equation for Emcompress Formulations

$K_a = 1.647$	$c = -7.126$
$K_b = 0.580$	$d = 1.858$

These data showed that the experimental data from dissolution testing match the theoretical predicted data, especially in the first 120 min of dissolution testing. This implies that the dissolution profiles can be predicted, and that this approach can be used to optimize the hydrophilic polymer concentration in the matrix using a minimum number of experiments.

CONCLUSIONS

Theophylline sustained-release matrices were prepared successfully by the direct compression method using hydrophilic swellable polymers. At a low polymer level (10% w/w), the diluent plays a more significant role in controlling the drug release. At high levels (30% and 40%), Methocel K4 M Premium appears to control the drug release from the matrices.

There was no significant difference in drug release between matrices containing 30% polymer and matrices containing 40% polymer, indicating that a 30% polymer level is sufficient to control the drug release.

At the 10% polymer level, Avicel PH-101 matrix gave the highest drug release, and Emcompress matrices gave the lowest release. Lactose Fast Flo matrices gave an intermediate release. At a 30% or 40% polymer level, all diluents gave the same release profiles, except Lactose Fast Flo matrices gave a slightly higher rate than Avicel PH-101 or Emcompress matrices only at 240 min and 360 min of testing dissolution.

This investigation showed that the drug release from hydrophilic matrices can be optimized using only a minimum number of experiments.

REFERENCES

1. L. Lachman, H. A. Lieberman, and J. L. Kanig, *The Theory and Practice of Industrial Pharmacy*, Lea and Febiger, Philadelphia, 1986.
2. J. T. Cartensen and C. Ertell, Drug Dev. Ind. Pharm., 16, 1121 (1990).
3. K. V. Ranga and K. Padmalatha, Int. J. Pharm., 48, 1 (1988).
4. J. E. Hogan, Drug Dev. Ind. Pharm., 15, 975 (1989).
5. R. W. Korsmeyer, E. Doelker, E. Buri, and P. Peppas, Int. J. Pharm., 15, 25 (1983).
6. J. L. Ford, M. H. Rubinstein, F. McCaul, J. E. Hogan, and P. J. Edgar, Int. J. Pharm., 24, 339 (1985).
7. M. Nakano, N. Ohmori, A. Ogata, K. Sugimoto, and Y. Tobino, J. Pharm. Sci., 72, 378 (1983).
8. N. A. Peppas and J. J. Sahlin, Int. J. Pharm., 57, 169 (1989).
9. P. Colombo, U. Gazzaniga, L. Maggi, and M. E. Sangalli, Int. J. Pharm., 40, 223 (1987).
10. V. Vigoreaux and E. S. Ghaly, Drug Dev. Ind. Pharm., 20, 2519 (1994).
11. H. Lapidus and N. G. Lordi, J. Pharm. Sci., 57, 1292 (1968).
12. N. Shah, G. Zhang, V. Apelian, F. Zeng, M. H. Infeld, and A. W. Malick, Pharm. Res., 10, 1693 (1993).