DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(8), 1345-1369 (1987)

EVALUATION OF ETHYLCELLULOSE AS A MATRIX FOR PROLONGED RELEASE FORMULATIONS. I. WATER SOLUBLE DRUGS: ACETAMINOPHEN AND THEOPHYLLINE

N.A.Shaikh,*S.E.Abidi and L.H.Block
School of Pharmacy, Duquesne University,
Pittsburgh, PA 15282

* Schering Corporation, Bloomfield, NJ.

ABSTRACT

In this study ethylcellulose was evaluated as a carrier for the preparation of prolonged release solid dispersions of relatively water soluble drugs, acetaminophen and theophylline. The solid dispersions containing various concentrations (7.5, 15.0 and 30.0 % by weight of drug) of ethylcellulose of different viscosity grades (21, 95, 209 and 350 cps) were prepared by the solvent method. The concentration of polymer in the formulation was the determining factor in controlling release rate of the drug, as the results indicate prolongation in release of the drug with increase in amount of ethylcellulose. The higher the

viscosity grade of ethylcellulose, slower the release of drug from the solid dispersions. The release of drug from the tablets was more prolonged compared to the granular solid dispersions. In vitro release of acetaminophen and theophylline was more or less similar in both dissolution media. The viscosity grade of ethylcellulose showed slight influence on the release rate of drug from the tablet formulations, while it was quite noticeable in granular solid dispersions.

INTRODUCTION

In recent years, considerable attention has been focused on the development of the formulations that will release drug at a controlled and/or predictable rate over a prolonged period of time. The technique of solid dispersion in which a drug is incorporated in an inert carrier or matrix has been extensively used to enhance the dissolution of poorly soluble drugs (1-5). However, the potential of solid dispersions as prolonged release formulations has not yet been fully explored. Depending on the nature of the carrier, whether hydrophilic or hydrophobic, drug release can either be accelerated or retarded, respectively (6). Thus incorporation of a drug in an inert, hydrophobic carrier such as ethylcellulose can possibly provide prolonged or sustained release due to association of drug particles with the carrier.

The main purpose of the present study was to evaluate the possible application of the inert, pH-insensitive, ethylcellulose polymer as a potential carrier for the preparation of prolonged release formulations of water soluble drugs, acetaminophen and theophylline, using the solid dispersion technique.

EXPERIMENTAL

Materials: Acetaminophen (Ruger Chemical Co., Irvington, NJ), anhydrous theophylline (Sigma Chemical Co., St. Louis, MO), Ethylcellulose N-22, Ethylcellulose N-100, Ethylcellulose N-200, Ethylcellulose N-300 (Ethylcelluloses of different viscosity grades were kindly provided by Hercules, Inc., Wilmington, DE), ethanol (Fisher Scientific, Pittsburgh, PA), magnesium stearate (Fisher Scientific, Fair Lawn, NJ), 0.1 N HCl and Sorenson's buffer pH 7.4.

Preparation of Solid Dispersions: Solid dispersions of various ethylcellulose and drug ratios were prepared by the solvent method. A colloidal dispersion was prepared by dispersing the requisite amount of ethylcellulose in ethanol with constant stirring. Drug was dissolved in minimum amount of ethanol and the solution was added to the colloidal dispersion. Solvent was allowed to evaporate and the thickened mass was then transferred

to Petri dishes and dried. The residue was comminuted and the resultant granules then passed through US standard sieves (40-100 mesh). The final product was transferred to tight containers.

Compression of Tablets: Tablets containing 300 mg of different solid dispersion formulations (40/100 mesh) were directly compressed with 0.5% w/w of magnesium stearate incorporated as a lubricant prior to compression. The tablets were prepared manually on a Carver press. Standard concave 7/16" diameter punches were used. The compression pressure was maintained for 2 - 5 seconds and then quickly released. Tablet hardness was kept constant within the range of 7 - 8 Kg on a Stokes hardness tester.

Determination of Drug Content: Solid dispersions were accurately weighed (200 mg) and placed in 500 ml volumetric flask containing 400 ml Sorenson's buffer solution (pH 7.4). The mixture was stirred for 24 hours at room temperature. Then the solution was diluted to 500 ml with buffer solution. Subsequently, a 5 ml aliquot of the solution was filtered through a 0.22 um membrane filter and then analyzed spectrophotometrically for total drug content. In case of tablets, the only difference was that instead of granules three tablets were crushed and placed in 500 ml volumetric flask containing buffer.

In Vitro Drug Release Studies: In vitro release studies of both granular and compressed solid dispersions were performed in a rotating bottle system (Van-Kel Industries, Inc., Chatham, NJ 07928) at 50 rpm and the dissolution media were maintained at 37°C. The media used were Sorenson's buffer solution (pH 7.4) and 0.1N HCl (pH 2.2). At predetermined times, the dissolution medium was removed in toto from the bottles and replaced with fresh solution, thus maintaining sink conditions. Aliquots were filtered and analyzed spectrophotometrically for acetaminophen or theophylline at 244 nm or 273 nm, respectively.

RESULTS AND DISCUSSION

In the case of acetaminophen solid dispersions (40/60, 60/80 and 40/100 mesh), an increase in the amount of ethylcellulose decreased the dissolution rate ($p<0.001$); results are shown in Figure 1. Increasing the viscosity grade of ethylcellulose further decreased the dissolution rate ($p<0.001$) as shown in Figure 2. The release profile of acetaminophen was almost similar in both media (Sorenson's buffer and 0.1 N HCl). However, the release rate was slightly faster in buffer compared to 0.1 N HCl ($p<0.001$): representative curves are shown in Figure 1. The dissolution plateau was reached within first four hours in all formulations except with higher viscosity grade (350 cps) and higher

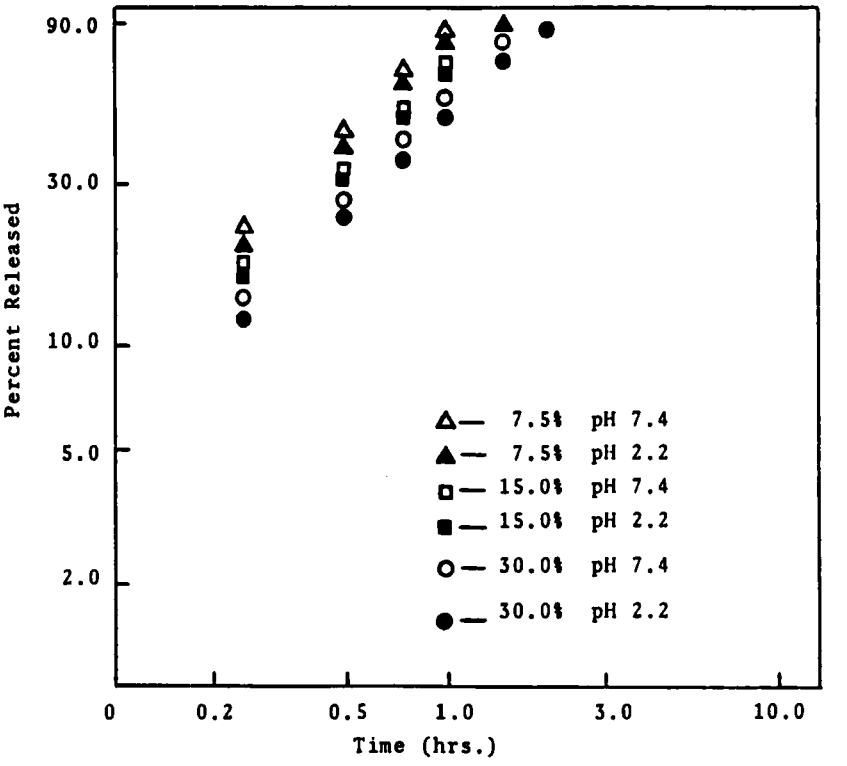

FIGURE 1. Release Profile of Acetaminophen/Ethylcellulose (209 cps) Solid Dispersions (40/60): Influence of Amount (%) of Ethylcellulose and the pH of the Dissolution Medium.

concentration (30 %) of ethylcellulose, indicating greater prolonged release. Control (acetaminophen powder) was completely dissolved in less than five minutes.

The release of theophylline from granular solid dispersions was much slower compared to the release of acetaminophen from similar formulations in the same dissolution medium. This could possibly be explained on

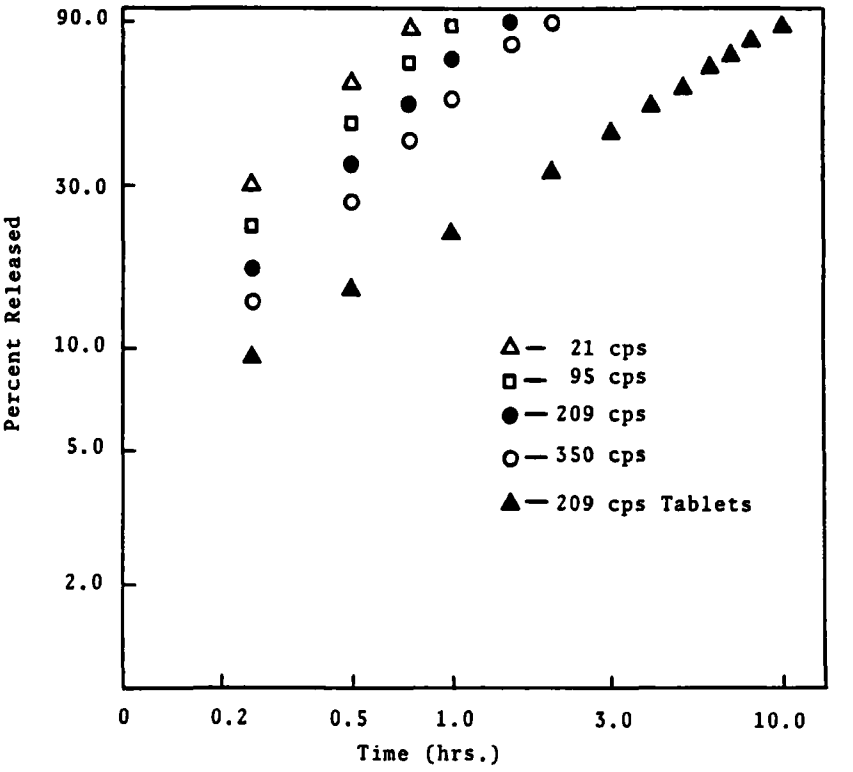

FIGURE 2. Release Profile of Acetaminophen/Ethylcellulose (15%) Solid Dispersions (40/60): Influence of Ethylcellulose Viscosity Grade.

the basis of their differing solubilities. The reported solubility of acetaminophen is 14.3 mg/ml in water while in the case of theophylline it is 8.3 mg/ml in water at 25°C (7). The release pattern of theophylline from solid dispersions of different viscosity grade and concentrations of ethylcellulose was more or less similar to that of acetaminophen. The release rate of theophylline was slightly slower in buffer solution pH

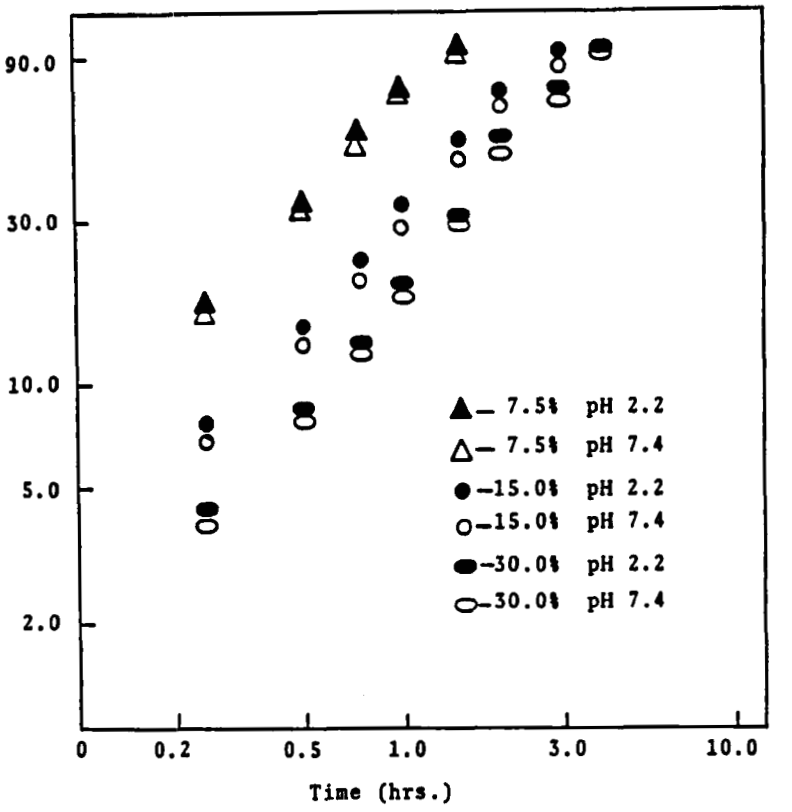

FIGURE 3. Release Profile of Theophylline/Ethylcellulose (209 cps) Solid Dispersions (40/60): Influence of Amount (%) of Ethylcellulose and the pH of Dissolution Medium.

7.4 compared to 0.1 N HCl ($p<0.001$), as shown in Figure 3. Control (theophylline powder) was completely dissolved within the first five minutes of the dissolution study.

The results (Figure 4) indicate that dissolution rate was faster with 40/100 mesh size granules than

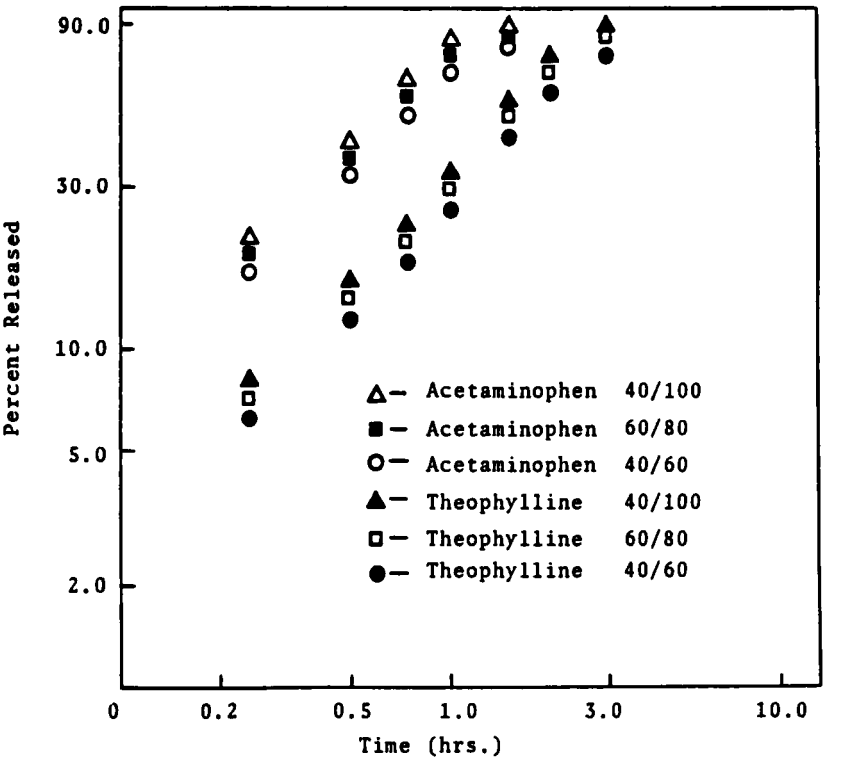

FIGURE 4. Effect of Particle Size on Drug Release from Solid Dispersions (209 cps).

60/80 mesh size granules and was found to be the slowest in the case of 40/60 granules. This may be attributed to the fact that smaller the particle size, greater the surface area and faster the dissolution rate.

The retardation of release was examined in terms of the time required for 90% of the drug to be released from the drug - polymer matrices. The data are listed in Tables 1-4.

TABLE 1

Time (hrs.)[a] for 90% Release of Acetaminophen from Granular Solid Dispersions in Sorenson's Buffer

Mesh Size	Viscosity grade,cps	Amount of Ethylcellulose 7.5%	15.0%	30.0%
40/60	21	0.450 (0.008)	0.807 (0.003)	0.867 (0.012)
	95	0.660 (0.003)	1.118 (0.002)	1.257 (0.011)
	209	1.176 (0.005)	1.316 (0.009)	1.721 (0.004)
	350	1.318 (0.012)	1.726 (0.011)	2.265 (0.022)
60/80	21	0.444 (0.002)	0.799 (0.006)	0.872 (0.008)
	95	0.652 (0.005)	1.101 (0.007)	1.242 (0.002)
	209	1.156 (0.008)	1.284 (0.011)	1.665 (0.036)
	350	1.277 (0.015)	1.648 (0.036)	2.223 (0.044)
40/100	21	0.437 (0.004)	0.788 (0.002)	0.853 (0.007)
	95	0.646 (0.007)	1.096 (0.002)	1.229 (0.016)
	209	1.133 (0.001)	1.239 (0.013)	1.608 (0.024)
	350	1.284 (0.031)	1.603 (0.001)	2.161 (0.012)

a : Mean of three runs (± S.D.)

TABLE 2

Time (hrs.)[a] for 90% Release of Theophylline from Granular Solid Dispersions in Sorenson's Buffer

Mesh Size	Viscosity grade, cps	Amount of Ethylcellulose 7.5%	15.0%	30.0%
40/60	21	0.6405 (0.008)	1.4415 (0.006)	1.8902 (0.029)
	95	0.8861 (0.009)	1.4833 (0.019)	2.8542 (0.221)
	209	1.4043 (0.022)	2.9501 (0.053)	3.7495 (0.012)
	350	1.8103 (0.027)	4.0969 (0.084)	7.3015 (0.001)
60/80	21	0.6221 (0.009)	1.3406 (0.015)	1.8405 (0.036)
	95	0.8572 (0.011)	1.4997 (0.002)	2.4987 (0.031)
	209	1.3575 (0.009)	2.7961 (0.066)	3.6759 (0.078)
	350	1.7099 (0.015)	3.8947 (0.024)	7.0362 (0.005)
40/100	21	0.6368 (0.007)	1.3580 (0.015)	1.7828 (0.027)
	95	0.8389 (0.006)	1.4545 (0.010)	2.4761 (0.062)
	209	1.3537 (0.002)	2.7356 (0.017)	3.6378 (0.057)
	350	1.7213 (0.019)	3.9820 (0.068)	6.6624 (0.026)

a : Mean of three runs (± S.D.)

TABLE 3

Time (hrs.)[a] for 90% Release of Acetaminophen from Directly Compressed Solid Dispersions

pH	Viscosity grade,cps	Amount of Ethylcellulose 7.5%	15.0%	30.0%
2.2	21		4.998 (0.088)	8.373 (0.271)
	95	4.228 (0.269)	6.621 (0.276)	10.724 (0.965)
	209	4.359 (0.222)	8.842 (0.088)	11.635 (0.691)
	350	4.603 (0.175)	9.249 (0.219)	11.734 (0.601)
7.4	21		5.118 (0.341)	8.532 (0.680)
	95	4.176 (0.207)	6.962 (0.047)	11.270 (1.044)
	209	4.454 (0.224)	9.582 (0.377)	12.025 (0.480)
	350	4.930 (0.117)	10.341 (0.443)	13.152 (1.831)

a : Mean of four runs (± S.D.)

TABLE 4

Time (hrs.)[a] for 90% Release of Theophylline from Directly Compressed Solid Dispersions

pH	Viscosity grade, cps	Amount of Ethylcellulose 7.5%	15.0%	30.0%
2.2	21	6.2354 (0.465)	8.3680 (0.405)	10.1868 (0.672)
	95	8.7318 (0.301)	8.9754 (0.338)	11.0645 (0.171)
	209	6.8483 (0.164)	7.6096 (0.517)	9.0373 (0.343)
	350	7.5298 (0.136)	10.1409 (0.244)	10.5747 (0.057)
7.4	21	6.7855 (0.183)	10.0207 (0.706)	12.6364 (0.229)
	95	9.9131 (0.169)	11.0984 (0.218)	13.8608 (0.457)
	209	8.0384 (0.679)	8.5919 (0.799)	10.5009 (0.523)
	350	7.8274 (0.086)	10.6590 (0.348)	13.6903 (0.356)

a : Mean of four runs (± S.D.)

The viscosity grade of ethylcellulose did not show a marked effect on prolongation of release characteristics of acetaminophen from the tablets. On the other hand, concentration of ethylcellulose has a substantial effect on the release rate. As the amount of ethylcellulose increased, dissolution time decreased ($p<0.001$) and that was found to be true for all formulations. Furthermore, the data indicate that the release profile was similar in both media, but again the release rate was slightly faster in Sorenson's buffer compared to 0.1 N HCl ($p<0.001$). The release of theophylline showed a similar trend, but again release rate of theophylline was much slower than the release rate of acetaminophen from the comparable formulations in the same dissolution medium. This could be accounted for by their differing solubilities.

The release of drug from the directly compressed solid dispersions was found to be much slower than for the granular solid dispersions (Figure 2). The difference in the release rate is attributed to the compact nature of the tabletted solid dispersions resulting in a greatly reduced surface area available for drug release. It was also observed in all cases that the tablets made from different solid dispersions by direct compression method remained intact throughout the dissolution study.

Linearization of Dissolution-Time Plots: Preliminary evaluations of data for both the granular and compressed solid dispersions indicated that the percentage of drug released as a function of time obeyed a log-log relationship (power function). Accordingly, the data were subjected to least squares analysis in accordance with the following relationship:

$$\ln Y = \ln A + B(\ln X)$$

where Y is the percentage of drug released, X is time, A is the intercept (at 1 hr.) and B is the slope.

The calculated intercepts varied substantially, while calculated slopes did not vary markedly. These intercepts presumably reflected the amount of drug available for dissolution at the outset of the study. The intercept values at 0.25 hr. were subsequently calculated to provide a more reasonable estimate of the initial extent of the retardation of dissolution and are presented in Tables 5 and 6, along with the slopes of the log-log plots. The similarities in the slopes were indicative of comparable release mechanisms while similar intercepts were indicative of comparable drug availability, at the solid/liquid interface, for dissolution.

A number of publications (8-11) have dealt with the mechanism by which a drug would be released from

TABLE 5
Summary of Power Function Fits for Directly Compressed Acetaminophen Solid Dispersions

pH	Viscosity grade, cps	Amount of Ethylcellulose 7.5% Intercept[a]	Slope	r[b]	15.0% Intercept[a]	Slope	r[b]	30.0% Intercept[a]	Slope	r[b]
2.2	21				10.57	0.715	0.998	7.78	0.697	0.998
	95	13.77	0.664	0.997	9.36	0.694	0.999	6.82	0.688	0.999
	209	13.47	0.665	0.998	9.05	0.644	0.999	6.76	0.674	0.999
	350	11.42	0.709	0.997	8.01	0.670	0.999	7.15	0.659	0.999
7.4	21				12.88	0.645	0.998	9.39	0.641	0.999
	95	14.31	0.654	0.999	15.15	0.623	0.999	8.78	0.612	0.999
	209	16.45	0.659	0.999	9.75	0.610	0.999	7.42	0.644	0.999
	350	13.02	0.649	0.998	9.90	0.593	0.999	8.03	0.612	0.999

a : Intercepts calculated at 0.25 hrs.

b : Correlation coefficient

TABLE 6
Summary of Power Function Fits for Directly Compressed Theophylline Solid Dispersions

pH	Viscosity grade,cps	Amount of Ethylcellulose 7.5% Intercept[a]	Slope	r^b	15.0% Intercept[a]	Slope	r^b	30.0% Intercept[a]	Slope	r^b
2.2	21	9.83	0.689	0.997	8.86	0.661	0.999	8.11	0.650	0.999
	95	8.31	0.671	0.998	7.48	0.695	0.998	6.62	0.689	0.999
	209	10.57	0.647	0.996	11.04	0.615	0.994	7.87	0.679	0.991
	350	11.19	0.612	0.995	6.55	0.708	0.999	2.92	0.916	0.993
7.4	21	9.07	0.695	0.996	7.64	0.669	0.999	6.59	0.666	0.999
	95	7.32	0.682	0.997	6.38	0.698	0.999	5.18	0.711	0.998
	209	9.30	0.663	0.996	9.88	0.626	0.994	6.54	0.702	0.997
	350	10.83	0.614	0.995	8.19	0.639	0.999	2.83	0.865	0.993

a : Intercepts calculated at 0.25 hrs.
b : Correlation coefficient

granular or tabletted dosage forms. The data obtained for granular solid dispersions of acetaminophen and theophylline were evaluated in accordance with Higuchi's equation for drug release from spherical matrices:

$$1 + 2(F) - 3(F)^{2/3} = (6DKC_s)t/(\tau a^2)$$

where F = Fraction of drug remaining
D = Diffusivity of drug in permeating fluid
K = Specific volume
Cs = Saturation solubility of the drug
t = Time
τ = Tortuosity of the matrix
a = Radius of the granule

In this equation, the term $(6DKCs/\tau a^2)$ is a constant "K". If "$1+2(F)-3(F)^{2/3}$" is plotted as a function of time, we should get a straight line passing through the origin with a slope of "K". As shown in Figure 5, data for the granular solid dispersions do not follow Higuchi's relationship which suggests that drug release from granular solid dispersions does not follow a diffusion-controlled matrix model. Nonetheless, a plot of percent released as a function of time does yield a straight line (r = 0.998) as shown in Figure 6, which is indicative of zero-order release kinetics.

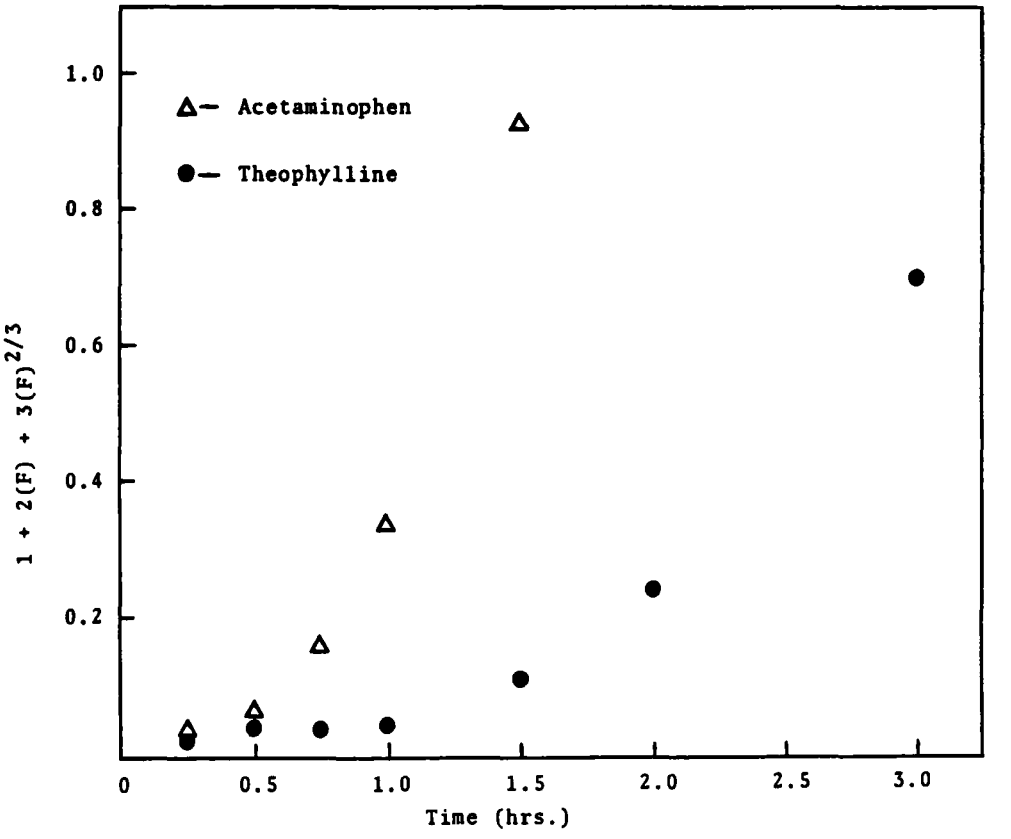

FIGURE 5. Higuchi Plot for Granular (40/100) Solid Dispersions.

Percent released from compressed solid dispersions as a function of square root of time (Figure 7); showed reasonable linearity (r = 0.997) which means that drug release from compressed solid dispersions follows a diffusion-controlled matrix model(11,12). The slopes of these plots are indicative of rate of release while negative intercepts show a lag time. Slopes, intercepts and correlation coefficients are summarized in Tables 7 and 8.

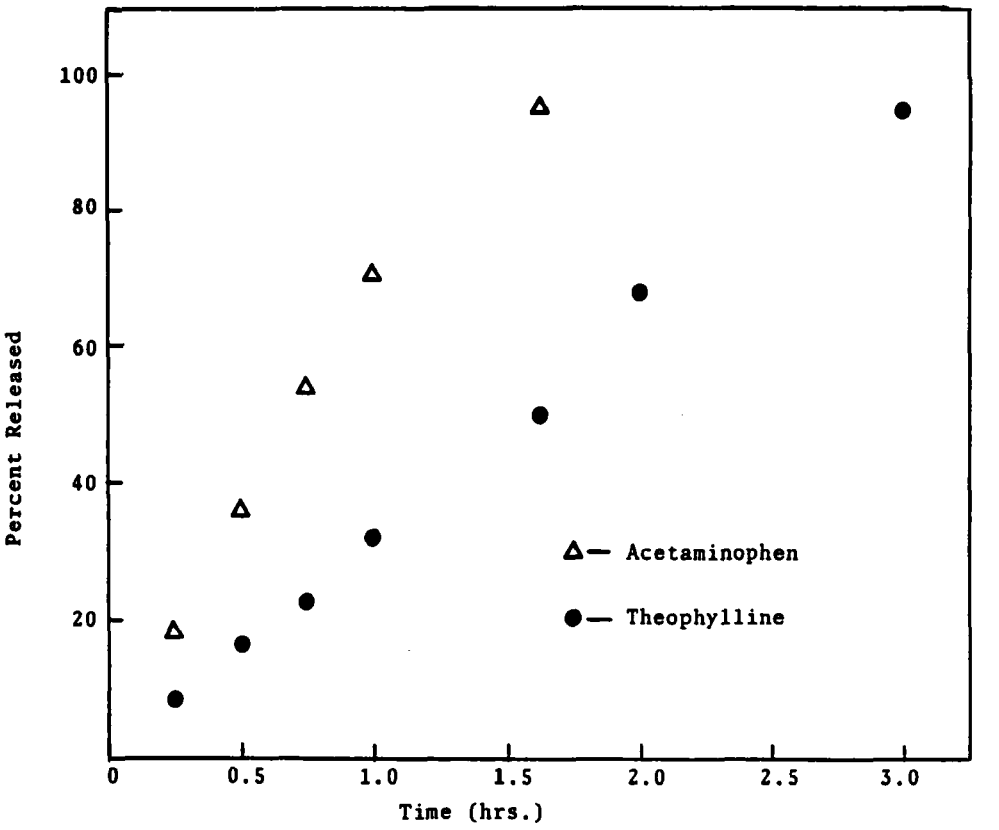

FIGURE 6. Percent of Drug Released from Granular (40/100) Solid Dispersions as a Function of Time.

The results indicate that ethylcellulose can be used as a retardent of drug release in prolonged release formulations of relatively water-soluble drugs. Furthermore, it has been shown that there are number of factors which influence drug release from drug-polymer matrices, such as pH of dissolution medium, particle size and diffusion of the drug through the matrix.

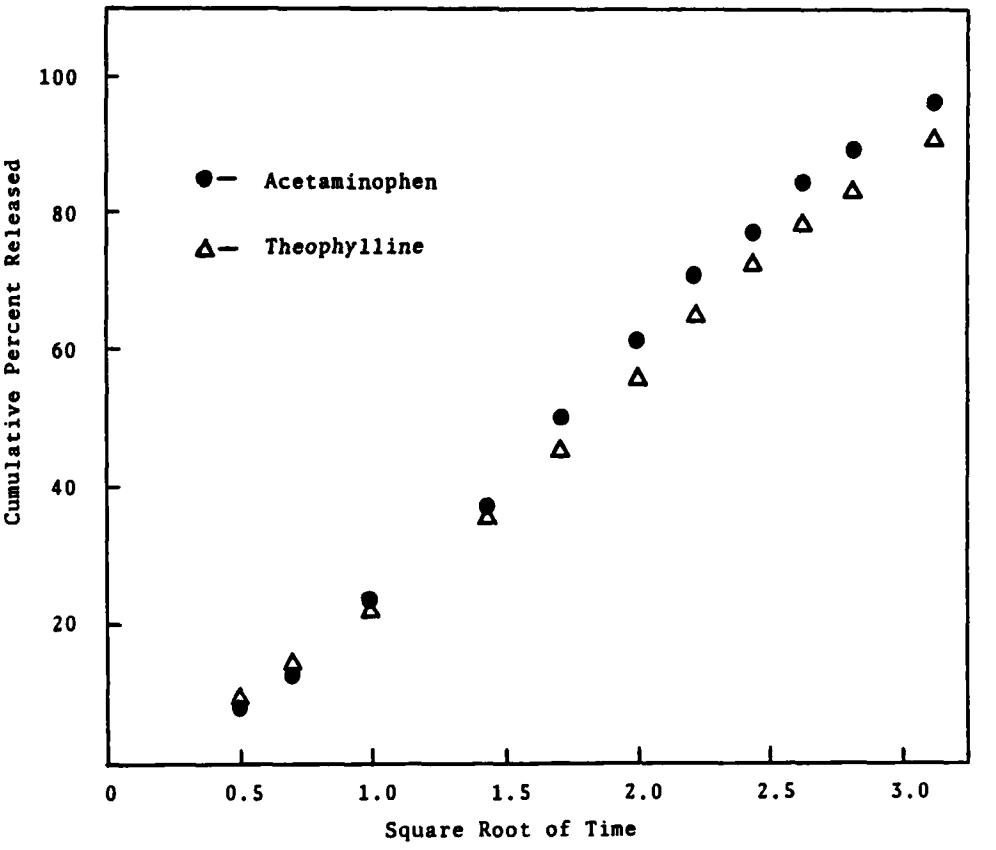

FIGURE 7. Higuchi Plot for Compressed (40/100) Solid Dispersions.

CONCLUSIONS

The release of the drug from granular solid dispersions follows zero-order kinetics while release from the compressed solid dispersions follows Higuchi's model for drug release from planar surfaces.

From the data presented, it can be concluded that a water-insoluble matrix, such as that provided by ethylcellulose, is an effective vehicle for prolonged-

TABLE 7

Summary of Higuchi's Model Fits for Directly Compressed Acetaminophen Solid Dispersions

pH	Viscosity grade, cps	Amount of Ethylcellulose								
		7.5%			15.0%			30.0%		
		Intercept	Slope	r[a]	Intercept	Slope	r[a]	Intercept	Slope	r[a]
2.2	21				- 13.33	44.75	0.998	- 11.01	33.39	0.999
	95	- 10.60	47.61	0.998	- 11.47	37.86	0.999	- 10.34	29.27	0.998
	209	- 11.01	47.10	0.997	- 8.16	31.94	0.998	- 10.15	28.29	0.998
	350	- 13.46	47.13	0.997	- 11.54	32.49	0.998	- 10.84	28.72	0.997
7.4	21				- 9.14	42.71	0.999	- 8.97	33.01	0.999
	95	- 11.20	48.65	0.999	- 9.84	47.20	0.999	- 6.65	28.03	0.997
	209	- 13.24	56.29	0.999	- 6.34	30.34	0.997	- 9.30	27.77	0.997
	350	- 9.79	43.93	0.999	- 5.73	29.10	0.998	- 7.77	26.54	0.997

a : Correlation coefficient

TABLE 8

Summary of Higuchi's Model Fits for Directly Compressed Theophylline Solid Dispersions

pH	Viscosity grade,cps	Amount of Ethylcellulose								
		7.5%			15.0%			30.0%		
		Intercept	Slope	r^a	Intercept	Slope	r^a	Intercept	Slope	r^a
2.2	21	- 10.69	38.86	0.999	- 10.70	33.92	0.999	- 10.64	30.85	0.995
	95	- 9.96	32.84	0.998	- 12.30	33.25	0.997	- 13.83	30.65	0.993
	209	- 7.69	36.20	0.996	- 4.34	33.18	0.991	- 10.33	32.21	0.999
	350	- 4.32	33.47	0.988	- 17.40	33.26	0.995	- 15.15	28.48	0.998
7.4	21	- 9.97	36.39	0.999	- 10.02	30.27	0.999	- 12.09	28.18	0.991
	95	- 8.96	29.86	0.999	- 11.64	29.21	0.997	- 13.35	26.66	0.990
	209	- 7.96	33.82	0.997	- 4.91	31.08	0.990	- 10.98	29.66	0.998
	350	- 4.61	32.76	0.991	- 17.29	32.89	0.999	- 11.70	23.10	0.998

a : Correlation coefficient

release drug delivery systems of water-soluble drugs. The concentration of polymer is the determining factor in controlling the release of drug from both granular and compressed solid dispersions. Viscosity grade of ethylcellulose showed a marked effect in the granular solid dispersions in contrast to the minimal effect demonstrated in the compressed solid dispersions. The *in vitro* release profile of acetaminophen was similar in both dissolution media although release at pH 7.4 was somewhat more rapid than at pH 2.2 ($p<0.001$). For theophylline, release at pH 2.2 was found to be more rapid than at pH 7.4 ($p<0.001$).

REFERENCES

1. Mayersohn, M., and Gibaldi, M., J. Pharm. Sci., 55, 1323 (1966).
2. Goldberg, A. H., Gibaldi, M., and Kanig, J. L., J. Pharm. Sci., 55, 482 (1966).
3. Simonelli, A. P., Mehta, S. C., and Higuchi, W. I., J. Pharm. Sci., 58, 538 (1969).
4. Bates, T. R., J. Pharm. Pharmacol., 21,710(1969).
5. Malone, M. H., Hochman, H. I., and Nieforth, K. A., J. Pharm. Sci., 55, 972 (1966).
6. Chiou, W. L., and Riegelman, S., J. Pharm. Sci., 60, 1281 (1971).
7. "Merck Index", 9th ed., Windholz, M., Merck & Co., Rahway, NJ, 1976, pp 1147.

8. Wurster, D., and Taylor, P. W., J. Pharm. Sci., 54, 169 (1965).

9. Carstensen, J. T., Brossard, C., Ylouses, L. D., Duchene, D., and Pulsieuz, P., J. Pharm. Sci., 72, 162 (1983).

10. Wagner, J. G., J. Pharm. Sci., 58, 1253 (1969).

11. Higuchi, T., J. Pharm. Sci., 50, 874 (1961).

12. Higuchi, T., J. Pharm. Sci., 52, 1145 (1963).