DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(4), 449-460 (1993)

DIRECT COMPRESSION CONTROLLED RELEASE TABLETS USING ETHYLCELLULOSE MATRICES

Sathyanarayana M. Upadrashta#, Pruthvipathy R. Katikaneni, Gregory A. Hileman* and Prakash R. Keshary*
School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64110-2499

ABSTRACT

Controlled release erodible matrix tablets were manufactured by a simple, direct compression process using ethylcellulose alone as the matrix former. Each of four different viscosity grades of ethylcellulose (10, 20, 45 and 100 cp) was dry mixed with either indomethacin or theophylline and a small amount of lubricant, then directly compressed into tablets. In initial trials, compression force was held constant, resulting in tablets of varying hardness. In a second study, the compression force was varied to produce tablets of equal hardness. Lower viscosity grades of ethylcellulose were more compressible than higher viscosity grades, allowing production of harder tablets for a given drug. Harder tablets resulted in controlled release of the drug over a longer time period. Dissolution studies indicated that tablet hardness is more important in determining dissolution rate than is the polymer viscosity grade. A mathematical model combining diffusion and erosion mechanisms was developed to describe drug release. Improved r^2 values over pure diffusion, erosion and diffusion/relaxation models were obtained. Examination of residuals indicated that the derived composite model was more appropriate for the data.

To whom correspondence should be addressed

* Marion Merrell Dow Inc., Kansas City, MO 64137.

INTRODUCTION

Ethylcellulose (EC) is an inert, hydrophobic polymer and has been extensively used as a pharmaceutical vehicle in a number of dosage forms: as a tablet binder (1), in preparing microcapsules and microspheres (2-3), as a coating material for tablets and granules (4-5) and as film forming and matrix forming materials for sustained release dosage forms (6-7). It has also been used as a matrix in the preparation of both water-soluble and sparingly water-soluble drugs using the solid dispersion technique (8-9). Preparation of these dosage forms required several unit operations. Especially noteworthy is that most of these processes require solubilization of all or part of the EC using organic solvents. Environmental issues are making these processes less tolerable and more expensive.

Direct compression is the preferred method of manufacture for producing tablets intended for immediate or sustained release. Even so, there have been very few (10) studies on the use of EC as a direct compression matrix. The present investigation is aimed at the potential use of neat (without added excipients) EC as a direct compression controlled release matrix forming material and to examine the effects of different viscosity grades of the polymer on the physical characteristics of those tablets. Indomethacin and theophylline were chosen as model drugs.

EXPERIMENTAL

Materials: Indomethacin and theophylline (anhydrous) were obtained from Sigma Chemical Company, St. Louis, MO. Magnesium stearate, USP, was obtained from Ruger Chemical Co., Irvington, NJ. Four viscosity grades (10, 20, 45 and 100 cp) of ethycellulose, NF were used. They were gifts (Standard Grade) from Dow Chemical Company, Midland, MI and have an ethoxyl content of 48.0 to 49.5%.

Experimental: Tablets were manufactured by a direct compression process using EC without added excipients. Sieved 80/100 mesh fractions of 10, 20, 45 and 100 cp viscosity grades of EC were used separately as matrix materials. A 1:1 ratio of drug to polymer was used for theophylline and 1:3

for indomethacin to represent typical drug doses in a suitable size tablet. The drug, ethylcellulose and 1% magnesium stearate were physically mixed and compressed at constant pressure or to tablets of equal hardness. Tablet weights were fixed at 202 mg and compressed using a 5/16 inch standard concave punch and die set on an automated Carver press (Model C-12, Fred S. Carver Co., Menomonee Falls,WI). Compression rate was 31 mm/sec and dwell time was 0.1 sec. In the first study, a peak pressure of 3000 psi was used for compressing each mixture. In a second study, compression force was varied to obtain tablets of equal hardness with each polymer/drug mixture.

Hardness : Tablet hardness was determined with Schleuniger hardness tester (Model 2E Vector Corp., Marion, Iowa) and the data are presented as an average of five determinations.

Dissolution studies: Dissolution testing was performed using USP method II (11). Distilled water was used as the dissolution medium for theophylline and phosphate buffer (pH 7.2) for indomethacin. The temperature of the medium and rate of agitation were maintained at 37°C and 100 rpm respectively. Samples (10 ml) were withdrawn at specified intervals and the drug concentrations were determined spectrophotometrically at 272 (theophylline) or 318 nm (indomethacin).

RESULTS AND DISCUSSION

With an increase in the viscosity grade, for either drug tested, a decrease in tablet hardness was observed. Results for tablets compressed at equal peak force (3000 psi) are shown in Table 1. Maximum achievable hardness was associated with 10 cp grade and the minimum with 100 cp grade. A significant inverse correlation was found ($r^2=0.992$) for indomethacin. A similar trend was also observed for theophylline indicating that higher viscosity grades were relatively less compressible than lower ones.

Dissolution profiles of indomethacin and theophylline prepared with different EC grades and compressed at 3000 psi are shown in Figure 1. 10 cp viscosity grade produced the slowest dissolution rates and 100 cp the fastest dissolution rates for both drugs tested. Harder tablets were associated

Table 1

Hardness values and dissolution half-lives of tablets prepared with ethylcellulose compressed at 3000 psi

Ethylcellulose viscosity grade (cp)	Hardness (kp)		Dissolution half-lives (hr)	
	Indomethacin	Theophylline	Indomethacin	Theophylline
10	14.82	10.7	40.1	5.50
20	14.38	10.1	37.0	4.55
45	12.76	7.3	12.1	2.30
100	10.40	6.5	6.9	2.05

with longer dissolution half-lives ($t_{1/2}$). Complete drug release was obtained in the case of theophylline prepared with 100 or 45 cp grades, whereas with indomethacin, only 74% was released with the 100 cp grade. This may be attributed to the differing drug solubilities or to a higher drug to polymer ratio with theophylline. All of the tablets eroded as evidenced by a decrease in physical dimensions during dissolution (12 hours).

In order to separate the hardness effects from constituent effects, tablets incorporating each ethylcellulose viscosity grade were compressed to constant hardness (6.2 kp for theophylline and 10.4 kp for indomethacin) by varying the compression force. For either drug, the maximum achievable hardness using 100 cp ethylcellulose was easily achieved with each of the lower viscosity grades using reduced pressure. Results are shown in Table 2. Pressure required to achieve 10.4 kp for indomethacin is logarithmically related to the polymer viscosity grade ($r^2 = 0.996$). A similar relationship was also observed for theophylline tablets.

The dissolution profiles of tablets prepared with indomethacin and theophylline at constant hardness are shown in Figure 2. An increase in the dissolution rates for both drugs was observed with decreased hardness. With indomethacin, decreasing tablet hardness from roughly 15 kp to 10 kp decreased $t_{1/2}$ from 40 hours to 8 hours. With 100 cp grade, maximum tablet hardness achievable was 10 kp, resulting in a $t_{1/2}$ of only 7 hours. At a given tablet hardness, $t_{1/2}$ was reduced as the polymer viscosity increased. This

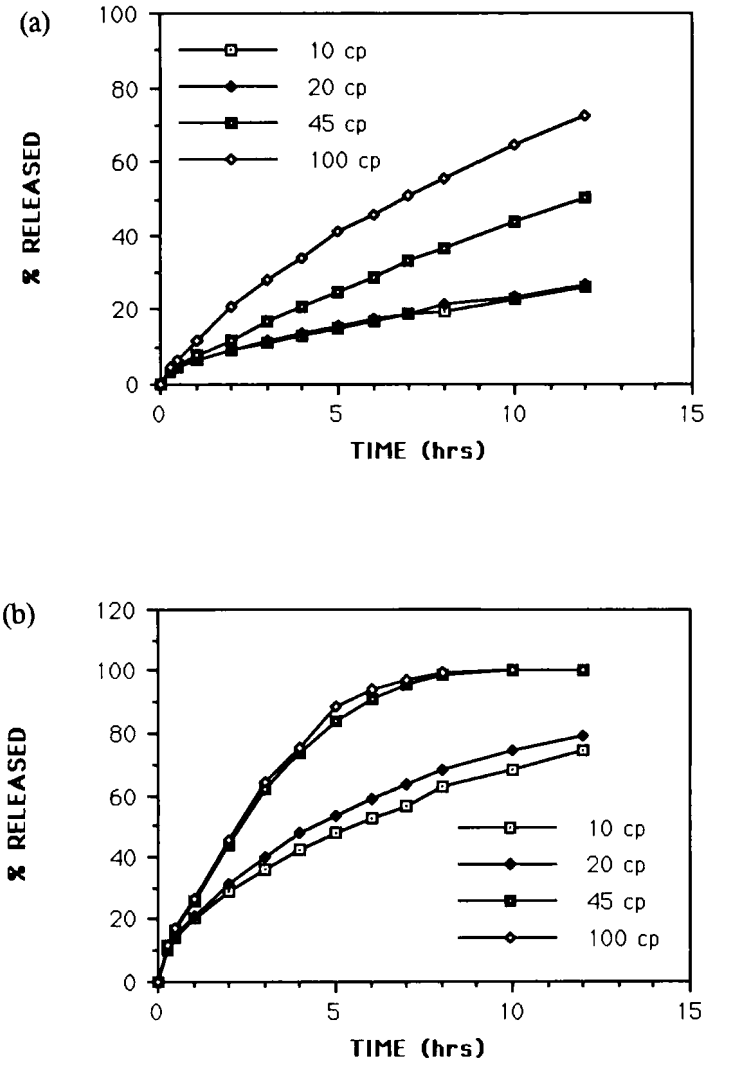

Figure 1. Dissolution profiles of tablets prepared with different viscosity grades of ethylcellulose compressed at constant pressure (3000 psi): (a) indomethacin and (b) theophylline

Table 2

Pressures and dissolution half-lives of tablets prepared with ethylcellulose compressed to constant hardness

Ethylcellulose viscosity grade (cp)	Pressure (psi)		Dissolution half-lives (hr)	
	Indomethacin	Theophylline	Indomethacin	Theophylline
10	1350	1400	8.1	3.25
20	1750	1500	11.7	3.15
45	2400	2600	11.8	2.15
100	3000	3000	6.9	2.05

trend towards shorter dissolution half-lives with higher viscosity was also observed at constant hardness with theophylline. 10 cp EC matrices gave a $t_{1/2}$ of approximately 3 hours, while 100 cp gave a $t_{1/2}$ of only 2 hours.

With either drug, tablet hardness affected $t_{1/2}$ to a greater extent than the polymer viscosity grade. Lower viscosity grades were more compressible than higher ones, allowing production of a wider range of tablet hardnessess, and thus dissolution rates, for either drug. These results suggest that in general, a low viscosity EC may provide a wider range of drug release rates which could be controlled at the time of manufacture simply by altering compression force.

In order to understand the release kinetics, the following models :

diffusion model (12) $$\frac{M_t}{M_\infty} = kt^{1/2}$$

erosion model (13) $$(1- \frac{M_t}{M_\infty})^{1/3} = 1- kt$$

diffusion/relaxation model (14) $$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}$$

were fitted to the dissolution data using a SAS multiple linear regression analysis (Proc Reg, SAS Institute Inc., Cary, NC, 1986 edition). The sum of squared residuals (SSR) and the coefficients of determination (r^2) for tablets prepared at constant hardness and constant pressure for both drugs are

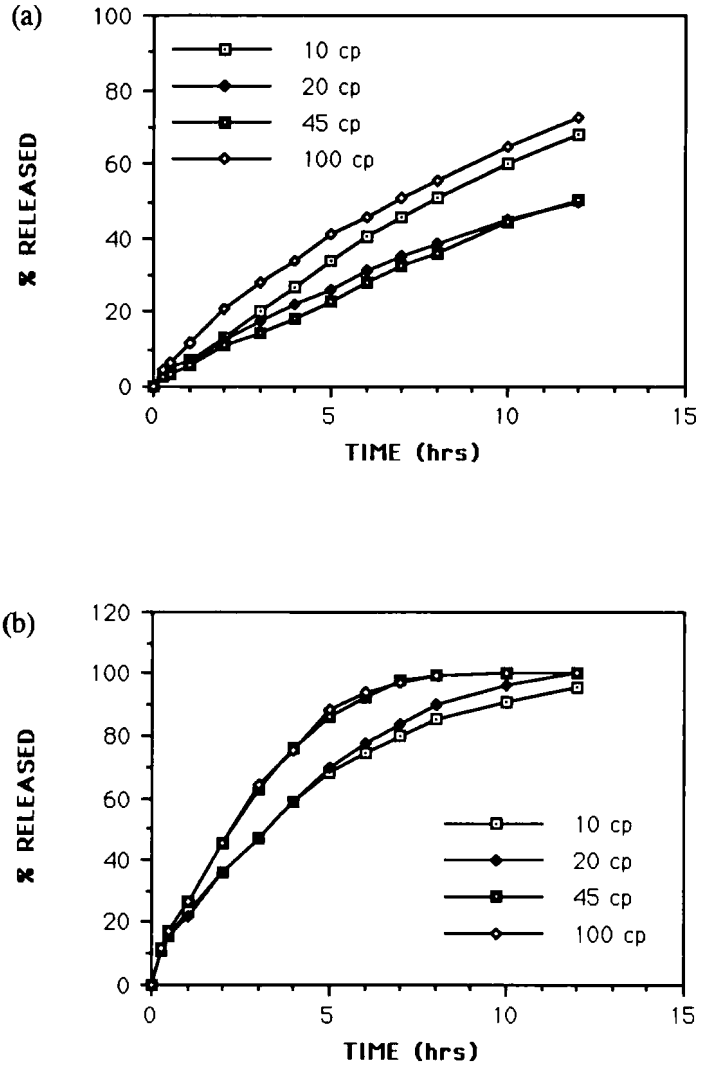

Figure 2. Dissolution profiles of tablets prepared with different viscosity grades of ethylcellulose compressed to constant hardness: (a) indomethacin (10.5 kp) and (b) theophylline (6.2 kp)

presented in Tables 3-6. All the models gave acceptable r^2 values. However, an examination of residual plots for each of these models revealed systematic deviations indicating lack-of-fit and inappropriateness of these models. For example, the Higuchi diffusion model consistently over predicted early and under predicted later, dissolution rates. By contrast, the erosion model under predicted early and over predicted later rates.

Erosion and diffusion models were combined to describe the release data in a more appropriate way. The cube-root (13) equation mentioned above was expanded and coupled with the diffusion/relaxation model as follows:
Starting with the erosion rate equation above:

$$(1- \frac{M_t}{M_\infty})^{1/3} = 1- kt$$

Cubing both sides gives:

$$1- \frac{M_t}{M_\infty} = 1 - 3kt + 3k^2t^2 - k^3t^3$$

Rearranging yields:

$$Q_e = \frac{M_t}{M_\infty} = k_1t + k_2t^2 + k_3t^3$$

where Q_e represents release of a drug from the surface of an eroding sphere. Higuchi described drug release from a non-eroding matrix in his classic square-root-of-time equation mentioned above. Peppas and Sahlin (14) proposed a model which incorporated rate effects of diffusion and relaxation phenomena:

$$\frac{M_t}{M_\infty} = k_4t^m + k_5t^{2m}$$

where the first term describes Fickian contribution and the second term, Case-II relaxational contribution. The coefficient m represents Fickian diffusion exponent for a device of any geometry exhibiting controlled release. When m = 0.5, the spherical case, this equation becomes:

$$Q_{dr} = \frac{M_t}{M_\infty} = k_4t^{1/2} + k_5t,$$

which essentially corrects the Higuchi pure diffusion model for relaxation of the spherical matrix by adding the linear term. Q_{dr} represents release by both diffusion and relaxation mechanisms. Combining Q_e with Q_{dr} one arrives at

Table 3

Ethylcellulose viscosity grade (cp)	Diffusion model		Erosion model		Diffusion/relaxation model		Diffusion/erosion model	
	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2
10	5.459	0.9981	13.725	0.9953	0.399	0.9999	0.244	0.9999
20	5.583	0.9982	13.724	0.9956	0.417	0.9999	0.369	0.9999
45	201.461	0.9783	12.172	0.9987	1.951	0.9998	0.620	0.9999
100	271.237	0.9874	7.018	0.9997	20.927	0.9990	1.594	0.9999

Table 4

Statistical data for theophylline tablets prepared with different viscosity grades compressed at constant pressure

Ethylcellulose viscosity grade (cp)	Diffusion model		Erosion model		Diffusion/relaxation model		Diffusion/erosion model	
	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2
10	11.07	0.9995	114.69	0.9957	8.44	0.9997	1.808	0.9999
20	24.46	0.9992	110.94	0.9966	32.51	0.9990	1.317	1.0000
45	708.22	0.9893	42.51	0.9994	719.18	0.9891	16.108	0.9998
100	888.15	0.9871	45.89	0.9993	841.19	0.9878	22.584	0.9997

(S.S.R. = Sum of Squared Residuals)

Table 5

Statistical data for indomethacin tablets prepared with different viscosity grades compressed at constant hardness

Ethylcellulose viscosity grade (cp)	Diffusion model		Erosion model		Diffusion/relaxation model		Diffusion/erosion model	
	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2
10	576.83	0.9664	6.224	0.9996	20.79	0.9988	4.085	0.9998
20	186.05	0.9814	9.305	0.9991	9.10	0.9991	0.838	0.9999
45	322.68	0.9640	6.840	0.9992	5.20	0.9994	2.180	0.9998
100	271.23	0.9874	7.018	0.9997	20.92	0.9990	1.594	0.9999

Table 6

Statistical data for theophylline tablets prepared with different viscosity grades compressed at constant hardness

Ethylcellulose viscosity grade (cp)	Diffusion model		Erosion model		Diffusion/relaxation model		Diffusion/erosion model	
	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2	S.S.R.	r^2
10	173.26	0.9965	88.00	0.9982	183.47	0.9963	10.46	0.9998
20	259.22	0.9951	103.66	0.9981	225.57	0.9958	13.35	0.9997
45	856.34	0.9875	40.68	0.9994	822.85	0.9880	18.63	0.9997
100	888.15	0.9871	45.89	0.9993	841.19	0.9878	22.58	0.9997

(S.S.R. = Sum of Suqared Residuals)

the following equation:

$$Q = Q_e + Q_{dr} = k_4 t^{1/2} + Kt + k_2 t^2 + k_3 t^3$$

where Q is the fraction of the drug released and K is a hybrid of two constants (k_1 and k_5) accounting for both erosion and relaxation phenomena. k_2 and k_3 are associated with the erosional component of release and k_4 with pure Fickian diffusion. Fitting this model to the current data yielded an r^2 of 0.9998 with randomly distributed residuals, indicating a superior fit and appropriateness of this composite model. This improvement over the other models is upheld with either drug tested and across all polymer viscosity grades.

CONCLUSIONS

The results of the present investigation demonstrate that ethylcellulose is a good direct compression excipient. The lower viscosity grades of ethylcellulose are more compressible than the higher viscosity grades, resulting in harder tablets. On the contrary, higher viscosity grades are less compressible and produce lower tablet hardnesses, which more importantly, yield drug release characteristics that are less sensitive to changes in compression force. With either drug tested, altering tablet hardness provided a much greater control over dissolution rate than did changing the polymer grade. So, in choosing a polymer viscosity grade for a direct compression controlled release product, a wider range of controlled dissolution rate is achievable with lower viscosity grades of EC. Conversely, if appropriate dissolution rate can be achieved using a higher viscosity grade polymer, the resulting product will be less sensitive to changes in compression force during manufacture. The release of either drug from the tablets followed a combined diffusion and erosion model. Finally, judicious choice of a particular polymer viscosity grade is, of course, drug dependent and requires consideration of drug delivery requirements and intrinsic drug characteristics.

REFERENCES

1. H. Delonca, J. Joachim, P. Suvikrom and G. Joachim, Farmaco, Ed. Prat., 30,165 (1975).

2. S. Benita and M. Donbrow, J. Pharm. Pharmacol., 34, 77 (1982).
3. S. Benita, D. Babay, A. Hoffman and M. Donbrow, Pharm. Res., 5, 178 (1988).
4. R.C. Rowe and S.F. Forse, J. Pharm. Pharmacol., 32, 583 (1980).
5. N. Sarisuta and J. Sirithunyalug, Drug Dev. Ind. Pharm., 14, 683 (1988).
6. M. Donbrow and M. Friedman, J. Pharm. Pharmacol., 26, 148 (1974).
7. L.E. Dahlinder, C. Graffner and J. Sjorgren, Acta Pharm. Suec., 10, 323 (1973).
8. N.A. Shaikh, S.E. Abidi and L.H. Block, Drug Dev. Ind. Pharm., 13, 1345 (1987).
9. N.A. Shaikh, S.E. Abidi and L.H. Block, Drug Dev. Ind. Pharm., 13, 2495 (1987).
10. S. I. Pather, Personal communication, 1990.
11. U.S. Pharmacopeia XXII/ National Formulary XVII, 1990.
12. T. Higuchi, J. Pharm. Sci., 50, 874 (1961).
13. D.Bidah and J.M. Vergnaud, Int. J. Pharm., 58, 215-220 (1990).
14. N.A. Peppas and J.J. Sahlin, Int. J. Pharm., 57, 169-172 (1989).