DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(14), 2495-2518 (1987)

EVALUATION OF ETHYLCELLULOSE AS A MATRIX FOR PROLONGED RELEASE FORMULATIONS. II. SPARINGLY WATER-SOLUBLE DRUGS : IBUPROFEN AND INDOMETHACIN

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ABSTRACT

The main purpose of this investigation was to evaluate ethylcellulose as a carrier for the preparation of prolonged release solid dispersions of sparingly water-soluble drugs, ibuprofen and indomethacin. Solid dispersions containing various concentrations of ethylcellulose of different viscosity grades were prepared by the solvent method. Tablets were directly compressed from solid dispersions (40/100 mesh) with 0.5% Primojel as a disintegrant and 0.5% magnesium stearate as a lubricant. In vitro release studies employed a rotating bottle system with

Sorenson's buffer solution (pH 7.4). It was found that prolongation of drug release was primarily associated with an increase in amount of ethylcellulose rather than the viscosity grade. Nonetheless, the higher the viscosity grade of ethylcellulose, the slower the release of drug from granular and compressed solid dispersions. The release rate of ibuprofen was faster than that of indomethacin from different solid dispersion formulations.

INTRODUCTION

Ethylcellulose is an inert, organosoluble and tasteless polymer (1). It has been widely used as a binder in tablet formulations and as a retardent of drug release in sustained release formulations (2). It has also been used as a coating or film-forming agent (3-6). Drug-polymer films have been formulated in attempts to achieve controlled release of the drug. Considerable data exist in the literature to demonstrate the application of ethylcellulose in the preparation of prolonged release microcapsules of various water-soluble drugs (7-12). It has also been used as a matrix for prolonged release formulations of water-soluble drugs using the solid dispersion technique (13).

Incorporation of a sparingly water-soluble drug in an inert, hydrophobic carrier such as ethylcellulose can possibly be used to achieve prolonged or sustained release characteristics, although this has not been investigated previously to our knowledge. The decrease in release rate from such a system may be due to the association of the drug particles with the hydrophobic carrier (14).

This study was prompted by the desire to evaluate the possible application of ethylcellulose as a potential carrier for the preparation of prolonged release formulations of sparingly water-soluble drugs (e.g., ibuprofen and indomethacin) using the solid dispersion technique.

EXPERIMENTAL

Materials: Ibuprofen (kindly supplied by The Upjohn Co., Kalamazoo, MI), indomethacin (Sigma Chemical Co., St. Louis, MO), Ethylcellulose N-22, Ethylcellulose N-100, Ethylcellulose N-200 and Ethylcellulose N-300 (Ethylcelluloses of different viscosity grades were provided by Hercules, Inc., Wilmington, DE), ethanol (Fisher Scientific, Pittsburgh, PA), Primojel (Generichem Corp., Little Falls, NJ), magnesium stearate (Fisher Scientific, Fair Lawn, NJ) and Sorenson's buffer (pH 7.4).

Preparation of Solid Dispersions: Solid dispersions of various ethylcellulose and drug ratios were prepared by the previously reported method (13).

Compression of Tablets: Tablets were directly compressed from different solid dispersion formulations (40/100 mesh) with and without Primojel, 0.5 % w/w, as a disintegrant. Magnesium stearate (0.5% w/w) was incorporated as a lubricant prior to compression. The tablets were compressed manually on a Carver press. Tablet hardness was kept constant within the range of 7-8 Kg on a Stokes hardness tester.

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) at 50 RPM using Sorenson's buffer (pH 7.4) maintained at 37°C. At predetermined times, the dissolution medium was completely removed from the bottles and replaced with fresh solution, thus maintaining sink conditions. Aliquots were filtered and analyzed spectrophotometrically for ibuprofen or indomethacin at 264 nm or 318 nm, respectively.

RESULTS AND DISCUSSION

The concentration of polymer in the formulation was the determining factor in controlling release rate of the drug. In the case of ibuprofen granular solid dispersions, 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 dissolution plateau was reached within four hours in all formulations.

The release of indomethacin from granular solid dispersions was much slower compared to the release of ibuprofen from similar formulations. This may be attributed to their differing solubilities. The reported solubility of ibuprofen is 331 mg/100 ml, whereas 170 mg/100 ml (buffer pH 7.5 at 37 °C) in the case of indomethacin (15). The release pattern of indomethacin from solid dispersions of different viscosity grades and concentrations of ethylcellulose was more or less similar to that of ibuprofen, representative curves are shown in Figure 3.

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

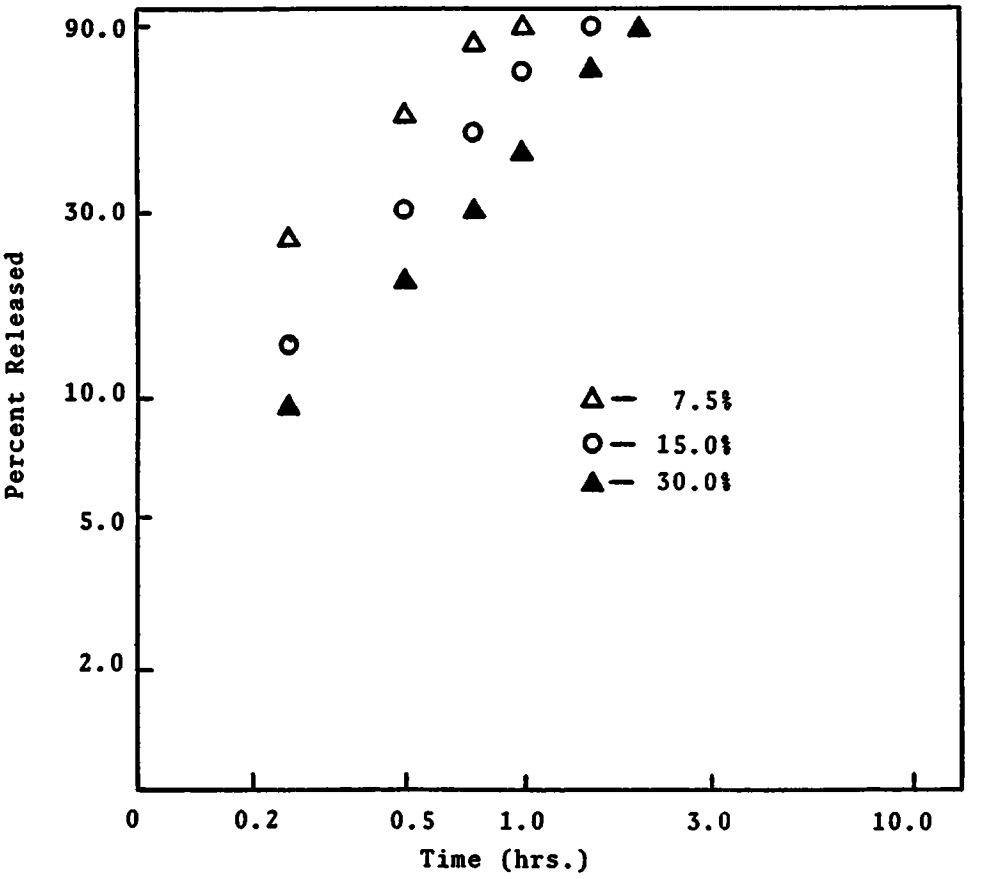

FIGURE 1. Release Profile of Ibuprofen/Ethylcellulose (209 cps) Solid Dispersions (40/60): Influence of Amount (%) of Ethylcellulose.

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.

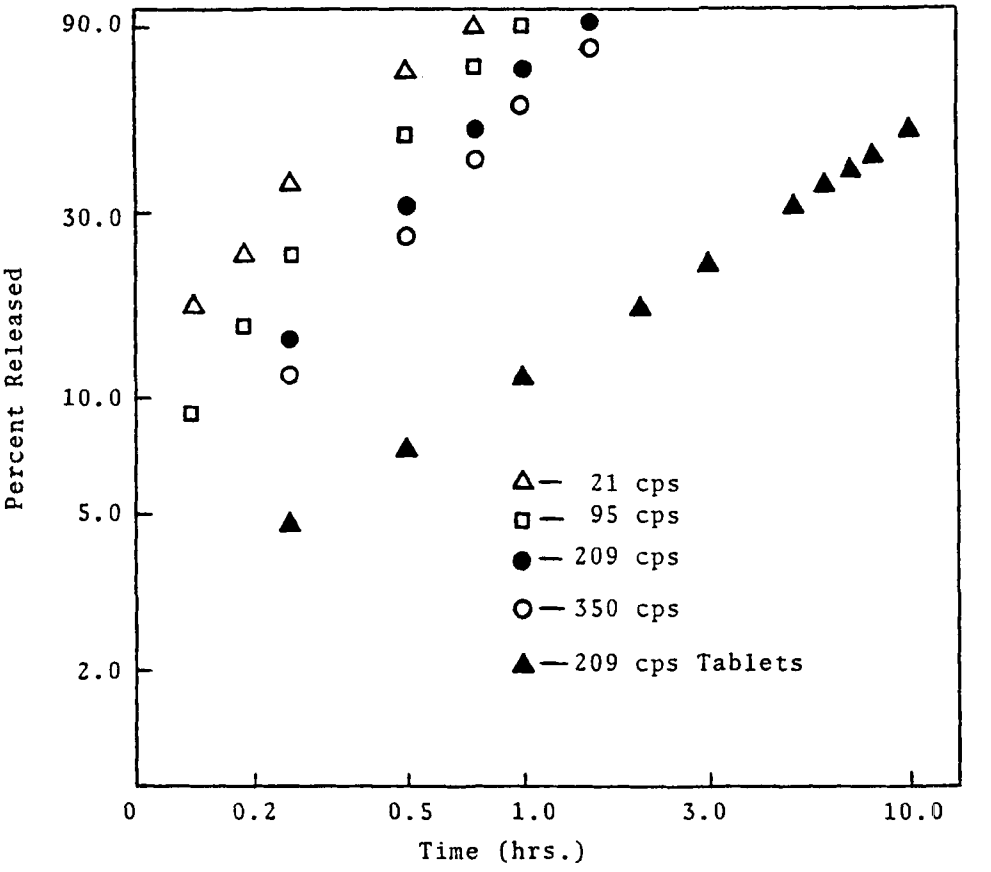

FIGURE 2. Release Profile of Ibuprofen/Ethylcellulose (15%) Solid Dispersions (40/60): Influence of Ethylcellulose Viscosity Grade.

It was found that the release of ibuprofen and indomethacin from the tablets showed a similar trend to that from the granular solid dispersions, but the release rate was extremely slow. The maximum amount released at the end of 12 hours was only 25-50% ; results are shown in Figure 5. This could be explained

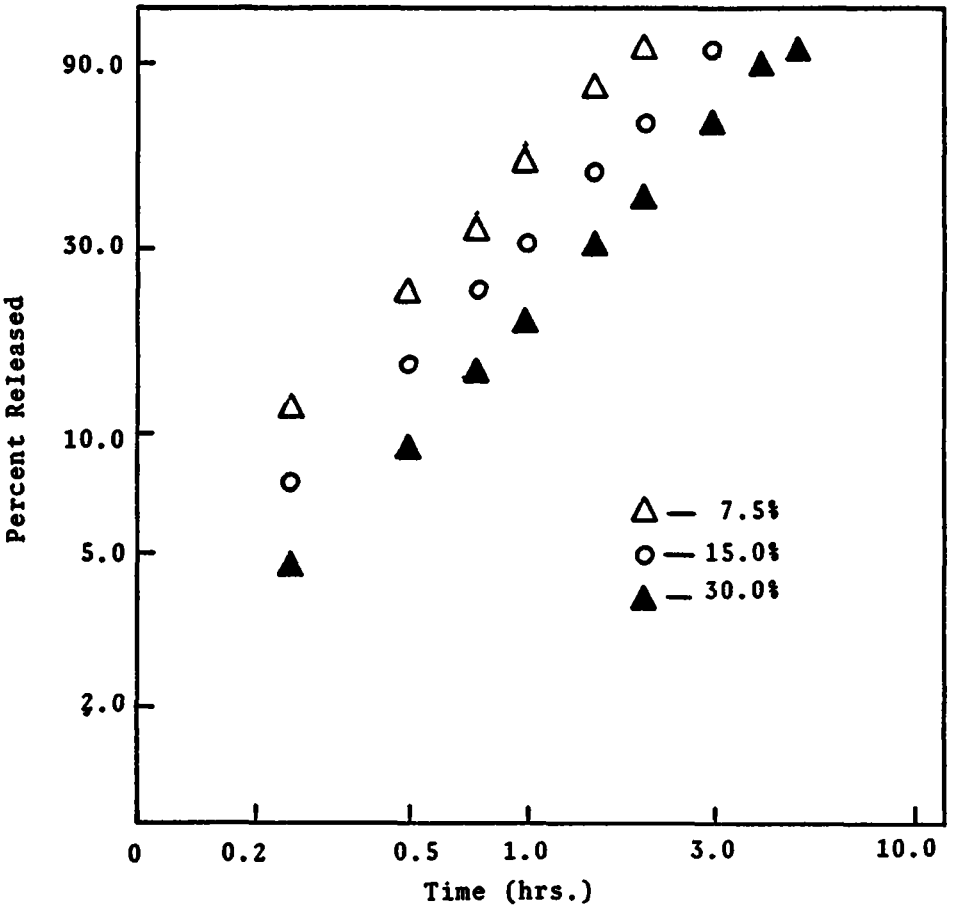

FIGURE 3. Release Profile of Indomethacin/Ethylcellulose (209 cps) Solid Dispersions (40/60): Influence of Amount (%) of Ethylcellulose.

on the basis of the poor aqueous solubilities of these drugs (15). These results led to the inclusion of a disintegrant (Primojel) in the formulations.

Tablets containing Primojel were found to swell somewhat during the course of the dissolution study.

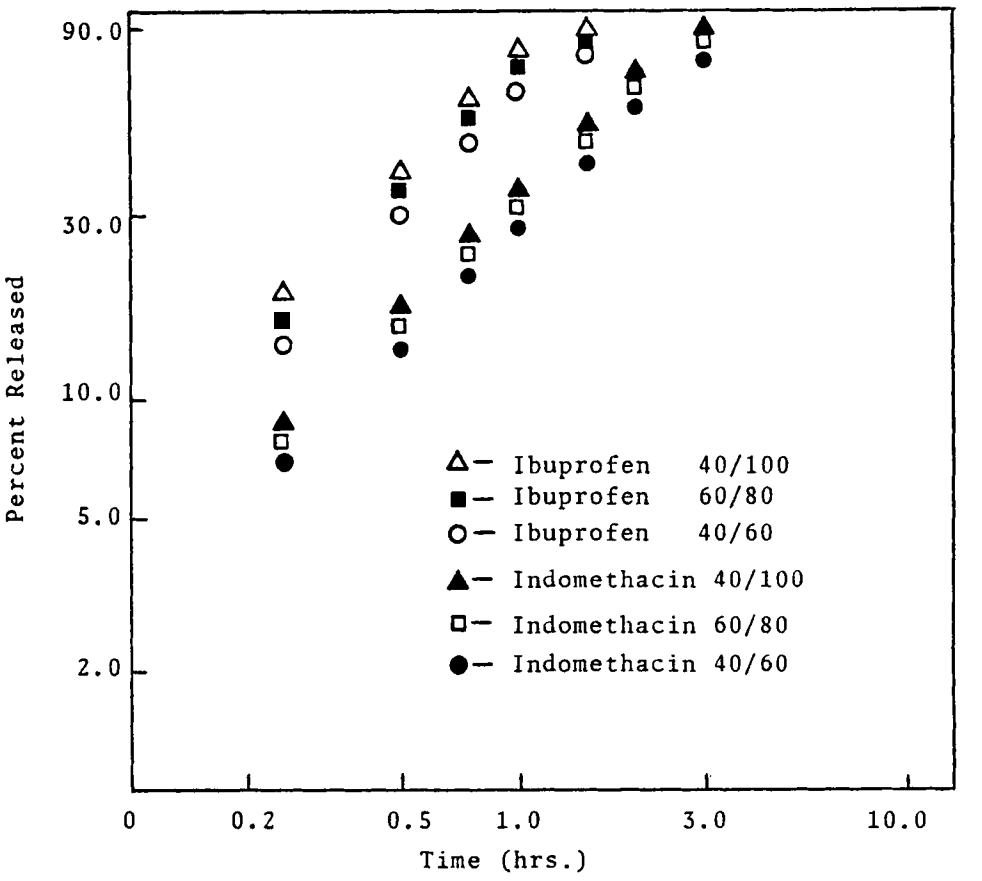

FIGURE 4. Effect of Particle Size on Drug Release from Solid Dispersions (209 cps).

These tablets did provide faster release of the drug than tablets prepared without Primojel (Figure 5). Although the low concentration (0.5% w/w) of the disintegrant was not sufficient to completely disintegrate the tablet, it did result in some hydration and swelling of the tablets during the course

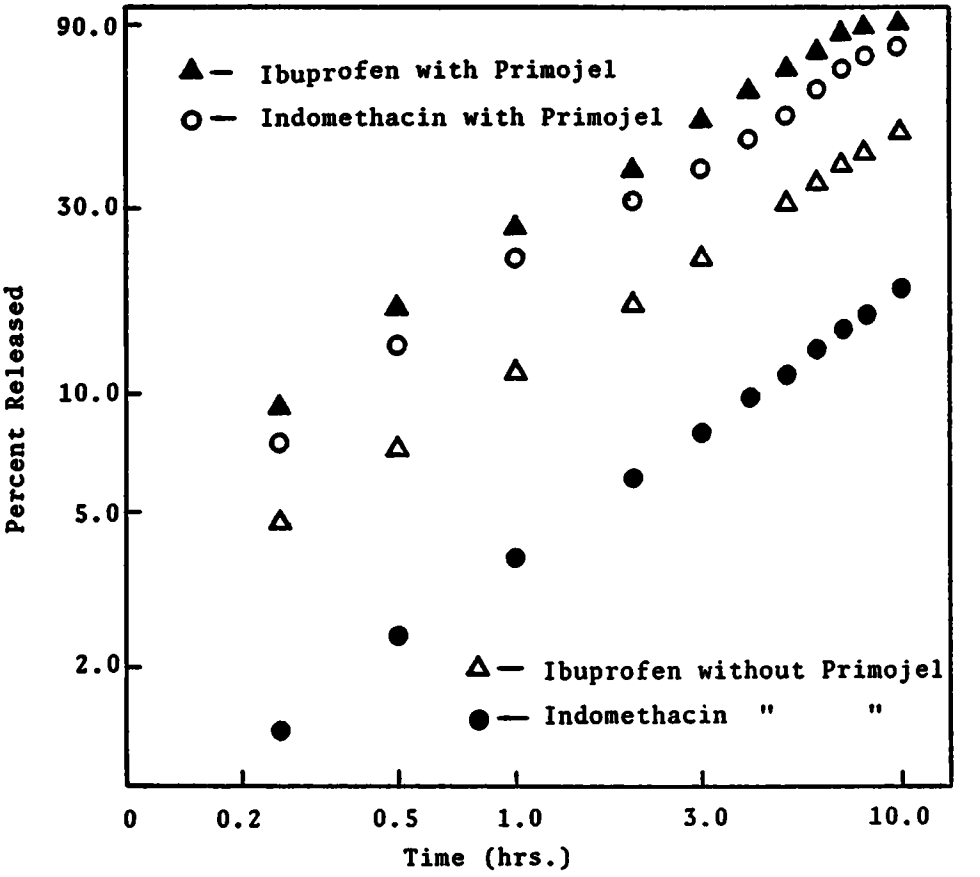

FIGURE 5. Effect of Primojel on Drug Release from Compressed Solid Dispersions.

of the dissolution study. These swollen matrices presumably result from greater initial water permeation into the tablets which, in turn, results in faster initial drug release. Following the initial incursion of the dissolution medium into the tablet, subsequent drug dissolution proceeded more slowly due to the decreased rate of water migration.

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 tabulated in Tables 1 - 4.

The percentage of drug released as a function of time for both granular and compressed solid dispersions obeyed an empirical log-log relationship (power function). The corresponding intercepts, slopes and correlation coefficients for the compressed solid dispersions (Tables 5 and 6) were calculated in accordance with the previously reported relationship (13).

The data obtained for granular solid dispersions of ibuprofen and indomethacin were evaluated in accordance with Higuchi's equation for drug release from spherical matrices (13,16). As shown in Figure 6, data for granular solid dispersions do not follow Higuchi's relationship. A plot of percent released as a function of time does yield a straight line ($r=0.999$) as shown in Figure 7, which suggests that drug release from granular solid dispersion follows zero-order kinetics, rather than diffusion-controlled matrix model.

Results for the compressed solid dispersions are shown in Figure 8. Slopes, intercepts and correlation

TABLE 1

Time (hrs.)[a] for 90% Release of Ibuprofen 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	0.454 (0.011)	0.629 (0.017)	1.141 (0.029)
	95	0.630 (0.016)	0.941 (0.009)	1.299 (0.059)
	209	0.876 (0.012)	1.354 (0.053)	1.900 (0.014)
	350	0.974 (0.006)	1.361 (0.051)	2.528 (0.115)
60/80	21	0.423 (0.028)	0.585 (0.017)	1.084 (0.012)
	95	0.573 (0.010)	0.846 (0.078)	1.214 (0.004)
	209	0.849 (0.014)	1.234 (0.062)	1.924 (0.099)
	350	0.915 (0.009)	1.277 (0.065)	2.315 (0.054)
40/100	21	0.422 (0.025)	0.564 (0.018)	0.866 (0.002)
	95	0.587 (0.028)	0.786 (0.041)	1.196 (0.049)
	209	0.742 (0.036)	1.279 (0.050)	1.402 (0.054)
	350	0.839 (0.030)	1.141 (0.004)	1.814 (0.124)

a : Mean of three runs (± S.D.)

TABLE 2

Time (hrs.)[a] for 90% Release of Indomethacin 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	0.874 (0.018)	1.295 (0.010)	1.962 (0.015)
	95	1.270 (0.004)	1.775 (0.029)	2.818 (0.022)
	209	1.809 (0.012)	2.864 (0.009)	4.355 (0.018)
	350	2.478 (0.021)	3.537 (0.005)	5.376 (0.013)
60/80	21	0.849 (0.014)	1.280 (0.003)	1.926 (0.016)
	95	1.262 (0.001)	1.734 (0.019)	2.781 (0.026)
	209	1.754 (0.015)	2.837 (0.026)	4.233 (0.034)
	350	2.424 (0.013)	3.431 (0.031)	5.258 (0.013)
40/100	21	0.805 (0.006)	1.311 (0.001)	1.899 (0.002)
	95	1.245 (0.001)	1.737 (0.003)	2.718 (0.016)
	209	1.767 (0.011)	2.799 (0.016)	4.272 (0.008)
	350	2.440 (0.015)	3.487 (0.018)	5.255 (0.005)

a : Mean of three runs (± S.D.)

TABLE 3

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

Viscosity grade,cps	Amount of Ethylcellulose 7.5%	15.0%	30.0%
21	6.399 (0.046)	6.913 (0.052)	7.336 (0.110)
95	7.777 (0.034)	8.417 (0.081)	9.213 (0.058)
209	8.402 (0.064)	11.134 (0.081)	11.585 (0.225)
350	8.743 (0.097)	11.846 (0.247)	13.158 (0.095)

a : Mean of four runs (± S.D.)

TABLE 4

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

Viscosity grade, cps	Amount of Ethylcellulose 7.5%	15.0%	30.0%
21	6.366 (0.040)	6.654 (0.077)	7.239 (0.153)
95	7.628 (0.040)	7.817 (0.074)	9.050 (0.094)
209	7.813 (0.047)	8.054 (0.089)	9.179 (0.138)
350	8.163 (0.086)	9.965 (0.192)	11.626 (0.106)

a : Mean of four runs (± S.D.)

TABLE 5

Summary of Power Function Fits for Directly Compressed Ibuprofen Solid Dispersions in Sorenson's Buffer

Viscosity grade, cps	Amount of Ethylcellulose								
	7.5%			15.0%			30.0%		
	Intercept[a]	Slope	r[b]	Intercept[a]	Slope	r[b]	Intercept[a]	Slope	r[b]
21	12.21	0.616	0.998	12.81	0.587	0.997	11.10	0.619	0.998
95	11.82	0.591	0.994	11.91	0.575	0.993	10.36	0.599	0.996
209	11.20	0.593	0.995	9.83	0.583	0.994	9.41	0.589	0.993
350	10.61	0.602	0.994	9.45	0.584	0.997	8.62	0.592	0.996

a : Intercept calculated at 0.25 hrs.

b : Correlation coefficient

TABLE 6

Summary of Power Function Fits for Directly Compressed Indomethacin Solid Dispersions in Sorenson' Buffer

Viscosity grade,cps	Amount of Ethylcellulose 7.5%			15.0%			30.0%		
	Intercept[a]	Slope	r[b]	Intercept[a]	Slope	r[b]	Intercept[a]	Slope	r[b]
21	12.64	0.607	0.998	11.99	0.615	0.999	10.75	0.632	0.998
95	11.91	0.592	0.994	11.38	0.601	0.993	10.11	0.609	0.997
209	10.50	0.624	0.995	9.82	0.638	0.992	6.93	0.712	0.981
350	10.89	0.606	0.995	7.61	0.671	0.995	7.75	0.639	0.999

a : Intercepts calculated at 0.25 hrs.

b : Correlation coefficient

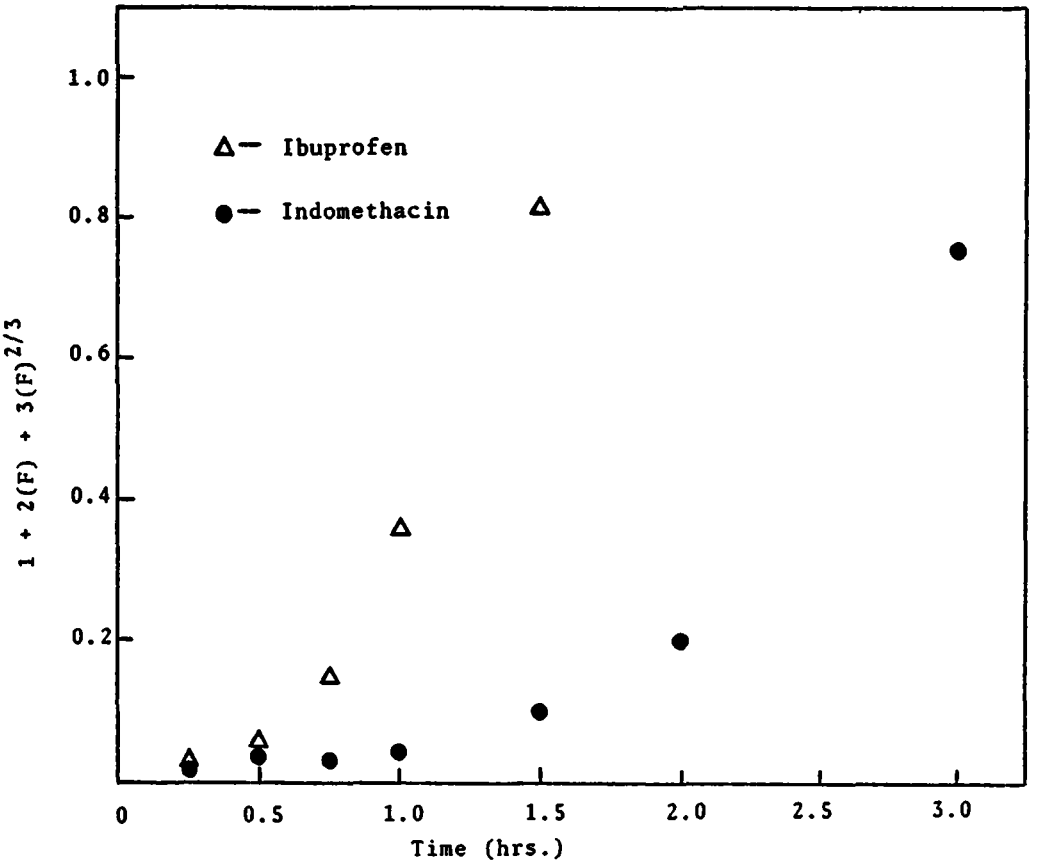

FIGURE 6. Higuchi Plot for Granular (40/100) Solid Dispersions.

coefficients are summarized in Tables 7 and 8. The data obtained for drug release from compressed solid dispersions obey Higuchi's equation for drug release from planar matrices. Thus, release is apparently diffusion-controlled (16,17).

The results indicate that the release mechanism of sparingly water-soluble drugs from ethylcellulose

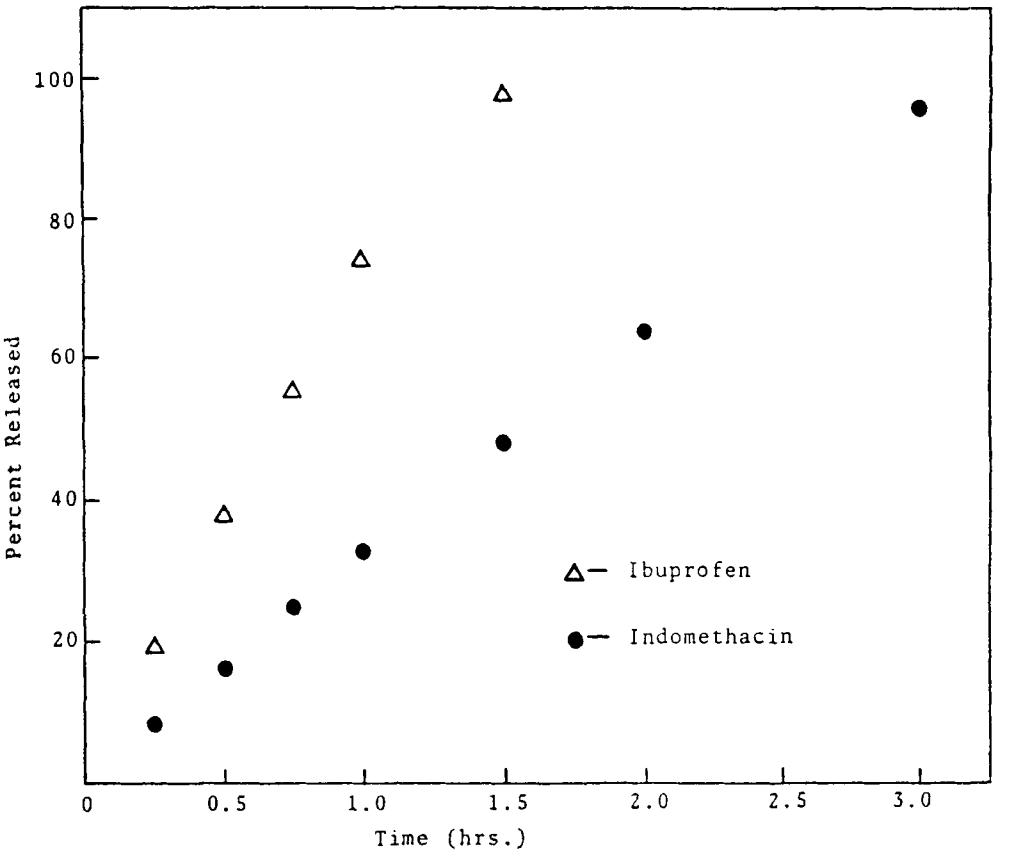

FIGURE 7. Percent of Drug Release from Granular (40/100) Solid Dispersions as a Function of Time.

matrices is more or less similar to the release mechanisms previously observed in the case of water-soluble drugs (13). The only difference is that the rate of release is considerably decreased in the case of sparingly water-soluble drugs compared to water-soluble drugs from similar formulations in the same dissolution medium. This can be explained on the

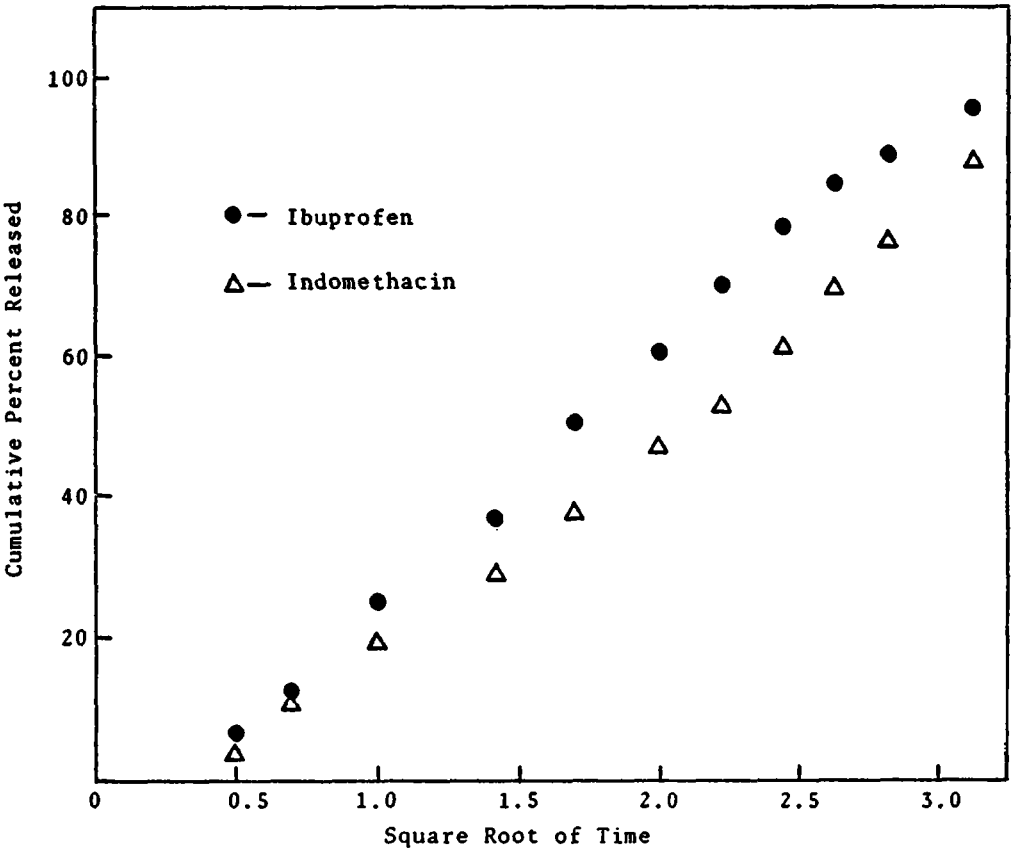

FIGURE 8. Higuchi Plot for Compressed (40/100) Solid Dispersions.

basis that the sparingly water-soluble drugs dispersed in a hydrophobic carrier (ethylcellulose) further increase hydrophobicity and decrease water permeation into the system which in turn further decreases the rate of release.

From the data presented, it can be concluded that ethylcellulose can also be used as a potential

TABLE 7

Summary of Higuchi's Model Fits for Directly Compressed Ibuprofen Solid Dispersions in Sorenson's Buffer

Viscosity grade,cps	Amount of Ethylcellulose								
	7.5%			15.0%			30.0%		
	Intercept	Slope	r^a	Intercept	Slope	r^a	Intercept	Slope	r^a
21	- 7.67	37.90	0.999	- 6.39	36.17	0.999	- 10.37	36.89	0.995
95	- 2.72	32.27	0.991	- 3.72	31.71	0.989	- 6.68	31.33	0.995
209	- 3.41	31.23	0.993	- 7.71	29.29	0.993	- 8.82	29.24	0.990
350	- 3.87	30.65	0.993	- 8.63	28.89	0.993	- 8.51	27.21	0.992

a : Correlation coefficient

TABLE 8

Summary of Higuchi's Model Fits for Directly Compressed Indomethacin Solid Dispersions in Sorenson's Buffer

Viscosity grade, cps	Amount of Ethylcellulose								
	7.5%			15.0%			30.0%		
	Intercept	Slope	r^a	Intercept	Slope	r^a	Intercept	Slope	r^a
21	- 7.51	38.09	0.999	- 8.04	37.37	0.999	- 11.37	37.54	0.994
95	- 2.61	32.58	0.988	- 2.96	32.19	0.988	- 7.66	32.00	0.994
209	- 5.27	33.10	0.990	- 5.56	32.44	0.994	- 10.98	31.77	0.996
350	- 4.03	31.90	0.990	- 11.39	31.31	0.998	- 11.08	29.33	0.994

a : Correlation coefficient

retardent of drug release in prolonged release formulations of sparingly water-soluble drugs such as ibuprofen and indomethacin. While both the amount and viscosity grade of ethylcellulose influence the release of drug from the drug-polymer matrices, the former factor has a greater effect than the latter on the magnitude of release.

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