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THE INFLUENCE OF BINDING SOLVENTS ON DRUG RELEASE FROM HYDROXYPROPYL METHYLCELLULOSE TABLETS

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ABSTRACT

The objective of this project was to evaluate the influence of binding solvents on drug release from hydroxypropylmethylcellulose (HPMC) tablets. The model drug used for this study was Indomethacin. HPMC 4000 and lactose were used to prepare the tablets. The experiment was designed based on a 3x5 factorial design. The drug/polymer ratio was examined at three levels, 2:1, 1:1, and 1:2. At each of these levels the solvent effects were examined at five levels. Within these five levels, four different combinations of water and ethanol (100% water, 60% water 40% ethanol, 40% water 60% ethanol, and 20% water 80% ethanol) were compared with the fifth level which is a matrix tablet prepared by direct compression without any solvents. The dissolution rates of the tablets were monitored using a rotating paddle dissolution apparatus. The cumulative percent of drug dissolved from the three matrix tablets are not significantly different ($p > 0.05$). The cumulative percent of drug dissolved at 2 hr from the various wet granulated tablets are significantly different ($p < 0.05$). Although no rank order correlation was observed among the tablets prepared with 100%, 60%, and 40% water, the cumulative percent of drug dissolved from the tablets prepared with 20% water are significantly lower from the other wet granulated tablets but higher than the matrix tablets.

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INTRODUCTION

Hydroxypropylmethylcellulose (HPMC) is a water soluble polymer which is frequently used in the formulation of controlled release dosage forms (1-3). The mechanisms by which it retards drug release include its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous fluid (4). The drug is released from the matrix by a combination of diffusion through and erosion of the gel (5,6). The drug diffusion through the HPMC matrix depends on the water solubility of the drug (7). The drug release can be modified by changing several formulation factors, such as type of excipients (8,9), presence of surfactant (3,10,11), and the viscosity of the HPMC (12-14).

The drug release through a matrix tablet can be characterized mathematically using the equation 1.

$$M_t/M_\infty = kt^n \qquad (1)$$

where M_t/M_∞ is the fractional release of the drug in time t, k is the kinetic constant, and n is the diffusional exponent for drug release. The value of n indicates the drug release mechanisms. The value of n is 0.5 for Fickian diffusion and 1 for case II diffusion. A value of n greater than 0.5 but less than 1 indicates a non-Fickian or anomalous diffusion, which is a mixture of Fickian and case II diffusion. When n is greater than 1 the drug release occurs through the super case II diffusion (15-17).

The objectives of the present study were to evaluate the influence of binding solvents on drug release from HPMC tablets and to characterize the release mechanisms. The model drug used for this study was indomethacin.

MATERIALS AND METHODS

Materials

Hydroxypropylmethylcellulose 4000 (Aldrich Chemical Co., U.S.A.) and Indomethacin U.S.P. (Spectrum Chemical Manufacturing Co., U.S.A.) were used as received. Lactose (Mallinckrodt Chemical Works, U.S.A.) was used as a diluent. Lubritab (Edward Mendell Co., U.S.A.) was used as a lubricating agent. Varying proportions of ethanol, 95% (Sigma Chemical Co., U.S.A.) was used as binding solvent.

Experimental design

The batch formulae for the tablets are as listed in Table 1. The experiment was designed based on a 3x5 factorial design. The drug/polymer ratio was examined at three levels, 2:1, 1:1, and 1:2. At each of these levels the solvent effects were examined at five levels. Within these five levels, four different combinations of water and ethanol (100% water, 60% water 40% ethanol, 40%

TABLE 1

Batch formula for the HPMC tablets[a]

Formulations	Indomethacin (mg)	HPMC (mg)	Lactose (mg)	Drug:Polymer	Solvent
A_1	40	20	65	2:1	none
A_2	40	20	65	2:1	100% water
A_3	40	20	65	2:1	60% water 40% ethanol
A_4	40	20	65	2:1	40% water 60% ethanol
A_5	40	20	65	2:1	20% water 80% ethanol
B_1	40	40	45	1:1	none
B_2	40	40	45	1:1	100% water
B_3	40	40	45	1:1	60% water 40% ethanol
B_4	40	40	45	1:1	40% water 60% ethanol
B_5	40	40	45	1:1	20% water 80% ethanol
C_1	40	80	5	1:2	none
C_2	40	80	5	1:2	100% water
C_3	40	80	5	1:2	60% water 40% ethanol
C_4	40	80	5	1:2	40% water 60% ethanol
C_5	40	80	5	1:2	20% water 80% ethanol

[a] Each tablet weighs 125 mg

water 60% ethanol, and 20% water 80% ethanol) were compared with the fifth level which is a matrix tablet prepared by direct compression without any solvent.

Preparation of Tablets

The drug, HPMC, and lactose were thoroughly mixed in a V-blender (The Petterson-Kelley Co., U.S.A.) for 10 minutes. The powder mixtures, except for the direct compressed tablets, were moisten thoroughly using either water or a mixture of water and ethanol, and passed through a 12 mesh sieve. The granules were dried at 40^0 C in a standard tray drier for 2 hr. The dried granules were passed through a 8 mesh sieve. The granules, powder mixtures for direct compressed tablets, were mixed with 1% lubritab using a mixing bag for 5 minutes. A weighed amount (125 mg) of the mixture was fed manually into a tablet die of a hydraulic press (Carver Inc., U.S.A.). The tablets were prepared at 3000 lb force using a flat-faced tablet punch and die with a flat steel plate as the lower retainer.

Dissolution Study

The dissolution rates of the tablets were monitored using a Vankel dissolution apparatus (Vankel, U.S.A.). 1000 ml of distilled water was used as dissolution media and the temperature was maintained at 37 ± 1^0 C. The USP II, rotating

paddle dissolution method was used at a rotation speed of 50 rpm. One milliliter samples were collected at various times by means of a filter pipet.

Analysis

The amount of indomethacin dissolved at any time was measured at a wavelength of 318 nm using a spectrophotometer (Beckman, U.S.A.).

Curve Fitting

Curve fitting was performed using the SigmaPlot graphic software package, version 5.0 (Jandel Co., U.S.A.). The dissolution data obtained between 5 and 120 minutes were fitted to the equation 1 and the best fit parameters (k and n) were calculated.

RESULTS AND DISCUSSION

Dissolution profiles are shown in Figures 1-3. The tablets prepared with 100% water as binding solvent showed higher release rates than the others. The amount of drug dissolved at any time t, reported as the average of six tablets. The cumulative percents of drug dissolved at 2 hr from the tablets are listed in Table 2. The cumulative percent of drug dissolved from the three direct compressed matrix tablets (A_1, B_1, and C_1) are not significantly different ($p > 0.05$). It proves that in absence of any solvent the total amount of indomethacin release is independent of the drug/polymer ratio (within the studied range). This observation is similar to the earlier report on the dissolution characteristics of indomethacin from HPMC tablets (12). The cumulative percent of drug dissolved at 2 hr from the various wet granulated tablets are significantly different ($p < 0.05$). This observation suggests that the use of binding solvents can significantly influence the drug release from the HPMC tablets. Although no rank order correlation was observed among the tablets prepared with 100%, 60%, and 40% water, the cumulative percent of drug dissolved from the tablets containing 20% water are significantly lower from the other wet granulated tablets but higher than the direct compressed matrix tablets. This observation suggests that in the preparation of wet granulated tablets, the use of higher amount of water, in the presence of lactose, enhances the dissolution rate. The amount of drug dissolved from the wet granulated tablets are higher than the direct compressed matrix tablets because of the differences in the dissolution mechanism. In the presence of water, the HPMC swells and forms a gel layer surrounding the tablets and drug release occur through the process of diffusion and erosion of the gel layer. The degree of swelling and the gel-forming ability of the HPMC changes in the presence of any solvent during the preparation of the tablets. Kawashima et al., reported that the presence of solvent reduces the gel-forming ability of water soluble cellulose derivative (18). The degree of reduction of this gel-forming ability of cellulose derivative depend on the nature of the solvent used during the wet granulation process. The maximum and minimum reduction of the gel-forming ability

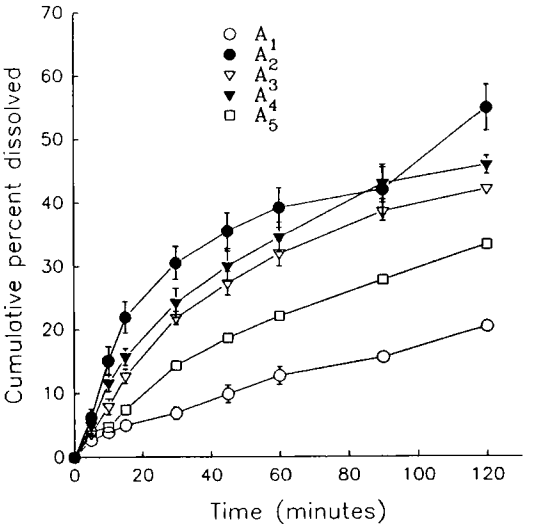

FIGURE 1. Comparison of dissolution profiles of formulations A_1-A_5. Each point represents the mean observation (n=6).

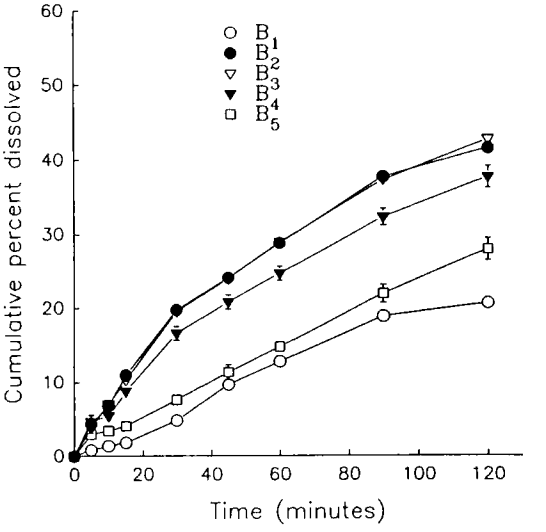

FIGURE 2. Comparison of dissolution profiles of formulations B_1-B_5. Each point represents the mean observation (n=6).

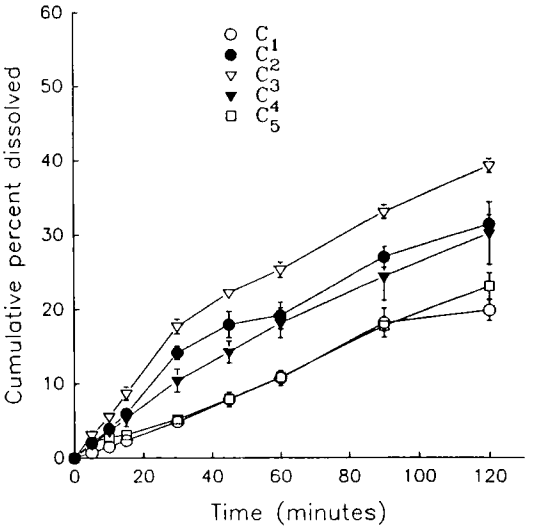

FIGURE 3. Comparison of dissolution profiles of formulations C_1-C_5. Each point represents the mean observation (n=6).

TABLE 2

Average Cumulative Percent of Indomethacin dissolved at 2 hour

Formulations	Mean (SD)	SNK group
A_1	20.40 (0.50)	
A_2	54.82 (3.63)	$A_2 > A_4 > A_3 > A_5 > A_1$
A_3	42.08 (0.29)	
A_4	45.85 (1.41)	
A_5	33.35 (0.63)	
B_1	20.68 (0.42)	
B_2	41.55 (0.79)	$B_3 = B_2 > B_4 > B_5 > B_1$
B_3	42.75 (0.71)	
B_4	37.67 (1.47)	
B_5	27.97 (1.49)	
C_1	19.90 (1.41)	
C_2	31.50 (1.23)	$C_3 > C_2 = C_4 > C_5 > C_1$
C_3	39.35 (0.92)	
C_4	30.25 (4.21)	
C_5	23.17 (1.76)	

SNK=Student-Newman-Keuls Multiple range test, $\alpha = 0.05$

TABLE 3

Best fit parameters, k and n, based on Eqn. $M_t/M_\infty = kt^n$

Formulations	Kinetic constant k	Diffusional exponent n	Coefficient of determination R^2
A_1	0.719 (0.140)[a]	0.693 (4.617)[a]	0.993
A_2	5.332 (0.218)	0.482 (0.107)	0.958
A_3	2.715 (0.228)	0.586 (9.034)	0.973
A_4	3.608 (0.170)	0.543 (7.323)	0.981
A_5	1.372 (0.145)	0.670 (4.973)	0.992
B_1	0.253 (0.436)	0.936 (0.104)	0.973
B_2	2.082 (0.171)	0.635 (6.173)	0.987
B_3	1.910 (0.152)	0.656 (5.305)	0.991
B_4	1.594 (0.136)	0.666 (4.688)	0.993
B_5	0.384 (0.153)	0.896 (3.824)	0.996
C_1	0.189 (0.382)	0.986 (8.597)	0.982
C_2	1.075 (0.251)	0.712 (8.020)	0.980
C_3	1.554 (0.185)	0.680 (6.210)	0.988
C_4	0.659 (9.828)	0.802 (2.764)	0.998
C_5	0.175 (0.251)	1.021 (5.441)	0.992

[a]standard error of mean; n=6

occurred in presence of 100% water and 100% ethanol, respectively, during the wet granulation process. Therefore, the granules prepared with 100% ethanol maintained the sustained drug release characteristics. Whereas, the use of higher amount of water resulted in a faster dissolution rate compared to the compressed matrix tablets.

The best fit parameters along with the coefficient of determination (R^2) values obtained from the equation 1 are listed in Table 3. The high values of R^2 suggest that this equation provides a good fit for the dissolution data. The comparisons of the kinetic constant k indicate that the value decreases with the increasing amount of HPMC in the tablets. Although no particular rank order correlation was obtained, in general, the presence of higher amount of water during the wet granulation process increases the value of k. The parameter n indicates the drug release mechanism. The listed values of n indicate that the values changed significantly due to the presence of water. The drug release from the tablets of formulation A followed non-Fickian or anomalous diffusion in absence of any solvents. The drug release continued to follow the same mechanism as long as the amount of water is low. Otherwise, it followed the simple Fickian diffusion. The drug release from the other two tablets (B_1 and C_1) of formulations B and C,

changed from anomalous to case II diffusion with the increase of HPMC concentration. In these cases the release mechanisms shifted towards the anomalous diffusion with the use of the higher amount of water during the wet granulation processes.

In conclusion, the use of binding solvents during the preparation of HPMC tablets significantly influences the drug release. The drug release increases as the percent of water increases. The presence of solvents, in general, affect the drug release mechanisms from the matrices and the relative proportion of water and ethanol plays a significant role in the release mechanism.

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