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COMMUNICATION

Hydroxypropyl Methylcellulose Mixtures: Effects and Kinetics of Release of an Insoluble Drug

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ABSTRACT

Matrix tablets manufactured from a practically insoluble drug using Methocel K4M, Methocel K100LV, and mixtures thereof exhibited non-Fickian dissolution properties governed by both diffusion and erosion (value of diffusional exponent in Peppas's transport equation 0.7). The effects of these two hydroxypropyl methylcellulose (HPMC) varieties were nonlinear and antagonistic.

INTRODUCTION

A large amount of literature exists concerning the utilization of hydroxypropyl methylcellulose (HPMC) as sustained-release control agent in oral dosage forms employing single types or combinations of them with chemically different polymers or other agents. On the other hand, there is apparently a notable paucity of published data dealing with the use of HPMC mixtures of different varieties. It has been shown that the release of a low-solubility drug from such combinations may be controlled by diffusion (atenolol–Methocel K100M/K100LV) (1). The present communication describes the results of a study of an insoluble, high-dose drug.

MATERIALS AND METHODS

All raw materials were of pharmacopeial (EP) quality. Methocel K4M (nominal viscosity 4000 cP) and Methocel K100LV (nominal viscosity 100 cP) were premium grades (Colorcon, England). The model drug employed contains an acidic vector (pK_a ca. 4.2) and is practically insoluble in water. Other excipients in the tablets were lactose, povidone, and magnesium stearate. Granulations were performed in an intensive mixer (Gral-25), and tablet compression was done in a rotary tableting machine (Manesty B3B).

EXPERIMENTAL

Five 5-kg wet granulations were prepared containing the following percentages of Methocel K4M/K100LV: 0/10, 2.5/7.5, 5/5, 7.5/2.5, and 10/0. Apart from this, the composition of all batches was identical. Following drying, sizing, and mixing with lubricant, the granulations were compacted to a nominal strength of 500 mg and similar hardness (20–23 kg). Subsequently, the tablet

Table 1

Dissolution Values for Percentage Drug Dissolved

Time (hr)	Batch 1: K4M 0%, K100LV 10%	Batch 2: K4M 2.5%, K100LV 7.5%	Batch 3: K4M 5.0%, K100LV 5.0%	Batch 4: K4M 7.5%, K100LV 2.5%	Batch 5: K4M 10%, K100LV 0%
1	36.08 (5.2)	26.20 (3.1)	16.11 (7.7)	9.86 (1.7)	7.87 (5.3)
4	95.53 (1.1)	65.19 (4.4)	39.92 (3.9)	25.78 (1.9)	20.84 (3.4)
8		98.53 (0.6)	65.21 (2.4)	43.10 (1.2)	33.16 (3.1)
12			88.60 (2.4)	59.68 (1.3)	43.91 (3.0)

C.V. values in parentheses.

batches were analyzed for dissolution at the following parameters: $n = 6$; simulated intestinal fluid without enzymes, pH 7.5 (2); 900 ml; 37°C; basket, 50 rpm; automatic ultraviolet quantitation at 280 nm; total time 12 hr.

RESULTS

The dissolution values expressed in percentage drug dissolved for the five batches are shown in Table 1.

DISCUSSION AND CONCLUSIONS

Figure 1 displays the fraction of drug dissolved versus Methocel K4M/K100LV levels in pseudo units (0–1). Evidently, the effects of the polymers are nonlinear and antagonistic. Statistical analysis of the data (Design-Expert, version 4.0.8, Stat-Ease, Inc., Minneapolis, MN) revealed that the fraction of drug dissolved F after 1 and 4 hr is best described by cubic models and after 8 and 12 hr by quadratic models (A and B are the Methocel K4M and K100LV levels, respectively):

$$F(1\text{ hr}) = 0.0792A + 0.3613B - 0.2243AB - 0.1194AB(A - B)$$

$$F(4\text{ hr}) = 0.21A + 0.956B - 0.708AB - 0.11AB(A - B)$$

$$F(8\text{ hr}) = 0.331A + 1.438B - 0.935AB$$

$$F(12\text{ hr}) = 0.4391A + 1.8593B - 1.0527AB$$

Peppas's transport equation $M_t/M_\infty = kt^n$ (M_t/M_∞ fraction

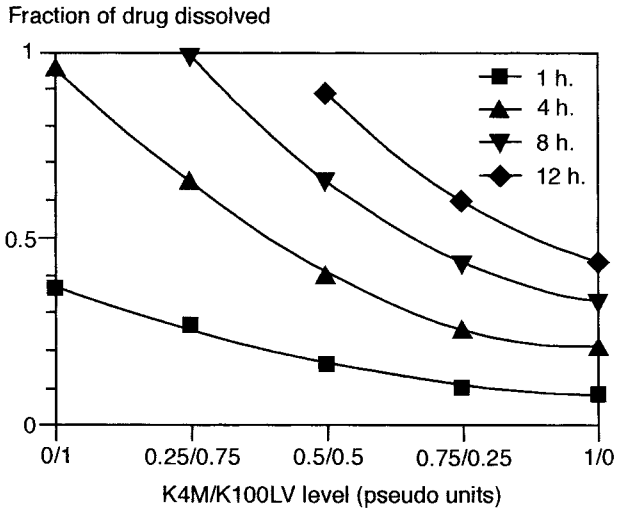

Figure 1. Fraction of drug dissolved versus K4M/K100LV level.

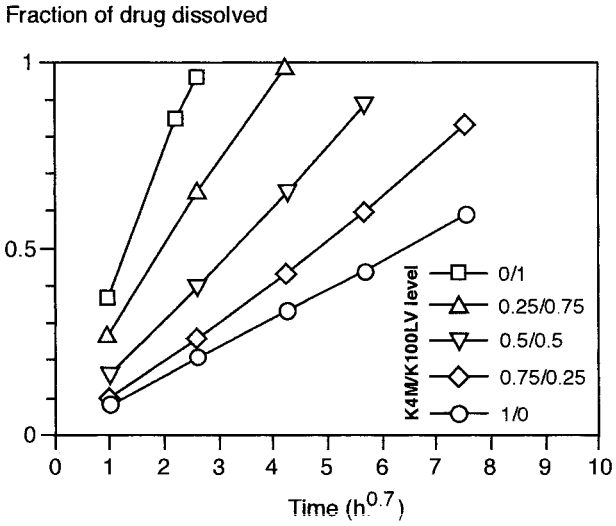

Figure 2. Fraction of drug dissolved versus time ($hr^{0.7}$).

dissolved at time t, with k a constant and n the diffusional exponent) (3,4) was employed to investigate the drug release kinetics from the five formulations. Computation (DeltaGraph, version 2.0, DeltaPoint, Inc., Monterey, CA) furnished a mean value of $n = 0.69$ (range 0.64–0.72). As shown graphically in Fig. 2, in which the fraction of drug dissolved is plotted as function of time ($hr^{0.7}$), the curves for the different Methocel K4M/K100LV levels are not far from linear. This indicates that the drug release is governed by both diffusion and erosion.

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