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COMMUNICATION

Oxazepam Dissolution Rate from Hydroxypropylmethylcellulose Matrices

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ABSTRACT

The effect of some formulation variables on the release rate of oxazepam from hydroxypropylmethylcellulose (HPMC) has been investigated. The principal factors affecting this parameter were the content and molecular weight of HPMC, and the drug particle size. pH modified the oxazepam solubility; however, the liberation mechanism was not affected. The oxazepam release mechanism from these matrices has been examined. Values of the diffusional exponent n were in the range 0.61–0.74, indicating that the release of drug was controlled by both diffusion and erosion. When the tablets contained 30% HPMC K100 and the oxazepam particle size was 0.210–0.250 mm, near-zero-order kinetics was obtained (n = 0.85), indicating that erosion plays an important role in the oxazepam liberation.

INTRODUCTION

Hydrophilic matrix systems have attracted considerable attention in recent years as sustained-release devices for the delivery of drugs. Hydroxypropylmethylcellulose (HPMC) is a hydrophilic cellulose ether widely used as an excipient in controlled-release preparations.

One mechanism proposed for drug release from HPMC matrices involves liquid penetration into the dry matrix, hydration and swelling of HPMC, diffusion of dissolved drug, and erosion of the polymer layer (1–4).

The Higuchi equation (5)

$$Q = [Dt(2A - C_s)C_s]^{1/2}$$

controls the liberation process when the passage of the drug occurs only via diffusion trough the polymer layer. Q is the amount of drug released after time t per unit exposed area, D the diffusivity of the drug, A the total amount of drug present in the matrix per unit volume, and C_s is the solubility of the drug in the matrix.

Korsmeyer et al. (6) used a simple empirical equation to describe general solute release behavior from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t/M_∞ is the fraction of drug release, k a kinetic constant, t the release time, and n the diffusional exponent for drug released. The value of n gives an indication of the release mechanism. When $n = 1$, the release rate is independent of time and is the desirable mechanism in oral controlled drug delivery; $n = 0.5$ for Fickian diffusion; and when $0.5 < n < 1$, the diffusion and non-Fickian transport are implicated (7).

A modification of the Korsmeyer equation, with the introduction of a lag period (t_0) prior to release, is essential to describe accurately the quantity of drug released (8).

$$Q = k(t - t_0)^n$$

where Q is the percentage of drug released at time t and t_0 is the lag time.

The purpose of this study is to examine the effect of various viscosity grades of HPMC, drug particle size, drug:HPMC ratio, and pH on the mechanism of drug released, and specifically, the role of erosion and diffusion in controlling the release of oxazepam. This drug has been utilized as a diffusion model of weak bases.

MATERIALS AND METHODS

Materials

Oxazepam were kindly supplied by Ifidesa Aristegui of Spain. Two viscosity grades of hydroxypropylmethylcellulose (Colorcon, Spain) were used. They were Methocel K100 and Methocel K4M, and their 2% aqueous solutions were 106 and 3850 cps, respectively. Lactose (Panreac), magnesium stearate (Merck Sharp and Dohme of Spain), and Aerosil 200 (Degussa AG) were used as excipients. All the reagents were pure and of analytical grade.

Tablet Formulation

The tablets weighed 100 mg and contained 5 mg oxazepam, 1% magnesium stearate, 0.5% aerosil 200, and a variable amount of lactose. The following variations in tablet formulas were utilized:

a. Effect of viscosity grade of HPMC and oxazepam:HPMC ratio: Using the two viscosity grades of HPMC, tablets were made containing 90, 60, or 30 mg HPMC. The 0.074- to 0.149-mm size fraction of oxazepam was used.
b. Effect of particle size of oxazepam: Tablets were compressed with 30 mg HPMC K100 using size fractions of 0.210–0.250 and 0.074–0.149 mm.

Dissolution Studies

The dissolution rates of the tablets were monitored using a USP23-NF18 dissolution apparatus (Dissolutest 07170025). Every experiment was conducted under the following conditions: 900 ml of dissolution medium was introduced into each of 6 1-liter glass vessels, at 37 ± 0.1°C. The dissolution fluid as either 0.1 N hydrochloric acid or phosphate buffer (pH 4.0). A rotation speed of 100 rpm was used.

Dissolution studies were performed six times for each batch of tablets. Samples were filtered trought a 0.8-mm membrane filter (Prolabo) and the oxazepam concentration was spectrophotometrically determined for pH 1 and pH 4 at 235 and 230 nm, respectively, using a Hewlett-Packard HP 8452A Diode Array Spectrophotometer.

RESULTS AND DISCUSSION

Evaluation was carried out of the effect on the drug released, of the content and molecular weight of the polymer, oxazepam particle size, and pH. According to the Higuchi equation (5), the dissolution profiles of oxazepam with HPMC were plotted as square root of time (Fig. 1). In general, observations showed deviations of the linearity and the existence of a lag period. Therefore, the results were fitted to the modified Korsmeyer equation:

$$Q = k(t - t_0)^n$$

The values of k, t_0, n, and the coefficient of determination, r^2, following regression of dissolution data, are given in Table 1. The t_0 values were similar to the lag times obtained by Higuchi-type equation:

$$Q = bt^{0.5} + a$$

with b presented as a root time dissolution rate constant and a as a constant. The lag period is defined as $-a/b$.

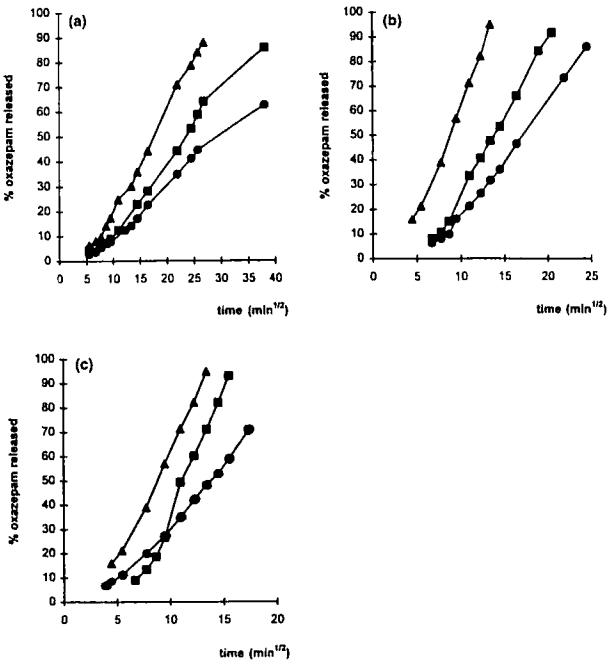

Figure 1. Oxazepam dissolution profiles from HPMC matrices (37°C, 100 rpm, pH 1). (a) HPMC K4M (%): ●, 90; ■, 60; ▲, 30. (b) HPMC K100 (%): ●, 90; ■, 60; ▲, 30. (c) HPMC K100 (30%): ▲, 0.074- to 0.149-mm size; ■, 0.210- to 0.250-mm size; ●, pH 4.

The k values confirm earlier findings (8–16) that the dissolution rates from HPMC matrices decreases with an increase in polymer content. In general, the lag times t_0 were almost unaffected by the HPMC quantity, which is in accordance with the results obtained by Ford et al. (8) for HPMC K15M matrices, containing promethacine hydrochloride. The low value of t_0 in matrices with 30% HPMC K100 is in relation with the low content and viscosity of the polymer.

As the molecular weight of polymer increased, the release rate (k) of oxazepam decreased, when the HPMC content was 60% and 30%. Many authors have reported this conclusion (17–20). No relationship was found between the lag time t_0 and the viscosity.

It is observed in our study that the content and molecular weight of HPMC does not modify the release mechanism. The n values (0.61–0.74) showed that the oxazepam release from HPMC matrices were a mixture of both erosion and diffusion control; however, the main mechanism of release was by diffusion. This is in accordance with the results obtained by Pérez-Marcos et al. (16) for HPMC K4M matrices containing propanolol hydrochloride.

At constant drug:HPMC ratio, the oxazepam dissolution rates (k) decreased as the particle size increased, which is in accordance with the results of Ford et al. (13) for HPMC K15M matrices containing indomethacin. However, the lag time t_0 and the n values increased when the oxazepam particle size was 0.210–0.250 mm. In this case, the erosion was the most important factor controlling the rate of drug release from the system. It was indicative of a near-zero-order release. Ford et al. (13) found also that for HPMC K15M containing diazepam, $n = 0.85$, aproximating zero-order kinetics.

The oxazepam release rate (k) is reduced when the pH increased. At pH 4 the oxazepam solubility decreases and this factor affects the release rate. Malfroid and Bentejac (10) and Meddeb et al. (14) obtained similar results by modifying the pH. In our study the lag time t_0 and the release mechanism were not affected.

Table 1

Values of k, t_0, n, and r^2 for Oxazepam–HPMC Matrices (Particle Size 0.074–0.149 mm; pH 1; 100 rpm)

	HPMC K4M (%)			HPMC K100 (%)				
	90	60	30	90	60	30	30[a]	30[b]
k (min^{-n})	0.78	0.87	0.94	0.77	1.52	2.14	1.05	1.08
t_0 (min)	28.1	27.3	20.6	33.5	37.8	5.8	37.0	3.9
n	0.61	0.64	0.69	0.74	0.69	0.73	0.85	0.73
r^2	0.98	0.98	0.99	0.99	0.99	0.99	0.99	0.99

[a]Particle size: 0.210–0.250 mm.
[b]pH 4.

CONCLUSIONS

The oxazepam release mechanism from HPMC matrices is controlled by both diffusion and erosion. Drug particle size has an influence. An increase on this factor may be that erosion of the HPMC matrices becomes an important factor in the liberation of the drug. In this case, the release mechanism is near-zero-order (n = 0.85). The lag time and the oxazepam liberation are affected by particle size.

The content and molecular weight of HPMC have an influence on the oxazepam release rates but do not modify the release mechanism.

pH affects the release rate because it modifies the oxazepam solubility; however, the lag time and the liberation mechanism are not affected.

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