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COMMUNICATION

Release of Acetazolamide from Swellable Hydroxypropylmethylcellulose Matrix Tablets

Betül Dortunç* and Nesrin Günal

Marmara University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 81010 Istanbul, Turkey

ABSTRACT

Controlled-release swellable tablets were prepared by a simple direct compression process using hydroxypropylmethylcellulose (HPMC) as the matrix former. The effects of the viscosity and concentration of the polymer and the pH of the dissolution medium on the release behavior of acetazolamide were investigated. The influence of the drug particle size was also evaluated. Ten, 15, 20, and 25% of two different viscosity grades of HPMC were dry mixed with acetazolamide, Fast Flo Lactose, and magnesium stearate, then directly compressed into tablets. The experimental tablets were tested for their drug contents, weight variations, and hardnesses. Dissolution tests were carried out under sink conditions at three different pH values: pH 1.2, 5.4, and 7.4. Release rate data were evaluated according to the equation $\log M_t/M_\infty = \log k + n \log t$.

INTRODUCTION

Acetazolamide is an inhibitor of carbonic anhydrase and is extensively used in medicine in the treatment of glaucoma or as a diuretic drug. As it has a half-life of 4.1 hr, a controlled-release system is regarded as desirable to produce minimal plasma fluctuations and to decrease adverse drug reaction incidences (1).

The purpose of this study was to achieve controlled release of acetazolamide by preparing swellable systems using hydroxypropylmethylcellulose (HPMC) as matrix former.

*To whom correspondence should be addressed.

EXPERIMENTAL

Materials

Acetazolamide (mean particle size: Az 1 = 98 mm (DIF), Az 2 < 1 mm [Cyanamid]), Methocel K4M, K15M (Colorcon), Fast Flo Lactose (FMC), and Mg stearate (Merck), were used. Dissolution media included pH 1.2 = simulated gastric fluid without enzymes, pH 5.4 mixture of pH 1.2 (200 ml), and pH 7.4 (800 ml) solutions, and pH 7.4 phosphate buffer solution (USP XXII). Other chemicals were all of analytical grade and were used as received.

Methods

Solubility Measurement of Acetazolamide Samples at Various pH Values

Acetazolamide (Az 1 and Az 2) in an amount in excess of its solubility was dispersed in 50 ml of dissolution media in a 100-ml stoppered bottle and shaken in a wet bath at 37°C until saturation. Samples of 0.2 ml were withdrawn, diluted, and assayed spectrophotometrically at 265 nm (Shimadzu UV 2100). Calibration curves were used for the determination of the amounts dissolved. Mean values of three determinations are given.

Formulation and Preparation of the Matrix Tablets

Ten, 15, 20, and 25% of two different grades of HPMC (K4M and K15M) were dry mixed with 56% acetazolamide, a sufficient quantity of Fast Flo Lactose to make the tablets 900 mg, and 1% magnesium stearate, then directly compressed into oblong tablets weighing 900 mg and containing 500 mg drug (Manesty Tablet Press). For each formulation the minimum compression force necessary to form a tablet was chosen.

Assay of the Tablets

Three tablets of each formulation were determined according to the TF 1974.

Weight Variation of the Tablets

For each formulation, 10 tablets were examined.

Hardness of the Tablets

Three tablets of each formulation were examined using Monsanto hardness tester.

Dissolution Rate Studies

The dissolution rates of the pure drug samples and the matrix tablets were studied using USP paddle method at 100 rpm, 37°C, and under sink conditions (Modal-Technik AG-4000). One hundred-milligram samples of pure drug and tablets containing 500 mg acetazolamide were added to 900 ml of the dissolution media pH 1.2, 5.4, and 7.4. Certain volumes were withdrawn and replaced with fresh medium at fixed time intervals. The samples were assayed spectrophotometrically at 265 nm after suitable dilution. The dissolution of acetazolamide samples and matrix tablets was determined over a period of 1 hr and 12 hr, respectively. It was shown by TLC that the drug is stable under these conditions (2). No interference of the ingredients was determined. The reported data are the means of three determinations.

RESULTS AND DISCUSSION

Controlled drug release systems are subject to important pH changes of pH 1.2 to 8.0 in the gastrointestinal tract. The pH of 1–2 for an empty stomach may change due to the type of food it receives. The amount of food and personal differences affect the rate of emptying of the stomach, too. The pH of the intestine is 6.4 when empty and can be 7.75 when full. For these reasons, instead of determining the release rate at intestinal pH, where the drug remains longest, it should be tested at the different pHs it is likely to meet in the body, to get a good in vitro–in vivo correlation. In this work three different pH values were used for the solubility and dissolution rate tests of the drug and for the evaluation of the systems prepared.

The equilibrium solubility of pure acetazolamide in dissolution media pH 1.2, 5.4, and 7.4 was found to be 1.25 mg/ml, 1.54 mg/ml, and 2.64 mg/ml, respectively. The solubility of acetazolamide, a weak acid, increases with increasing pH. The dissolution rate data of the pure acetazolamide samples are in compliance with the solubility results.

Tablet shaped matrix systems were prepared using HPMC, an inert hydrophilic polymer, by direct compression method due to its easy and economic application (3,4). HPMC is directly compressable, but as the drug/polymer ratios used in this work were not suitable for direct compression, Fast-Flo Lactose was added because of its good flowability and compressability. For each formulation the lowest pressure necessary was

applied. Tablets with crushing strengths from 9 to 15 kg were obtained. Hardness slightly increased with increasing amount of HPMC, but the differences in the applied pressure and the resulting tablet strengths are reported to have no effect on the release of the drug from hydrophilic matrices. Drug release proceeds via diffusion through the gel layer and/or erosion of this layer and is apparently independent of the state of the dry polymer matrix (5,6).

All the tablets were acceptable in regard to weight variation and acetazolamide content. The dissolution analysis was run at three different pH values over a 12-hr dissolution time span and some of the results are shown in Figs. 1 and 2. To characterize the release mechanism, the dissolution data ($M_t/M_\infty < 0.60$) were evaluated according to the equation:

$$\log M_t/M_\infty = \log k + n \log t \quad (7)$$

The release of the drug from the matrices decreases when the polymer amount is increased. The viscosity of the polymer also affects the release rate. The higher the viscosity grade, the slower the release rate. Increase in polymer amount, molecular weight, and viscosity leads to an increase in the gel layer and therefore to a slower release of the drug (3,5,7–9). Acetazolamide is a weak acid with pK_a 7.2 and the release rate is markedly affected by the pH of the dissolution medium. All these effects on the release rate can also be determined by examining the k values in Table 1. Among these systems the matrix tablets containing 10% K4M showed the desired results, but as these matrices didn't always maintain their integrity while swelling, the system containing 15% K4M was preferred for optimization. In order to increase the rate and amount released from this system with 15% K4M, it was prepared with an acetazolamide sample having particles smaller than 1 mm (Az 2) and tested. The desired rate and amount of release, namely 500 mg/12 hr, was achieved as shown in Fig. 3.

The release mechanism of the drug from almost all the matrices follows a nearly Fickian path; the values of *n* show deviations according to the polymer ratio, polymer type, and pH of the dissolution media (Table 1). The results shown are the means of three experiments.

CONCLUSIONS

A successful controlled-release swellable matrix tablet containing 500 mg acetazolamide was prepared by di-

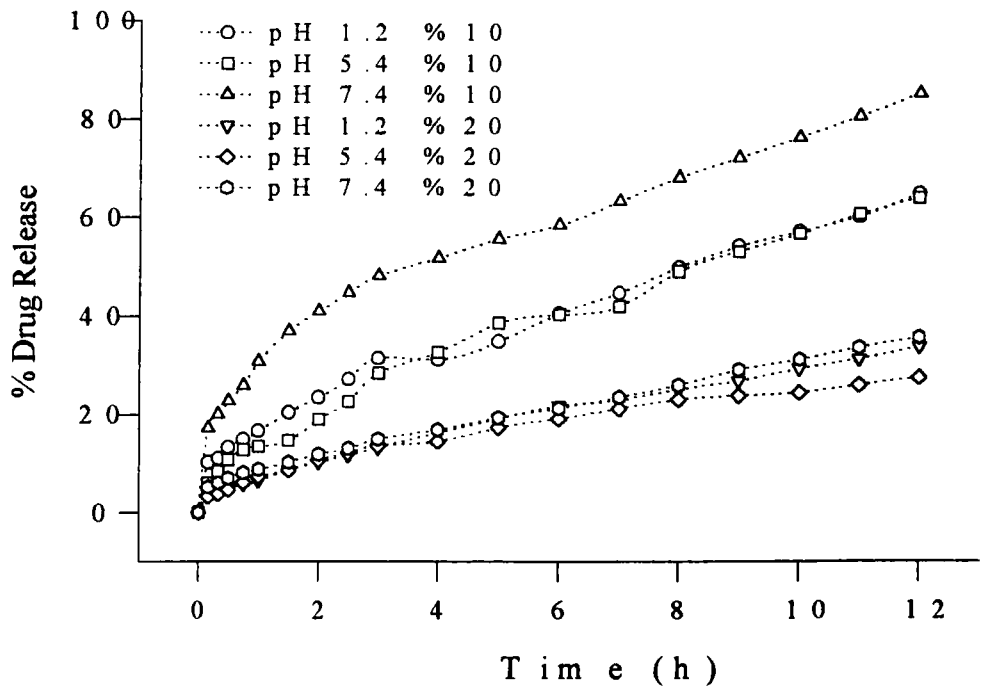

Figure 1. Acetazolamide release from the matrices prepared with 10% and 20% HPMC K4M.

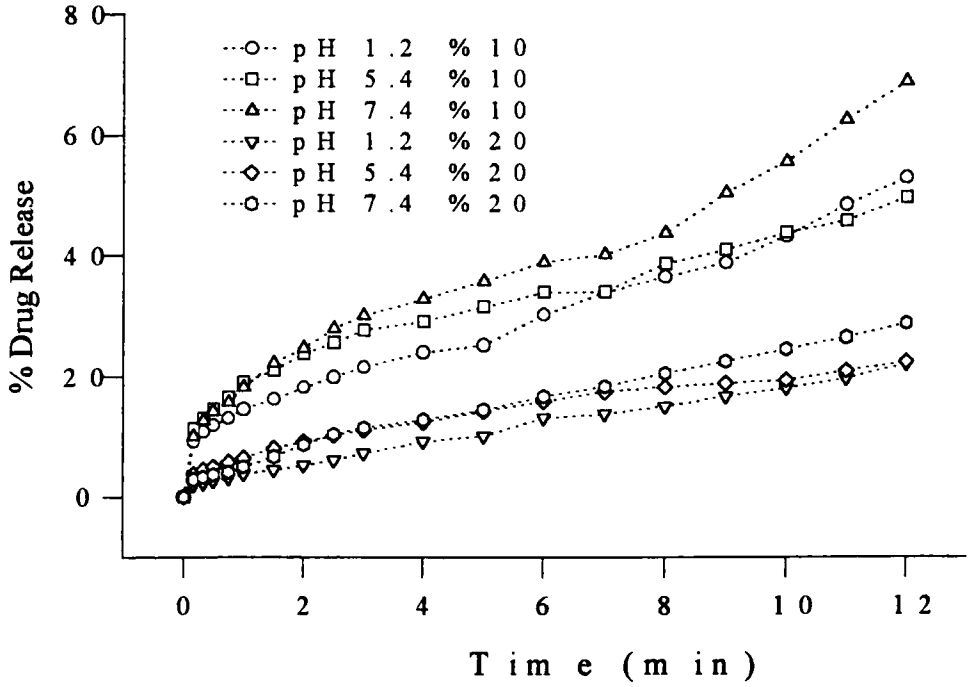

Figure 2. Acetazolamide release from the matrices prepared with 10% and 20% HPMC K15M.

Table 1

Release Mechanism Parameters Found

Methocel Type Ratio	pH	K4M 1.2	K4M 5.4	K4M 7.4	K15M 1.2	K15M 5.4	K15M 7.4
10%	k	0.029	0.015	0.068	0.029	0.046	0.036
(Az 1)	n	0.453	0.563	0.369	0.406	0.343	0.406
	r	0.989	0.992	0.994	0.976	0.994	0.993
15%	k	0.012	0.009	0.021	0.012	0.006	0.026
(Az 1)	n	0.552	0.596	0.479	0.465	0.561	0.418
	r	0.988	0.994	0.989	0.984	0.997	0.981
15%	k	0.027	0.012	0.027	—	—	—
(Az 2)	n	0.430	0.586	0.490	—	—	—
	r	0.977	0.994	0.985	—	—	—
20%	k	0.008	0.008	0.014	0.003	0.011	0.012
(Az 1)	n	0.563	0.530	0.469	0.611	0.444	0.505
	r	0.987	0.997	0.986	0.987	0.995	0.843
25%	k	0.009	0.007	0.007	0.003	0.005	0.005
(Az 1)	n	0.445	0.464	0.584	0.589	0.504	0.564
	r	0.986	0.990	0.987	0.981	0.995	0.983

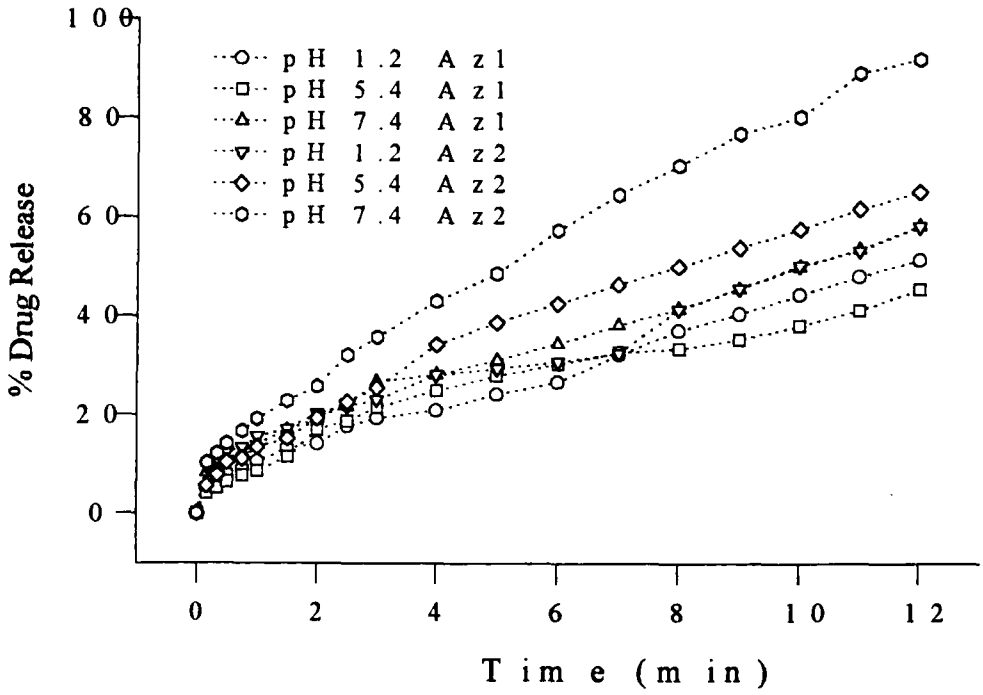

Figure 3. Release from the matrices prepared with 15% HPMC K4M and the acetazolamide samples with mean particle sizes of Az 1 = 98 mm and Az 2 < 1 mm.

rect compression and with 15% K4M matrix former. The drug was released over the targeted period of 12 hr with a mechanism that nearly fits Fick's Law.

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