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Report

Drug Release from Tablets Containing Cellulose Acetate Phthalate As an Additive or Enteric-Coating Material

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A formulation containing cellulose acetate phthalate for preparing enteric-coated granules was developed with the use of granulation and microencapsulation techniques. Drug release from tablets or tabletted microcapsules was measured in a disintegration apparatus and an *in vitro* variable-pH release simulator of the flow type. The release mechanism for the tablets or tabletted microcapsules was determined with the Higuchi matrix model, a first-order kinetic model, and the Weibull distribution function. Adding acetone directly to the mixture of sulfamethoxazole and cellulose acetate phthalate resulted in enteric-coated granules with more prolonged release than other granulation methods. Microencapsulation of the granules significantly delayed the drug release and enhanced the effectiveness of the enteric coating. Microencapsulated granules show release patterns that are sustained and can be simulated with three different release models, i.e., with square-root time plotting, diffusional first-order plotting, and Weibull distribution plotting. The enteric-coating behavior of the tablets was more clearly demonstrated with the variable-pH release simulator than with a fixed-pH dissolution method.

KEY WORDS: microencapsulation; cellulose acetate phthalate; enteric-coated granules; drug release *in vitro;* sulfamethoxazole.

INTRODUCTION

Cellulose acetate phthalate is a physiologically inert polymer widely used as an enteric-coating material. The pH dependence of cellulose acetate phthalate, which is due to the presence of ionizable phthalate groups, has already been studied (1–3). Many formulations also employ cellulose acetate phthalate in waterproof coats and in enteric coats for tablets, pills, and granules (4,5). We have previously used spray-dried solutions containing the ammonium salts of cellulose acetate phthalate and sulfamethoxazole for the purpose of preparing enteric-coated microcapsules (6); however, interactions between cellulose acetate phthalate and sulfamethoxazole occurred during spray-drying (7). In the present study, a simple procedure was developed with cellulose acetate phthalate for preparing enteric-coated granules. These granules were tabletted in order to compare their release behavior. Furthermore, the granules were microencapsulated with ethylcellulose by a coacervation-phase separation method. Drug release from tablets or tabletted microcapsules was also determined with a disintegration apparatus and an *in vitro* release simulator to evaluate their enteric coation function.

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MATERIALS AND METHODS

Preparation of Granules

The formulations for preparing enteric-coated granules are tabulated in Table I, and the preparation methods were as follows.

Method I: Formulation A

Sulfamethoxazole (Shionogi Pharm. Co., Japan) and different sizes of cellulose acetate phthalate powders (CAP; Kishida Chem. Co., Japan) were mixed in a plastic vinyl bag for 7 min by hand shaking, then transferred to a large-volume mortar (Labo-mill, Yamato, Japan) and mixed for 5 min. A 10% (w/v) acacia (Wako Pure Chem. Indus., Japan) solution was slowly added and kneaded for 7 min. The mass was granulated in a wet granulator (Erweka, FRG) and dried in a fluid-bed drier (Glatt, FRG) at 50°C for 30 min.

Method II: Formulation B

Sulfamethoxazole was placed in a large-volume mortar, and a 10% (w/v) CAP–acetone solution was added drop by drop and kneaded until the acetone was nearly evaporated. A 10% (w/v) acacia solution was slowly added, and the mixture kneaded for 7 min and then treated as in method I.

Method III: Formulation C

The granulation procedure of method III was similar to that of methods I and II. Acetone was slowly added before a 10% (w/v) acacia solution was added.

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Table I. Formulations for Preparation of Enteric-Coated Granules

Formulation	Sulfamethoxazole (g)	Cellulose acetate phthalate (g) 60–80 mesh	80–150 mesh	150–200 mesh	>200 mesh	10% acetone solution (ml)	Acetone (ml)	10% acacia solution (ml)
A_1	20	20						40
A_2	20		20					40
A_3	20			20				40
A_4	20				20			40
B_1	40					15		20
B_2	40					30		20
B_3	40					60		20
B_4	40					90		20
C_1	20				20		20	10
C_2	20				20		40	10

All the granules were sieved into suitable fractions with JIS standard sieves. Granule sizes between 32 mesh (500 μm) and 80 mesh (177 μm) were used for tabletting. Mixtures (1:1) of fractioned granules and microcrystalline cellulose (Avicel-101, Asahi Kasei Kogyo K.K., Japan) were tabletted in a single-punch tablet machine (Erweka, FRG).

Preparation of Microcapsules

Granules (5 g), ethylcellulose (3 g; Ethocel 100 cps; ethoxy content, 49.5%; Dow Chemical Co., USA), and cyclohexane solution (300 ml) were used for microencapsulation. The microcapsules were prepared by a phase separation method similar to that previously described (8–10). The microcapsules were mixed with microcrystalline cellulose (1:1) and tabletted with a single-punch tablet machine.

Dissolution Studies of Tablets

The dissolution test of a tablet was undertaken using the JP IX disintegration apparatus and test solution (pH 1.2 and pH 7.5) at 37°C. Tests were also conducted with an *in vitro* release simulator with a flow-type dissolution container in which the pH of the medium was continuously changed to simulate the pH change on the surface of the tablets in the GI tract. The apparatus and dissolution method were previously described (6). Sulfamethoxazole in the medium was determined spectrophotometrically (pH 1.2, 267 nm; pH 7.5, 258 nm) with a double-beam spectrophotometer (Model 556, Hitachi, Japan).

Dissolution Data Analysis

The release mechanisms of drugs from matrix was analyzed via three different models.

Higuchi Matrix Model

Drug diffusibility from the matrix is the rate-determining factor in the release mechanism (11) according to Eq. (1).

$$Q = [D(2A - C_s)C_s t]^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area at time t, D is the drug's apparent diffusion coefficient in the matrix, A is the total drug content, and C_s is the drug solubility. Equation (2), describing drug release from the microcapsules or pellets, can be derived from Eq. (1) (12).

$$C_r = 100 \cdot S_v(2DC_s t/A)^{1/2} \quad (2)$$

where C_r is the percentage of drug released and S_v is the specific surface area. This equation describes drug release (%) as a function of the square root of time and can be simplified:

$$C_r = K_h t^{1/2} \quad (3)$$

$$K_h = \text{slope} = 100 \cdot S_v(2DC_s/A)^{1/2} \quad (4)$$

where K_h is the slope of the linear plot and represents the release rate constant.

First-Order Kinetics

The classical first-order equation was used for evaluation of a membrane-controlled mechanism of the encapsulated drug. The diffusion law can be expressed as follows (13):

$$\log W = \log W_o - \frac{K_f t}{2.303} \quad (5)$$

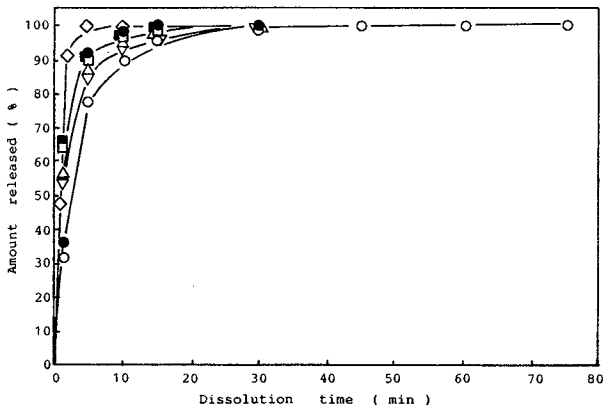

Fig. 1. Release of sulfamethoxazole from tablets prepared from Formulation A. (◇) Sulfamethoxazole powder; (△) Formulation A_1; (□, ■) Formulation A_2; (▽) Formulation A_3; (○, ●) Formulation A_4. Open symbols, in pH 1.2; filled symbols, in pH 7.5.

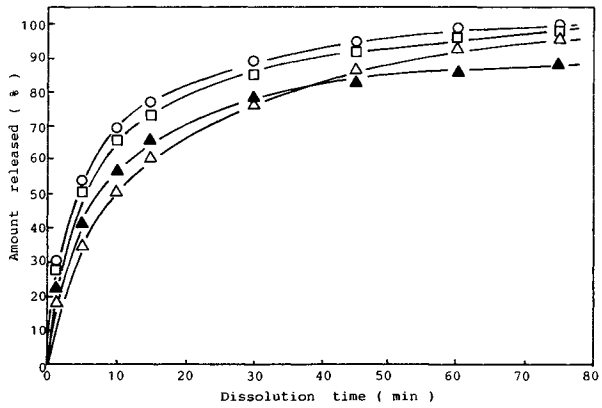

Fig. 2. Release of sulfamethoxazole from tablets prepared from Formulation B in pH 1.2 solution. (○) Formulation B_1; (□) Formulation B_2; (△) Formulation B_3; (▲) Formulation B_4.

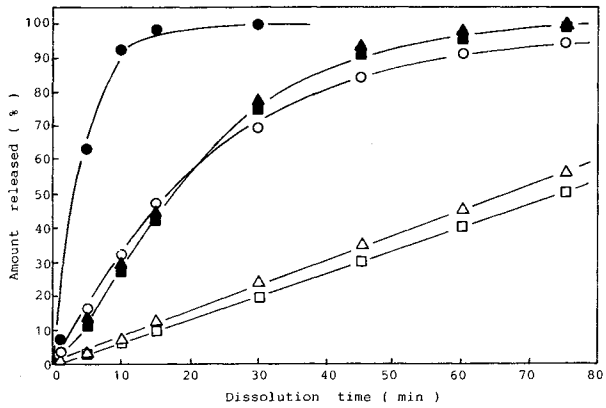

Fig. 4. Release of sulfamethoxazole from tabletted microcapsules prepared from different formulations. (○, ●) Formulation A_3 MC; (△, ▲) Formulation B_1 MC; (□, ■) Formulation B_4 MC. Open symbols, in pH 1.2; filled symbols, in pH 7.5. MC, microcapsules.

where W_o is the initial quantity of drug in the matrix, W is the quantity of drug remaining in the matrix, and K_f is a first-order release constant.

Weibull Distribution Function

Since the tablets quickly disintegrated into small granules after which dissolution started, the Weibull distribution was used to fit the dissolution curves (14).

$$\log[-\ln(W/W_o)] = b\log(t - T_i) - \log a \quad (6)$$

$$a = (T_d)^b \quad (7)$$

where a is a scale parameter and b is a shape parameter. T_i is a location parameter, and T_d represents the time interval necessary to dissolve 63.2% of the drug.

RESULTS AND DISCUSSION

Dissolution Behavior of Tablets in the Disintegration Apparatus

Drug release from the tablets prepared with CAP as an additive (Formulation A) in the disintegration test solutions was determined with a disintegration apparatus (Fig. 1). The tablets disintegrated immediately in both pH 1.2 and pH 7.5 solutions, leading to a fast dissolution rate of the drug. Therefore, CAP in this formulation did not show any enteric-coating property. When CAP–acetone solution was directly added to the sulfamethoxazole particles (Formulation B), the dissolution rate of these tablets was slower than that of Formulation A tablets (Fig. 2). The larger the amount of CAP–acetone solution, the more delayed the dissolution rate. Possibly CAP is coated onto the sulfamethoxazole particles, forming an enteric-coating film with a resulting slower dissolution rate. However, in the initial 40 min of dissolution, tablets prepared with 90 ml of CAP–acetone solution resulted in a higher dissolution rate than tablets prepared with 60 ml of CAP–acetone solution. Scanning electron microscopy suggested that sulfamethoxazole dissolves in acetone and salts out to some degree on the surface of the CAP agglomerates during drying. Formulation C, in which ace-

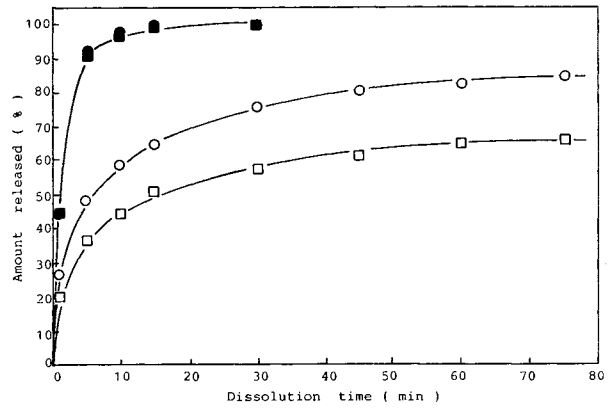

Fig. 3. Release of sulfamethoxazole from tablets prepared from Formulation C. (○, ●) Formulation C_1; (□, ■) Formulation C_2. Open symbols, in pH 1.2; filled symbols, in pH 7.5.

Table II. Evaluation of the Release Mechanism of Sulfamethoxazole Release from Different Types of Tablets

Formulation	Release mechanism		
	First-order kinetic (r^2)[a]	Higuchi matrix model (r^2)	Weibull function (r^2)
A_1	− (0.9884)	− (0.9637)	− (0.9889)
A_2	− (0.9898)	− (0.9736)	− (0.9638)
A_3	− (0.9840)	− (0.9825)	− (0.9763)
A_4	− (0.9825)	− (0.9845)	− (0.9504)
B_1	− (0.9813)	+ (0.9983)	− (0.9794)
B_2	− (0.9846)	+ (0.9973)	− (0.9877)
B_3	− (0.9837)	+ (0.9989)	− (0.9761)
B_4	− (0.9763)	+ (0.9979)	− (0.9894)
C_1	− (0.9874)	− (0.9837)	+ (0.9950)
C_2	− (0.9843)	− (0.9869)	+ (0.9941)
A_3 MC[b]	+ (0.9996)	+ (0.9954)	+ (0.9978)
B_1 MC	+ (0.9957)	+ (0.9995)	+ (0.9953)
B_4 MC	+ (0.9967)	+ (0.9987)	+ (0.9992)

[a] Linear regression coefficient of slope.
[b] Microcapsule.

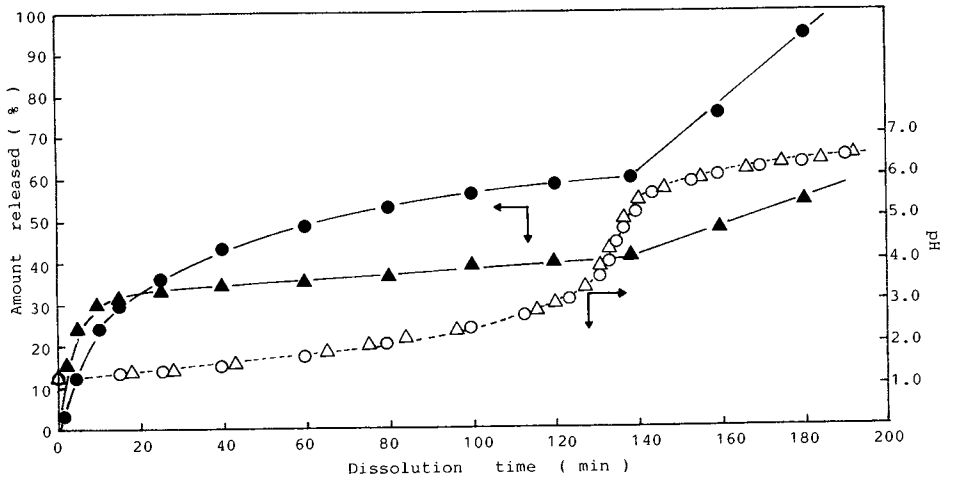

Fig. 5. Drug release (filled symbols) and pH change (open symbols) patterns in a flow-type simulator for tablets prepared from Formulation C. (○, ●) Formulation C_1; (△, ▲) Formulation C_2.

tone was directly added to the mixtures of sulfamethoxazole and CAP, produced the dissolution curve shown in Fig. 3. Drug release from these tablets was significantly slower at pH 1.2 than at pH 7.5. The effectiveness of the enteric-coating of Formulation C was greater than that of other formulations. Furthermore, the larger the amount of acetone used, the slower the dissolution behavior.

Drug released from the tabletted microcapsules is shown in Fig. 4. The dissolution curves in the pH 7.5 solution were distinguished by their much faster release rate from those in the pH 1.2 solution, and the prolonged-release behavior of tabletted microcapsules in the acidic solution was pronounced, showing again the effectiveness of the enteric coating of the microencapsulated granules. This result might have been due to the fact that the microencapsulated granules were compressed, forming a CAP–ethylcellulose matrix-like pellet that resulted in the prolongation of drug.

The release mechanism of tablets prepared with different granulation methods and microencapsulation technique was examined. Three different models of the release mechanism were tested with Eqs. (1) to (7). The linearity of slope was evaluated by estimating their linear regression coefficients (Table II). Drug release from Formulation A does not conform with any of the release mechanisms because of rapid disintegration and dissolution. Formulations B and C fit the Higuchi matrix model and Weibull function, respectively. However, the release from tabletted microcapsules fit the three different release mechanisms equally well. This suggests that the microencapsulated granules belonged to the prolonged-release matrix-type pellets.

Dissolution Behavior of Tablets in a Flow-Type Simulator

As an orally administered drug preparation moves from the stomach (pH 1–3) through the pylorus to the duodenum (pH 5–7), its pH environment continuously changes. The upper small intestine is likely to be slightly acidic. Thus, to simulate the *in vivo* pH environment, it was desirable to conduct the enteric test in a dissolution medium whose pH continuously changes from 1.2 to 7.0 rather than in a me-

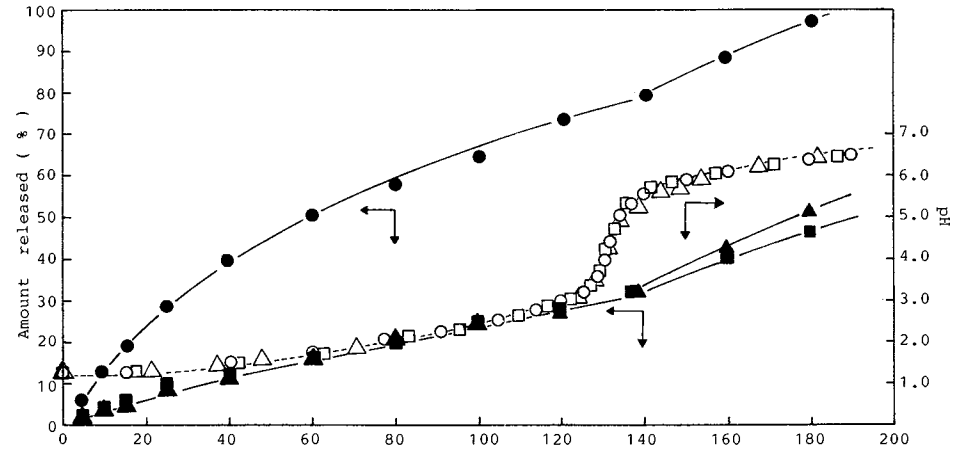

Fig. 6. Drug release (filled symbols) and pH change (open symbols) patterns in a flow-type simulator for tabletted microcapsules prepared from different formulations. (○, ●) Formulation A_3 MC; (△, ▲) Formulation B_1 MC; (□, ■) Formulation B_4 MC. MC, microcapsules.

dium with a fixed pH. Release patterns of tablets prepared from the mixtures of microcrystalline cellulose and the different granules with or without microencapsulation were examined with an *in vitro* release simulator (Figs. 5 and 6). The pH change of the medium from 1.2 to 7.0 with dissolution time followed a sigmoidal curve, with only small changes between experiments. The drug release from tablets prepared from Formulation C was relatively fast over 20 min, followed by a constant release rate (Fig. 5). After the dissolution time of 140 min at pH 5.0–5.5, the release rate increased rapidly again, which caused an inflection on the release curves. It is reasonable to assume that this inflection point corresponds to the starting point of the enteric action. This result agreed with release profiles of the enteric-coated microcapsules prepared by the spray-drying technique (6). Moreover, the present study also confirms that CAP dissolves at approximately pH 5.4 (15). The release pattern of the tabletted microcapsules did not clearly indicate the inflection point on the release curves, but after pH 5.4 was reached the dissolution rate tended to increase (Fig. 6). The present study suggests that the enteric-coating activity of the tablets was more clearly demonstrated with the flow-type variable-pH release simulator than by studying dissolution at a constant pH value.

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