Application of Curdlan to Controlled Drug Delivery. I. The Preparation and Evaluation of Theophylline-Containing Curdlan Tablets

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To study the use of curdlan, a natural β-1,3-glucan, in drug delivery, *in vitro* release studies were carried out with curdlan tablets containing theophylline. Tablets were readily prepared by compressing three different curdlan and theophylline mixtures, namely, a physical mixture, spray-dried curdlan particles with theophylline powder, and spray-dried particles of curdlan/theophylline solution. Drug release from the tablets prepared from spray-dried particles of curdlan/theophylline was lowest. The release rate was constant from 1 to 8 hr, and 59% cumulative release was obtained at 8 hr. Drug release from curdlan tablets was unaffected by pH or various ions; these curdlan tablets might also control drug release *in vivo* after oral administration. Application of Higuchi's equation indicated that drug release from curdlan tablets was diffusion-controlled. The release profiles of the curdlan tablets were compared to those of a commercial theophylline sustained-release tablet.

KEY WORDS: curdlan; tablets; controlled-release; theophylline; spray-dried particles; non-disintegrable preparations.

INTRODUCTION

The polysaccharide curdlan (β-1,3-glucan) is produced by a mutant strain (10C3K) of the bacterium, *Alcaligenes faecalis* var. *myxogenes* 10C3. This linear homopolymer is not water soluble but dissolves in alkaline solutions. When a curdlan suspension is heated to 60°C and cooled, a thermally reversible gel is obtained (low-set gel). On the other hand, a firm resilient gel, which is thermally irreversible, is formed at 80°C or higher (high-set gel). The low-set gel is formed by three-dimensional network structure of hydrogen bonds, while the hydrophobic bonds, in addition to hydrogen bonds, are formed in a high-set gel (1,2). The high-set gel appears to have rigid three-dimensional network structure compared to a low-set gel (2). The gel strength also depends on curdlan concentrations, ions, and additives (3,4). In addition, the gel is more elastic than agar gels prepared under the same conditions (3).

No acute toxicity was observed following oral administration of curdlan (10 g/kg body weight) to rats and mice (5). Curdlan has been officially approved and used as a food additive (6), but it has not yet been applied to pharmaceutical preparations.

In the present study, curdlan tablets containing theophylline were prepared by direct compression, and drug release from the tablets was studied. Theophylline was chosen as a model drug since it is readily absorbed even from the lower regions of the colon (7) and is, therefore, suitable for 24-hr sustained-release oral dosage forms. We also compared the release characteristics of the curdlan tablets to those of a marketed theophylline controlled-release dosage form of the preparations developed recently (8–10).

MATERIALS AND METHODS

Materials

Curdlan was purchased from Wako Pure Chemicals, Co., Ltd., and theophylline was obtained from Nacalai Tesque Inc. They were used after being passed through 50-mesh (300-μm) sieves. All other chemicals and solvents were of analytical reagent grade and were used without further purification. Theo-Dur tablets containing 100 mg theophylline were purchased from Mitsubishi Chemicals, Co.

Tablet Preparation

Three types of theophylline/curdlan mixtures were directly compressed at the force of either 50, 200, or 300 kg/cm^2 for 4 or 10 min by using a Shimadzu hand press for KBr tablets for IR spectroscopy. These mixtures were prepared as follows. (i) Physical mixture: powders of theophylline and curdlan were mixed in a mortar at a drug:curdlan weight ratio of 1:2. (ii) Mixture of theophylline powder and spray-dried curdlan particles: 1% (w/v) curdlan in 5% (w/v) ammonia solution was spray-dried to yield curdlan particles. The spray-dried curdlan particles and theophylline powder were mixed in the same manner as the physical mixture. (iii) Spray-dried particles of theophylline/curdlan solution: 1% (w/v) curdlan ammonia solution containing 0.10, 0.33, 0.50, and 2.0% (w/v) of theophylline (theophylline:curdlan ratios, 1:10, 1:3, 1:2, and 2:1, respectively) was spray-dried.

Spray-Drying Condition

A spray-dryer, Pulvis Mini-Spray, Model GA-31, Yamato Scientific Co., Ltd., was used. The curdlan or the drug and curdlan ammonia solution was kept at room temperature or 70 ± 2°C and subsequently fed to the spray-dryer. The inlet temperature of the drying chamber was set at either 70 or 200°C, and the outlet temperature was 20–25 or 60–80°C, respectively. Air pressure was 1.0 kg/cm^2 and the flow rate of the solution was set at 7 ml/min.

Release Studies

Release of theophylline from various tablets was determined using a JP XI dissolution test apparatus with a paddle stirrer or a rotating basket at 100 rpm. The dissolution media used were 500 ml of JP XI disintegration test medium No. 1 (pH 1.2), isotonic phosphate buffer (pH 7.4), alkaline borate buffer (pH 9.0), isotonic sodium chloride solution, 0.1 and 0.3 *M* $CaCl_2$ solutions, and distilled water. The media were kept at 37 ± 0.5°C during measurements. Aliquots of the

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sample solutions were withdrawn at appropriate time intervals and filtered through a 0.22-μm membrane filter, and the volume of the medium was kept constant by replacement. The sample solution was analyzed spectrophotometrically for theophylline at 270 nm using a Shimadzu UV 260 spectrophotometer.

RESULTS

Conditions for Tablet Preparation

Tablets were prepared with curdlan powder or spray-dried curdlan particles with or without theophylline, free from any other additives, by direct compression. The drug release profiles of the tablets prepared from spray-dried particles of theophylline/curdlan (1:3) solution by applying a compression force of 50, 200, or 300 kg/cm^2 for either 4 or 10 min were identical. Therefore, the tablets were subsequently prepared under the compression force of 200 kg/cm^2 for 4 min throughout the experiments.

Drug Release Studies

Effect of Type of the Drug/Curdlan Mixtures

The drug release profiles of tablets prepared from the three types of theophylline/curdlan mixtures are shown in Fig. 1. The tablets prepared from the physical mixture disintegrated within 30–60 min, and drug release was complete within 1 hr. The tablets prepared from the mixture of the drug powder and spray-dried curdlan particles did not disintegrate and showed an increase in drug release 2 hr after initiation of the experiment, and 95% cumulative release was observed at 8 hr. In contrast, the tablets prepared from the spray-dried particles of theophylline/curdlan showed 10% drug release within the initial 30 min, then the release was depressed, and its rate was constant from 1 to 8 hr. Only 59% cumulative release was observed at 8 hr. More than 95% of the loaded drug was released in the medium within 32 hr. In Fig. 1, the release profile of theophylline powder commercially obtained is also depicted as a control.

Effect of Temperature During Particle Manufacturing

The curdlan/theophylline solution kept at room temperature was spray-dried at 70°C to obtain particles corresponding to the low-set gel of curdlan. Alternatively, the solution was kept at 70°C and spray-dried at 200°C to obtain the high-set gel particles. The particles obtained in the latter case were further heated at 100 or 140°C for 2 hr. The drug release profiles with the tablets prepared from the four heat treatments are shown in Fig. 2. The release from these tablets was constant from 1 to 8 hr after a small initial burst. There were no differences in size distribution (3 ± 1 μm) between particles obtained by spray-drying at two different inlet temperatures. The inlet temperatures did not affect the drug release. However, the drug release of heat-treated tablets was depressed by 15% compared to nontreated preparations, calculated from the slope of the linear portion of the curves in Fig. 2.

Effect of Drug Content

The tablets (weight, 300 mg) containing either 27, 75, 100, or 200 mg theophylline were prepared from the spray-dried particles of theophylline/curdlan. Release studies of the tablets were performed in isotonic phosphate buffer (pH 7.4) at 37 ± 0.5°C. The drug release rates of these tablets were nearly constant after an initial small burst. The release rates based on released amounts increased with initial drug loads, while the release rates expressed as a percentage are similar for the tablets with 75 and 100 mg theophylline. However, the highest-load tablets (200 mg theophylline) show the slowest release, while the lowest (27 mg) show the fastest relative release (Fig. 3). The Higuchi plots shown in Fig. 3 show a linear release profile.

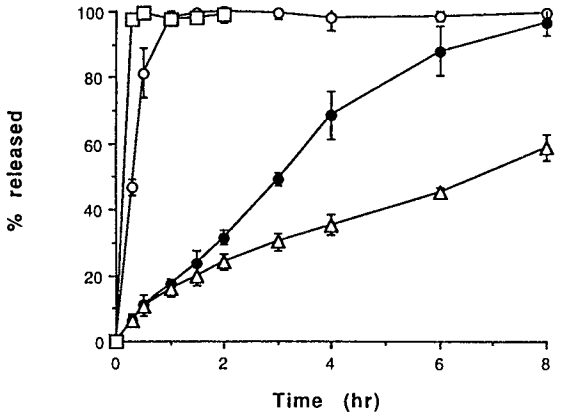

Fig. 1. Release profiles of theophylline from tablets (300 mg) prepared from 1:2 mixture of theophylline and curdlan in isotonic phosphate buffer (pH 7.4) at 37 ± 0.5°C. (○) Tablets of physical powder mixture of theophylline and curdlan; (●) tablets of mixture of theophylline powder and curdlan spray-dried particles; (△) tablets of theophylline/curdlan spray-dried particles; (□) theophylline powder. The vertical bar represents the SD of three runs.

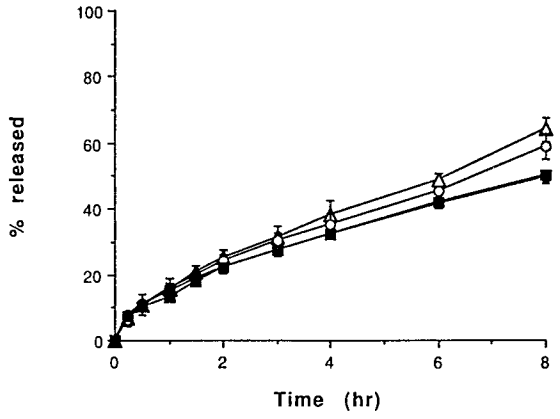

Fig. 2. Effect of heat applied during and after the spray-drying process on release of theophylline from tablets (300 mg) of theophylline:curdlan (1:2) in isotonic phosphate buffer (pH 7.4) at 37 ± 0.5°C. (△) Temperature at the inlet was 70°C; (○) temperature at the inlet was 200°C (without further heating); (■) temperature at the inlet was 200°C (further heating at 100°C for 2 hr); (▲) temperature at the inlet was 200°C (further heating at 140°C for 2 hr). The vertical bar represents the SD of three runs.

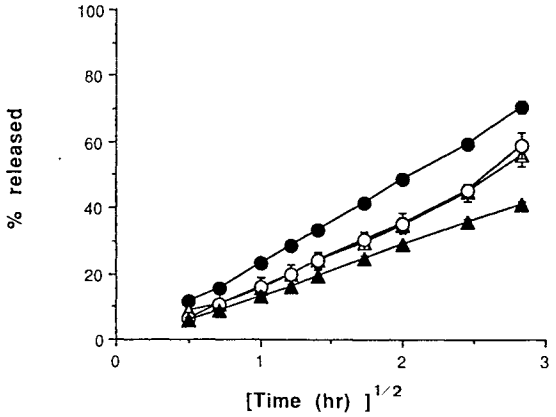

Fig. 3. Effect of theophylline amount contained in a tablet (300 mg) on the drug release in isotonic phosphate buffer (pH 7.4) at 37 ± 0.5°C. (●) 27 mg theophylline; (△) 75 mg; (○) 100 mg; (▲) 200 mg. The vertical bar represents the SD of three runs.

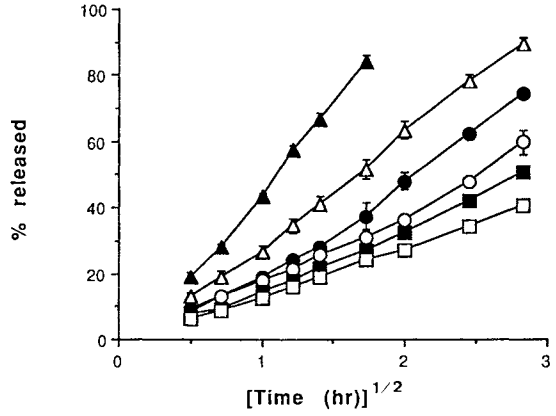

Fig. 4. Effect of surface area on release of theophylline from tablets (theophylline:curdlan = 1:3) in isotonic phosphate buffer (pH 7.4) at 37 ± 0.5°C using a paddle method (100 rpm). (▲) a; (△) b; (●) c; (○) d; (■) e; (□) f in Table I. The vertical bar represents the SD of three runs.

Effect of Surface Area

In order to check the effect of surface area of tablets on drug release, tablets were prepared with two sizes of die and punch sets with spray-dried particles. The information on surface areas and drug amounts incorporated in the tablets is listed in Table I. The weight ratio of curdlan to theophylline was 3:1 in all tablets, while the weight of the tablets was different (160 mg for a and b, 320 mg for c and d, 480 mg for e and f). The tablets of a, c, and e (1.3-cm diameter) were prepared with the same die and punch set, and those of b, d, and f (1.0-cm diameter) were made with the other set. Each Higuchi plot shows a linear release profile (Fig. 4). It is clear from Fig. 4 that the larger the surface area, the faster the release rate (a > b, c > d, e > f). In addition, as the weight of the tablets, prepared by the identical die and punch set, increases, the drug release rate decreases (a > c > e, b > d > f). The surface areas (cm^2) relating to drug release for a unit weight (1 g) of theophylline are also listed in Table I. As the values for surface area per weight of theophylline decrease, release rates decrease in the same order, as shown in Fig. 4.

Effect of Release Media

Release studies were carried out in several release media by a paddle method or a rotating-basket method of the dissolution test in JP XI. Drug release profiles in these media (pH 1.2, 7.4, and 9.0; ions containing Ca^{2+}, Na^+, K^+, PO_4^{3-}, BO_3^{3-}, and Cl^-) were almost identical, even using two different stirring elements.

Comparison of the Theophylline/Curdlan Tablets to Theo-Dur

In order to evaluate the curdlan tablets prepared from spray-dried particles, the release profiles were compared to those of Theo-Dur in JP XI disintegration test medium No. 1 (pH 1.2) and isotonic phosphate buffer (pH 7.4). Theo-Dur is a commercially available sustained-release tablet containing 100 mg theophylline, the same amount of theophylline as in the curdlan tablet. As depicted in Fig. 5, the release profiles of Theo-Dur and the curdlan trial tablets were similar in the pH 1.2 medium. However, the release from these tablets differs significantly in the pH 7.4 medium. At this pH, Theo-Dur tablets degraded 3 hr after immersion. The curdlan tablet showed an identical release pattern in two different pH media. In addition, the standard deviations for each data point of the curdlan tablets are very small.

Table I. Drug Amount, Tablet Weight, Surface Area, and Higuchi's Parameter of Theophylline/Curdlan (1:3) Tablet

	Tablets					
	a	b	c	d	e	f
Tablet diameter (cm)	1.3	1.0	1.3	1.0	1.3	1.0
Tablet weight (mg)	160.3	164.3	318.6	318.3	484.3	486.5
Theophylline (mg)	44.2	41.3	88.7	87.7	148.5	121.7
Surface area (cm^2)	3.04	2.05	3.36	2.47	3.74	2.95
SA/wt (cm^2/g)[a]	68.7	49.7	37.8	28.2	25.2	24.3
k[b]	53.9	33.8	28.5	21.2	18.7	14.9
r[c]	0.999	0.999	0.994	0.994	0.996	0.999

[a] Surface area of tablet per unit weight of theophylline (cm^2/g).
[b] Higuchi's constant in Eq. (4).
[c] Correlation coefficient for each regression line of the Higuchi plots in Fig. 4.

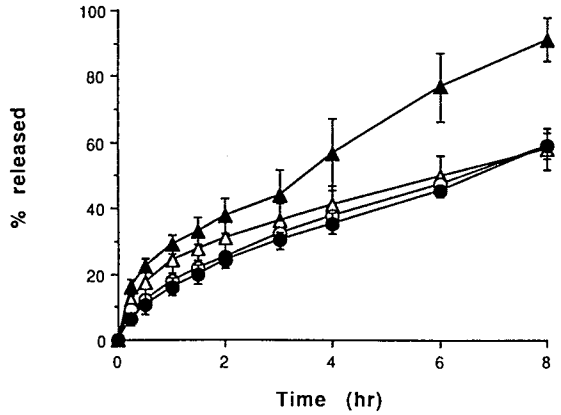

Fig. 5. Release profiles of Theo-Dur and curdlan tablets (300 mg) of theophylline:curdlan (1:2) in isotonic phosphate buffer (pH 7.4) and JP XI disintegration test medium No. 1 (pH 1.2) at 37 ± 0.5°C using a paddle method (100 rpm). (▲) Theo-Dur in pH 7.4 medium; (△) Theo-Dur in pH 1.2 medium; (●) curdlan tablets in pH 7.4 medium; (○) curdlan tablets in pH 1.2 medium. The vertical bar represents the SD of three runs.

DISCUSSION

In this study, curdlan tablets were prepared from mixtures by direct compression. The tablets prepared from a physical mixture disintegrated in 30–60 min in the media. When spray-dried curdlan was used, a nondisintegrable tablet was obtained, possibly because of the lower degree and/or slower rate of swelling of the spray-dried particles. The depressed release profile (Fig. 1) for the tablets prepared from the spray-dried theophylline/curdlan particles may be attributed both to the slower hydration speed of the tablet and to the incorporation of the drug into the chain helices of curdlan, since both were initially dissolved, treated with heat, at least 70°C, and then solidified in fine particles.

Drug release from the tablets prepared from spray-dried particles of curdlan low-set gel and high-set gel was similar (Fig. 2); therefore, gel strength and conformation might not affect the drug release, and drug release was only slightly depressed by additional heat treatment of the high-set gel (Fig. 2). Partial crystallization of the drug and curdlan might have occurred as a result of heating, whereas particles obtained by a spray-dry process appear largely in amorphous forms or in incomplete crystal forms.

The drug release from a homogeneous polymer matrix can be evaluated by Higuchi's equation (11). If $A \gg C_s$;

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

$$f = Q \cdot S/(A \cdot V) \quad (2)$$

$$f = S/V\,(2 \cdot D \cdot C_s \cdot t/A)^{1/2} \quad (3)$$

$$f = k \cdot (t)^{1/2} \quad (4)$$

$$k = S/V\,(2 \cdot D \cdot C_s/A)^{1/2}$$

where Q is the amount of drug released per unit area of matrix at time t, A is the total amount of the drug in unit volume of matrix, D is the diffusion coefficient of the drug in the matrix, C_s is the solubility of the drug in the permeating medium, S is the surface area of the matrix, V is the volume of the matrix, k is a constant, and f is the fraction of drug released at time t. Equation (1) indicates that the amount of drug released is proportional to the square roots of time.

Higuchi plots for data on the curdlan tablets containing various drug amounts and surface area are shown in Figs. 3 and 4, respectively. The percentage drug release as a function of square root of time is linear, indicating that drug release from curdlan tablets is diffusion-controlled. The slopes of the release curves in Fig. 3 increase as the theophylline content decreases, as expected from Eq. (3). Similarly, surface area and volume of the matrix influence the drug release as expected from Eq. (3) (Fig. 4). A parameter k obtained from the slope of each curve in Fig. 4 and the respective correlation coefficient are summarized in Table I. Each k value is plotted in Fig. 6 as a function of tablet surface area (cm^2) per weight (g) of theophylline. The straight line obtained indicates that adjusting the tablet surface area allows manipulation of the drug release rate to achieve the desired effect.

The dissolution rate of theophylline varies with pH. However, the release rates of theophylline from the curdlan tablets were almost the same at pH 1.2, 7.4, and 9.0. Further, ions in the media including Na^+, K^+, PO_4^{3-}, BO_3^{3-}, and Cl^- did not affect the drug release. Therefore, the interaction between theophylline and curdlan is unlikely to be chemical, but rather physical incorporation, i.e., the drug molecules are trapped in the curdlan network structure or in the multiple-chain helices (12). It has been reported that curdlan alkaline solutions turn into gel by adding Ca^{2+}. The network structure might be constructed by the interaction of Ca^{2+} with the dissociated OH group of curdlan (5). However, Ca^{2+} had no effect on theophylline release.

In conclusion, curdlan has an advantage over traditional vehicles for controlled-drug release tablets since drug release is not influenced by the nature of the media surrounding tablets. Thus, release may proceed at a constant rate, following a small initial burst of drug. This result is in contrast to the change of theophylline release observed with Theo-Dur as a function of pH.

Upon immersion of the curdlan tablet in an aqueous medium, the absorption of solution followed by gradual gelation was observed from the outer surface of the tablet.

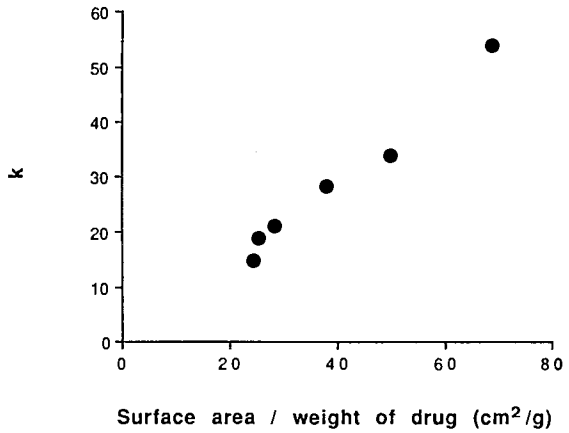

Fig. 6. Relationship between the constant k of Higuchi's equation and the surface area per unit weight of the drug (cm^2/g) for release of theophylline (see Table I).

Complete tablet shape was maintained even over 10 hr *in vitro* after immersion. Therefore, the tablet could maintain the shape in the GI tract for an extended period of time. As theophylline can be absorbed even from the lower region of the colon, nondisintegrable preparations are preferable to disintegrating tablets for controlled release over an extended period. In conclusion, curdlan is an appropriate vehicle for controlled release of drugs which are absorbed throughout the extended GI tract.

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