Controlled Drug Release of Highly Water-Soluble Pentoxifylline from Time-Limit Disintegration-Type Wax Matrix Tablets

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Received February 18, 1993; accepted September 20, 1993

A pulsatile drug release system with a dry-coated tablet containing pentoxifylline was investigated for controlling drug release in the gastrointestinal tract. The system consisted of a core tablet with disintegrator and outer layer, which obtained compression from the ground mixtures of pentoxifylline and behenic acid. Drug release from a dry-coated tablet was investigated at 37°C in JPXII 2nd fluid at pH 6.8. The drug release from the outer layer was fitted to the Cobby model. The drug release from the wax matrix increased significantly after tablet disintegration; therefore, the drug release profiles showed typical sigmoidal curves. The disintegration time depended on the weight fraction of the core tablet, and the drug release rate after disintegration increased with increasing drug concentration in the core tablet. The relationship between the time required for 50% drug release and the disintegration time was linear, indicating that the drug release rate was controlled by regulating the disintegration time.

KEY WORDS: drug release behavior; drug delivery system; sustained release; pentoxifylline; time-limit disintegration; pulsatile release-type wax matrix tablets.

INTRODUCTION

Higuchi (1) reported the first pseudo-steady-state model for drug diffusion from a matrix in ointment and creams, which was later generalized (2). Folkman and Long (3) applied the polymeric matrix to the controlled release of drugs. Cobby *et al.* (4) extended Higuchi's equation to the wax matrix tablet by introducing the boundary retreating concept, in which the dissolution boundary layer retreats to the inside of the tablet as drug release proceeds, and proposed equations for drug release from various tablet shapes. Paul and McSpanden (5) provided an exact mathematical description of the problem, and an improvement of Higuchi's model was reported by Lee (6). There are many studies concerning the controlled drug delivery of pharmaceuticals (7–14).

On the other hand, Skelly and Chen (15) reported problems in obtaining approval from the Food and Drug Administration for controlled-release drug products. They suggested the importance of an "ideal input function" of individual drugs for a given "drug delivery system" for effective therapeutic use and listed the functions as examples. Hence, the pharmaceutical technology for controlling the drug release rate and release pattern depending on the physicochemical properties of individual drugs is critical. Since it is possible to apply various drug release patterns using pulse release, such a dosage form may be useful for controlled-release preparations. Pulsed-release oral dosage forms were reported by Conte *et al.* (16) using a polymer matrix as a three-layer tablet. Ishino *et al.* (17,18) described a dry-coated wax matrix tablet containing hydrogenated castor oil, polyethylene glycol, and disintegrants in the core tablet and showed the pulsed-drug release profiles *in vitro* and *in vivo*.

Pentoxifylline (19) [1-(5-oxohexyl)-3,7-dimethylxanthine] has been approved in the United States and Japan for use in the treatment of patients with intermittent claudication due to chronic occlusive arterial disease and, also, to treat cerebrovascular disease. Since pentoxifylline is water soluble (20) (solubility in water at 37°C, 191 mg/mL), after oral administration to humans the maximum drug concentration in the blood is found after 1–3 hr, and 98% of the drug is eliminated within 24 hr, it is not easy to maintain effective drug concentrations in the blood. Therefore, a sustained-release preparation (Trental) which is a film-coated tablet has been developed for effective practical therapy. Thus, the drug is suitable for use in a controlled-release preparation for effective therapeutic effects.

In the present study, we prepared dry-coated wax matrix tablets of the time-limit disintegration type, containing pentoxifylline as a model water-soluble drug, wax, and disintegrants, by means of cogrinding without any additional compounds. This simplified the analysis of the mechanism.

MATERIALS AND METHODS

Materials. A bulk powder (Lot 300202) of pentoxifylline was obtained from Shiratori Pharmaceutical Co. Ltd., Japan. Behenic acid (Lot 81104) was obtained from Nippon Oil & Fats Co. Ltd., Japan. The disintegrator, partly pregelatinized starch (PCS), was obtained from Asahikasei Co., Japan.

Preparation of Dry-Coated Wax Matrix Tablets. Various concentrations of powdered mixtures (10 g) containing pentoxifylline and wax were ground in a capacity ceramic centrifugal ball mill (Fritsch Co. Ltd.) for 10 min. The diameters and numbers of balls were 24 mm × 4. The speed was 225 rpm at 20 ± 3°C and 60 ± 15% relative humidity (RH). The ground powders were stored in a closed container at −35°C. The formulations of the wax tablets are given in Table I. The dry-coated tablets for dissolution studies were prepared as follows: The ground powder mixture and 5% (w/w) of the disintegrator were compressed in a cylindrical die 0.5 cm in diameter by flat surface punching to make the core tablet. For the outer layer, 33% of the ground powder was compressed in a cylindrical die 0.8 cm in diameter with flat surface punches. The core tablet was placed in the middle of the external layer, then 67% of the ground powder for the outer layer was placed in the die. A 200-mg sample of ground mixture powder was compressed in the die at a compression speed of 1.5 cm/min at 1000 kg/cm^2 using an accurate compression/tension testing machine (Autograph Model IS-5000, Shimadzu Co.). The compressed pellet was kept in the die for 5 min at that compression pressure. Figure 1 shows the geometric structure of the dry-coated wax matrix tablet. The ejected tablets were stored at 20 ± 3°C and 60 ±

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0724-8741/94/0300-0351$07.00/0

Table I. Formulation of Pentoxifylline–Wax Mixtures[a]

Sample	Outer layer: Drug conc. (%, w/w)	Outer layer: Weight mg	Outer layer: Weight %	Core tablet: Drug conc. (%, w/w)	Core tablet: Weight mg	Core tablet: Weight %	Disintegrators (mg)
B	33	160	80	31	40	20	2
C	33	140	70	31	60	30	3
D	33	120	60	31	80	40	4
E	33	160	80	47	40	20	2
F	33	140	70	47	60	30	3
G	33	120	60	47	80	40	4
H	33	160	80	63	40	20	2
I	33	140	70	63	60	30	3
J	33	120	60	63	80	40	4

[a] All mixtures were ground in a ball mill for 10 min as described under Materials and Methods; the plain wax tablet (sample A) was obtained from the ground wax product containing 33% drug.

15% RH for 1 hr, then the diameter and thickness were measured with a micrometer. Thereafter the tablet porosities including the void space of air and pentoxifylline powder were calculated from the geometric values of the tablets and the powder densities.

Dissolution Study. The dissolution profiles of the pentoxifylline–wax matrix tablets were investigated in JPXII 2nd fluid (pH 6.8). A sample tablet was introduced, using a sinker, into 600 mL of dissolution medium in a 1000-mL round-bottomed flask with a plastic cover. The flask was fixed on a sample holder in a thermostatically regulated water bath maintained at 37 ± 0.5°C and stirred by paddle at 100 rpm. The solution was introduced into a quartz flow-through cell with a peristaltic pump and the drug concentration was measured spectrophotometrically (UV 120-02, Shimadzu Co.) at 298 nm, then recorded on the chart recorder. Each value is the average of three measurements.

RESULTS AND DISCUSSION

Effect of Grinding Time on Drug Release Profiles of Pentoxifylline–Wax Matrix Tablets

Figure 2 shows the drug release profiles of various dry-coated pentoxifylline–wax matrix tablets (Table I) in JPXII 2nd fluid at 37°C. The plain wax matrix tablet did not disintegrate during the dissolution test and the plain-type wax matrix tablet (A tablet) followed the Cobby equation [Eq. (1)] (4).

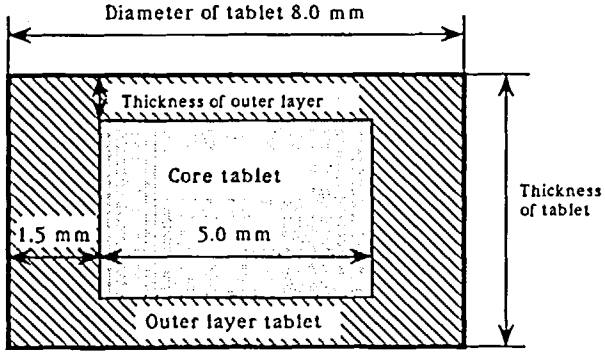

Fig. 1. Geometrical structure of dry-coated pentoxifylline–wax matrix tablets.

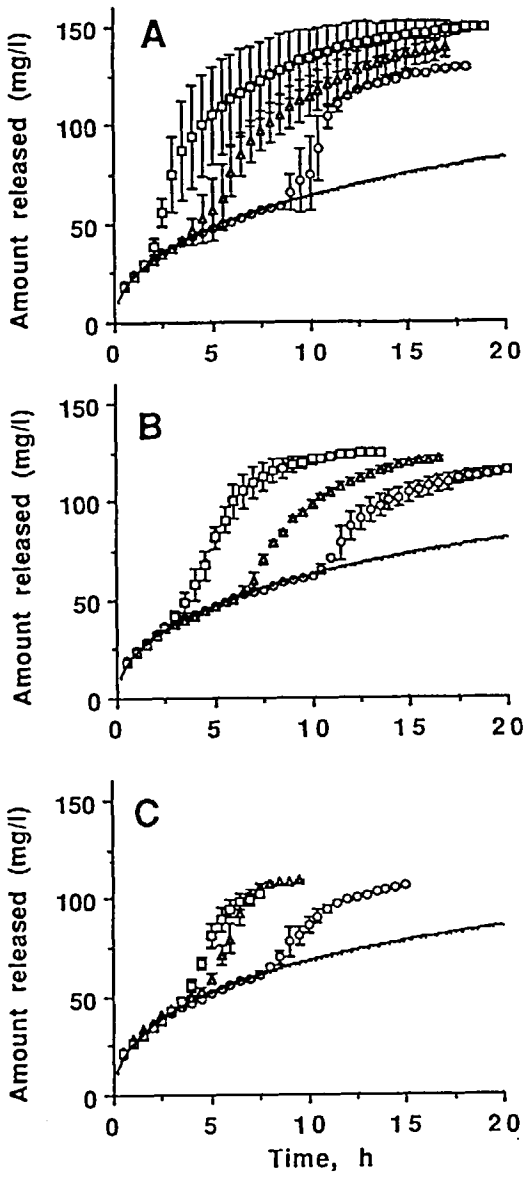

Fig. 2. Drug release profiles from various dry-coated wax matrix tablets. (A) Core tablet drug concentration, 63% (tablets H, I, and J); (B) Core tablet drug concentration, 47% (tablets E, F, and G); (C) core tablet drug concentration, 31% (tablets B, C, and D). (□) 40% of weight in the core (tablets D, G, and J); (△) 30% (tablets C, F, and I); (○) 20% (tablets B, E, and H). Dotted lines represent theoretical values.

$$f_t = (q + 2)K_r t^{1/2} - (2q + 1)(K_r t^{1/2})^2 + q(K_r t^{1/2})^3 \quad (1)$$

$$q = r_o/h_o \quad (2)$$

$$K_r = K_b/r_o = (2/r_o)[D\epsilon C_s/\{\tau(2A - \epsilon C_s)\}]^{1/2} \quad (3)$$

where f_t is the fraction of the drug released at time t, K_r is the release rate constant, r_o is the initial tablet radius, h_o is the initial tablet half-thickness, q is the ratio of the factors, K_b is the boundary retreat rate constant, D is the diffusion coef-

ficient of the drug, C_s is the solubility of drug in the dissolution medium, τ is the tortuosity of the pore, A is the concentration of drug in the matrix, and ϵ is the porosity of the matrix.

In contrast, the dry-coated wax matrix tablet retained its original form for a relatively long period, but after the solution penetrated the core tablet, the wax tablet was disintegrated by the increased swelling pressure of the core tablet due to water penetration into the disintegrator, PCS, because the core contained 5% disintegrator. After that, the drug release rate increased rapidly as the tablet surface area increased and the profile was a typical sigmoid type.

All initial drug release profiles of the dry-coated wax tablets showed that the drug was released from the outer layer before tablet disintegration, but the drug concentration increased rapidly thereafter, because the surface area of the tablet increased, and drug was released from the core tablet. The drug release profiles before disintegration were analyzed based on the Cobby equation [Eq. (1)], and the kinetic parameters were estimated using the SIMPLEX method in the nonlinear least-squares computer program MULTI (21). The theoretical values are shown by the dotted lines in Fig. 2. The disintegration times were estimated from the profiles of the observed and theoretical values and defined at the point detached from the theoretical curve. Since the disintegration time of the wax tablet increased with decreasing core tablet weight, it is concluded that it depended on the water penetration time (17) through the minimum thickness of the outer layer, because the outer layer thickness was much less than 1.5 mm (the thickness of the die wall face as shown in Fig. 1). The drug release rate after disintegration increased with increasing drug concentration in the core tablet.

Figure 3 shows the drug release profiles of G and I tablets. Skelly and Chen (15) suggested that the "ideal input function," as one example of a given "drug delivery system" for 12- and 24-hr doses, might be a zero-order function, as shown in Fig. 3. In the present wax matrix systems, the profile of tablet I fitted the input function for 12-hr dosing,

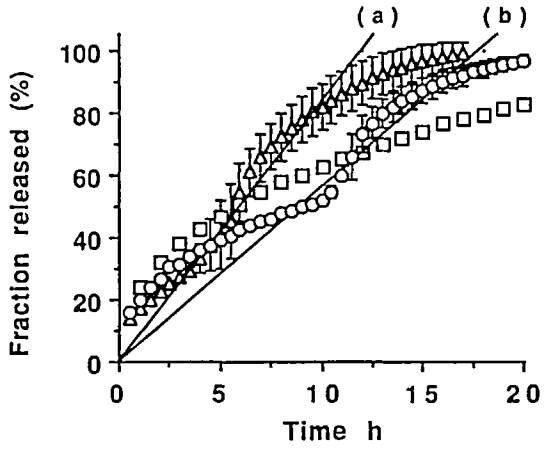

Fig. 3. Drug release profiles of the present system as input functions for 12- and 24-hr doses. (△) Dry-coated wax tablet (tablet I); (○) dry-coated wax tablet (tablet G); (□) plain-type wax tablet (tablet A). (a) Ideal input function for a 12-hr dose; (b) acceptable input function for a 24-hr dose.

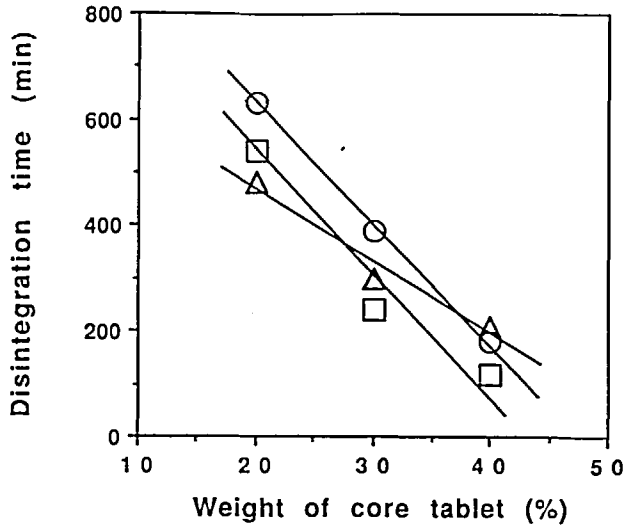

Fig. 4. Relationship between the core tablet weight and the disintegration time of various dry-coated wax matrix tablets: (□) 63% of drug concentration in the core tablet; (○) 47%; (△) 31%.

and that of tablet G represented an acceptable level for a 24-hr dose. These results indicated that the dry-coated wax matrix systems were useful in controlling the input function.

Figure 4 shows the relationship between the disintegration time and the weight of the core tablet. The disintegration time decreased with the weight of the core tablet, because the thickness of the outer layer decreased with an increase in the weight ratio of the core tablet. However, the slope of the straight line of the wax tablet differed slightly, depending on the core drug concentration. This result suggests that the

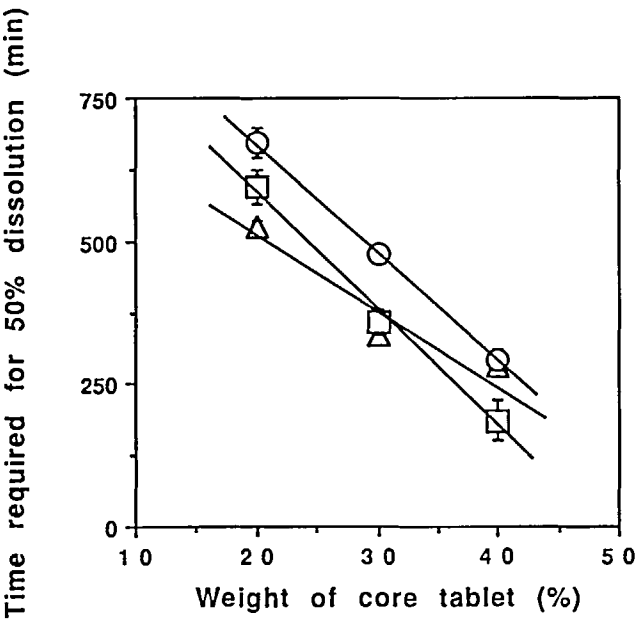

Fig. 5. Relationship between the core tablet weight and the time required for 50% dissolution of various dry-coated wax matrix tablets: (□) 63% of drug concentration for core tablet; (○) 47%; (△) 31%.

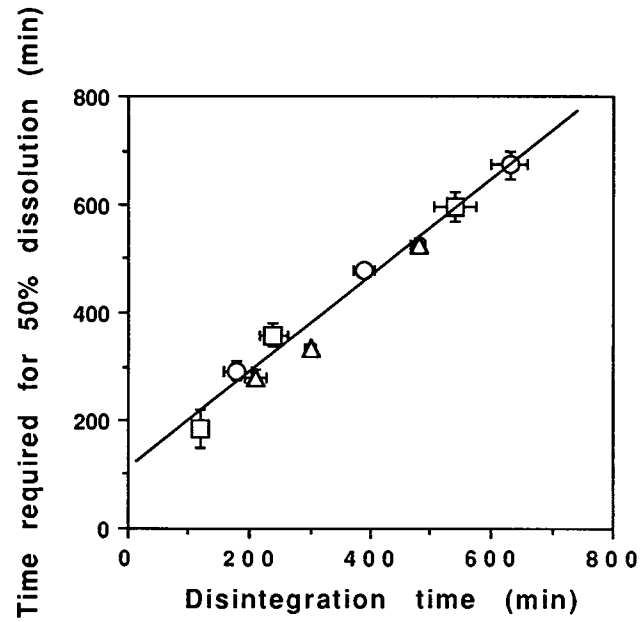

Fig. 6. Relationship between the time required for 50% dissolution and the disintegration time of various dry-coated wax matrix tablets: (□) 63% of drug concentration for core tablet; (○) 47%; (△) 31%.

disintegration time of the wax matrix tablet containing a low drug concentration in a smaller core tablet was more prolonged than that of the larger tablet. Since the low molecular mass of the organic compound conferred on it compression characteristics different from those of wax materials (plastic, elastic, and/or other compressive factors), the tablet porosity depended on the drug concentration.

Figure 5 shows the effect of the weight of the core tablet on the time required for 50% drug release ($T_{50\%}$) of various dry-coated wax matrix tablets. The $T_{50\%}$ values of three formulations were a straight line, but the slopes differed slightly, indicating that the compaction behavior of the wax tablet is dependent on the drug concentration. Since the $T_{50\%}$ depended on the weight of the core tablet, the drug release profiles could be controlled by this means.

Figure 6 shows the relationship between $T_{50\%}$ and disintegration time for various dry-coated wax matrix tablets. The relationships among all wax tablet formulations was linear, indicating that the drug release rate was controlled by regulating the disintegration time. Since the disintegration time of this wax matrix tablet could be controlled by the drug concentration in the core tablet and/or its weight, the drug release rate from the wax matrix can be controlled using the time-limited disintegration wax matrix tablet. The drug release profiles of this matrix system showed a particular sigmoid pattern, and the disintegration time was reproducible since it was controlled by the solution penetrating into the outer wax matrix layer. Therefore, it seems that with the pulsatile release-type system in the present study, i.e., a time-limited disintegration wax matrix tablet, the drug release pattern can be programmed by varying the formulations with regard to the drug concentration and/or the weight of the outer and core layers.

ACKNOWLEDGMENT

The authors wish to express their gratitude to Miss Akiko Hiraoka for technical assistance.

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