Absorption of Diltiazem in Beagle Dog from Pulsatile Release Tablet

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An orally applicable pulsatile drug delivery system in dry-coated tablet form was prepared using diltiazem hydrochloride as the model drug, and a polyvinyl chloride–hydrogenated castor oil–polyethyleneglycol mixture as the outer shell of the tablet. *In vitro* drug release from the prepared tablet exhibited a typical pulsatile pattern with a 7 h lag phase (non-drug release period). This dosage form was orally administered to three beagle dogs under non-fasting and fasting conditions, and the plasma concentration level of diltiazem was determined according to time after administration. The result of the *in vivo* study in non-fasting dogs suggested that the drug could be released in the gastrointestinal tract as in the *in vitro* test. However, under the fasting condition, a large difference in the plasma concentration profile was found, suggesting that the disintegration time of the tablet tended to be influenced by the feeding condition of subject.

Keywords dry-coated tablet; pulsatile drug release; diltiazem hydrochloride; *in vitro* dissolution; *in vivo* absorption; lag time; fed–fasting condition

Introduction

An orally applicable pulsatile release system should be useful for time-controlled or site specific delivery of a drug in the gastrointestinal tract. Such a system has particular applications in those disease states where a peak of plasma drug level is required during the night or directly after waking (*e.g.* insomnia, asthma, arthritis, ischemic heart disease, *etc.*), and also in those cases where the drug release or absorption is required to occur in the lower part of the intestine (*e.g.* treatment of ulcerative colitis, oral peptide delivery, *etc.*).[1)]

Previously, we reported that a dry-coated tablet system can achieve the pulsatile release of a drug on the basis of a time-controlled disintegration mechanism.[2)] The system consists of a core tablet, containing the active ingredient and disintegrants, and a less water permeable outer shell. When the hydrogenated caster oil (HCO)–polyethyleneglycol (PEG) matrix was used for the outer shell, the *in vitro* release initiation time was well controlled either by modifying the composition of HCO and PEG or altering the thickness of the outer shell. It is still questioned, however, whether such a pulsatile release system truly shows the similar dissolution behavior when it is administered to the human body, because the physicochemical environment in the gastrointestinal tract should be considerably different from that offered in dissolution testing. For instance, the mechanical force loaded on the tablet which can affect the disintegration time of the dry-coated tablet, and the amount and physical property of intestinal fluid, which can affect either the penetration speed of the fluid or the swelling of the disintegrant, are thought to differ substantially between *in vitro* and *in vivo* situations.

The objective of the present study is to evaluate the *in vitro–in vivo* correlation of drug release time. The absorption study was conducted using beagle dogs under non-fasting and fasting conditions. Diltiazem hydrochloride, which is known to be absorbed from the wide range of the intestine, was chosen as a model drug.[3)] Polyvinyl chloride (PVC) and HCO were used as components of the outer shell of tablet, because PVC is known to be superior in compactibility.[4)]

Experimental

Materials Diltiazem hydrochloride JP (DIL) was pulverized to about 10 μm prior to use. HCO was obtained from Kawaken Fine Chemical Co. (K_3wax®; mp 84—88 °C). Polyethyleneglycol 6000 (PEG) was obtained from Sankyo Kasei Kogyo Co. (mp 57—61 °C), and PVC was obtained from Wako Pure Chemical Industries, Ltd., and they were used without further purification. Carboxymethylcellulose calcium (ECG®; Gotoku Chemical Co.) was selected as a disintegration agent. Magnesium stearate (St-Mg) was added as a lubricant.

Granulation The granule used for the outer shell of the dry-coated tablet was prepared by the melt granulation technique. The weighed HCO, PVC and PEG powders were blended together. One hundred grams of the powder blend was melted in a vessel at 90—94 °C under continuous agitation. The homogeneous mass was cooled to room temperature and then pulverized using a mortar and pestle. The granules obtained were sized by passing them through a 20-mesh sieve. DIL, ECG® and St-Mg were blended together using a mortar and pestle. The powder blend obtained was used to make the core tablet.

Tabletting All the tabletting was performed using a reciprocating press (Autograph IS-5000, Shimadzu Seisakusyo) with a concave (the radius of curvature was 8 mm) punch and a die. The core tablets were compressed with a diameter of 6 mm. Applied force and punch velocity were 400 kg/cm^2 and 10 mm/min, respectively. The dry-coated tablets were prepared according to the conventional press coating technique; namely, a half amount of outer shell was filled into the die with a diameter of 10 mm to make the powder bed, then the core tablet was placed on the center of the powder bed. After being filled with the remaining half of the granules, the die content was compressed at 1273 kg/cm^2.

Dissolution Test Dissolution tests were conducted according to the paddle method described in JP XII. Nine hundred milliliters of distilled water thermostated at 37 °C was used as the dissolution fluid and stirred with a paddle at the rate of 100 rpm. A sinker was applied to prevent flotation of the tablet. The amount of drug released was spectrophotometrically assayed at 280 nm.

Absorption Study in Beagle Dogs Three healthy male beagle dogs (weighing 10.3, 13.0 and 13.2 kg) were used in this study. A dry-coated tablet (equivalent to 60 mg of DIL) was orally administered to each dog with 30 ml of water 30 min after the dogs were fed 150 g of solid food (DS; Oriental Yeast Co.) with 150 ml of water. After a washing out period of one week, another study was conducted using the same dogs under the fasting condition. After the drug administration, blood specimens (4 ml) were collected at each predetermined time. The plasma sample was analyzed for diltiazem using a reversed phase high performance liquid chromatography method.[5)]

Results and Discussion

The formula of the pulsatile release dry-coated tablet examined in the present study is summarized in Table I. ECG® was used in the core tablet as the disintegrant, PVC and HCO were used in the outer shell as water-insoluble matrix components, and PEG was used as the water-penetration controlling agent.

TABLE I. Formulation of Dry Coated Tablet Used in *in Vivo* Absorption Test

	Components	Sample formula (mg/tab.)
Core tablet	DIL	60.0
	ECG	18.0
	St-Mg	1.5
	Hydrogenated silicon dioxide	0.5
Outer shell	PVC	340
	HCO	100
	PEG	60
	St-Mg	10

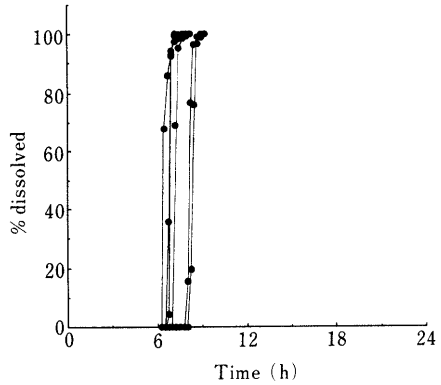

Fig. 1. *In Vitro* Dissolution Profile of DIL from Pulsatile Releasing System

Figure 1 shows the *in vitro* dissolution profiles of the tablet ($n=6$). Each tablet exhibited a typical pulsatile release profile; that is, the drug immediately released after a long period of time. As was reported previously, such an *in-vitro* profile was brought about by the time-controlled disintegration mechanism. Namely, in the dissolution process, the poor water permeable wall considerably delayed water penetration, resulting in the appearance of a long lag phase. However, once the penetrating water reached the core tablet, the disintegrant contained in the core tablet quickly swelled with enough force to break the outer shell, resulting in rapid release. The water penetration rate can be controlled by either the amount of PEG incorporated or the thickness of outer shell. The mean lag time of the present system was found to be about 7 h with a range of ± 1 h. The drug release rate following the lag time was quite fast, with all the drug being released within 15 min.

In order to examine the effect of the pulsatile drug release on the *in vivo* absorption of diltiazem, this dry-coated tablet was orally administrated to three beagle dogs under both fed and fasting conditions. Figure 2 shows the individual plasma concentration profile in which the tablet was administered under the fed condition. The plasma concentration of diltiazem sharply increased between 4 and 8 h after the administration, and the mean lag time calculated from the plasma concentration profiles agreed well with that found in the *in vitro* dissolution study. The results suggest that the tablet releases the drug in the gastrointestinal tract in almost the same manner as the *in vitro* drug release. In fact, the outer shells of the dry-

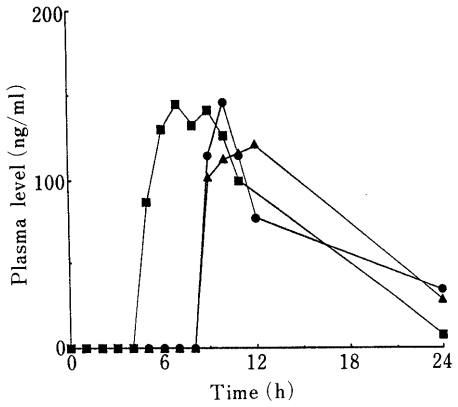

Fig. 2. Individual Plasma Level Profiles of DIL after Oral Administration of Pulsatile Releasing System in Dogs under the Fed Condition
Subject No.: ●, 8168; ▲, 6410; ■, 7185.

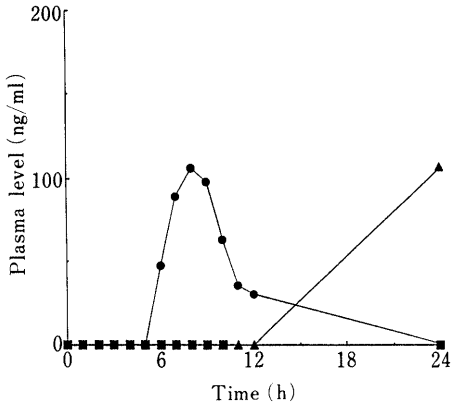

Fig. 3. Individual Plasma Level Profiles of DIL after Oral Administration of Pulsatile Releasing System in Dogs under the Fasting Condition
Subject No.: ●, 8168; ▲, 6410; ■, 7185.

coated tablets recovered from the feces of the beagle dogs were observed to be completely broken into two pieces, and in every case, the core tablets could not be found.

Figure 3 also shows the individual plasma concentration profile where the same tablet was administered under the fasting condition. Although the distinctive lag time was observed in one of the profiles, a considerably large difference was found among the dogs. From these results, it was suggested that the *in vivo* disintegration time of the tablet tends to be influenced by the feeding condition of subject. The major reason for the observed difference of variations in the plasma drug levels between the fed and fasting conditions might be related to the arrival site in the gastrointestinal tract influencing the lag time. In this experiment, a dry-coated tablet with a diameter of 10 mm was administered, so under the fed condition, the tablet would remain in stomach for many hours,[6] until the amount of fluid was enough to penetrate and to break outer shell. On the other hand, under the fasting condition, as the gastric emptying rate was fast, the tablet could travel more quickly to lower intestine, where the amount of fluid at the arrival site might not be sufficient to break the outer shell of the dry-coated tablet. Other as yet unknown factors may be concerned with this phenomena, such as a variance in the gastrointestinal contruction between the fed and fast condition of subjects.

The present investigation confirmed that a dry-coated tablet formulation with a PVC–HCO–PEG mixture can achieve the pulsatile release of a drug in *in vitro* and *in vivo* (under the fed condition) as well. The results suggested that the drug-free period of time regarding the plasma level could be estimated from the *in vitro* dissolution testing, as long as the tablet was administered under the fed condition. The dry-coated tablet form is considered to be a convenient way to achieve pulsatile drug release. Although the system presented here showed a considerable variance in plasma concentration profile of the drug in fasting dogs, further investigation would lead to a more acceptable system for time-controlled or site-specific drug delivery in the gastrointestinal tract.

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