Chem. Pharm. Bull. **40**(11) 3036—3041 (1992) Vol. 40, No. 11

Design and Preparation of Pulsatile Release Tablet as a New Oral Drug Delivery System

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To achieve time-controlled or site specific delivery of a drug in the gastrointestinal tract, an orally applicable pulsatile drug release system with the dry-coated tablet form was developed. The system consisted of a less water permeable outer shell and a swellable core tablet; from such a system, the drug was expected to be rapidly released after a certain period of time on the basis of the time-controlled disintegration mechanism. Various model disks of outer shell, consisting of hydrogenated castor oil and polyethyleneglycol 6000, were tested for their water penetration rate. The experimental results showed that water penetration proceeded obeying the boundary retreating mechanism, so that the lag time of the system could be controlled by changing either the thickness or the composition of the outer shell. The swelling force of various commercially available disintegrants was quantitatively compared, and it was found that carboxymethylcellulose calcium was the preferable disintegrant to be used for the core tablet. On the basis of the results of a series of fundamental studies, various pulsatile release tablets of isoniazid with different lag times were designed. In the *in vitro* dissolution test, typical pulsatile release was achieved for all the tablets prepared, and a good correlation was found between the observed lag time and the estimated lag time calculated from an empirical equation deduced from the thickness and polyethyleneglycol 6000 content of the outer shell.

Keywords pulsatile drug release; dry-coated tablet; swellable disintegrant; water penetration rate; isoniazid; hydrogenated castor oil; polyethyleneglycol 6000; time-controlled disintegration

Introduction

Recently much effort has been devoted to developing the drug delivery systems for oral application, most of which has aimed at the constant release from a dosage form to maintain a flatter plasma level for an extended period of time.[1] However, from the view point of the optimization of chemotherapy, maintaining a constant blood level of a drug is not always desirable. For instance, to reduce the nocturnal or early morning symptoms of some chronic diseases, such as ischemic heart disease, asthma, arthritis, *etc.*, drug therapy should be done so as to achieve an effective drug level only at the required time, so that unpleasant side-effects can be minimized. To avoid developing a tolerance, nitrates, antibiotics and contraceptive steroids may require rhythmic patterns of drug concentration.[2] For these cases, the drug release from a device should be "time-controlled" instead of "rate-controlled."[3] On the other hand, some drugs for the treatment of colon disease (*e.g.* ulcerative colitis) should be directly delivered to the target site in the gastrointestinal tract.[4] In addition, with great recent advancements in the biotechnology field, there has been increasing interest in utilizing the colon as an absorption site for new peptide and protein products.[5] For these cases, the drug release from a device should be "position-controlled."

A pulsatile releasing system, immediately releasing active agents after a controlled lag time, should be capable of releasing its drug content at either a predetermined time or at a specific site in the gastrointestinal tract. Although a lot of pulsatile release systems have been designed and investigated,[6] there are only a few orally applicable devices[7] due to the potential limitation of the size of product and the materials to be used.

A dry-coated tablet form, which we will discuss in this paper, may be one of the most feasible ways to achieve the desirable pulsatile release of a drug. The system usually consists of two parts, a core tablet containing an active ingredient and disintegration agent, and a poorly water permeable outer shell (Fig. 1). The outer shell can considerably delay the water penetration, so that a long lag time will appear prior to the beginning of the drug is release. Once the outer fluid reaches the inside, the core tablet will swell until the outer shell finally breaks, resulting in rapid release. In such a system, lag time can be controlled by altering the thickness or modifying the composition of outer shell, and rapid release following the lag time can be achieved when an appropriate disintegrant is applied.

The main purpose of our study is to develop a new technology for an orally applicable pulsatile release system. In this paper, a pulsatile release tablet was designed on the basis of the time-controlled disintegration principle. The effect of formulation variables on water penetration rate and disintegration was examined using the melt blend of hydrogenated castor oil (HCO) and polyethyleneglycol 6000 (PEG) as the outer shell and various commercially available disintegrants.

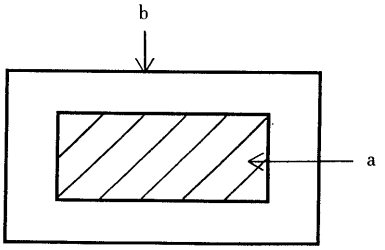

Fig. 1. Schematic Representation of Pulsatile Release Tablet with Dry-Coated Tablet Form

a, core tablet consisting of drug and disintegrant; b, outer shell consisting of less water permeable material.

Experimental

Materials Isoniazid JP (INZ) was obtained from Yukigosei Yakuhin Kogyo Co., and pulverized to about 7 μm prior to use. HCO was obtained from Kawaken Fine Chemical Co. (K_3wax®; mp 84—88 °C), PEG was obtained from Sanyo Kasei Kogyo Co. (mp 57—61 °C), and they were used as received. Microcrystalline cellulose (Avicel PH 101®; Asahi Kasei Co.), cornstarch (Nippon Shokuhin Kako Co.), cross linked polyvinylpyrrolidone (Kollidon CL®; BASF), carboxymethylstarch (Ex-

plotab®; Edward Mendell) and carboxymethylcellulose calcium (ECG®; Gotoku Chemical Co.) were used as the disintegrants. Magnesium stearate (St-Mg) was added as the lubricant. Hydroxypropyl cellulose (HPC-M®; Nippon Soda Co., Ltd.) was of JP grade.

Granulation The granule used for the outer shell was prepared by the melt granulation method. HCO and PEG powders were blended at various proportions (78 : 20, 63 : 35, 58 : 40, 48 : 50 and 38 : 60). A 100 g of the powder blend was melted in a vessel at 60—64 °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. A 75 g of INZ and 25 g of disintegrant were blended together using a mortar and pestle. The powder blend was used to make core tablets.

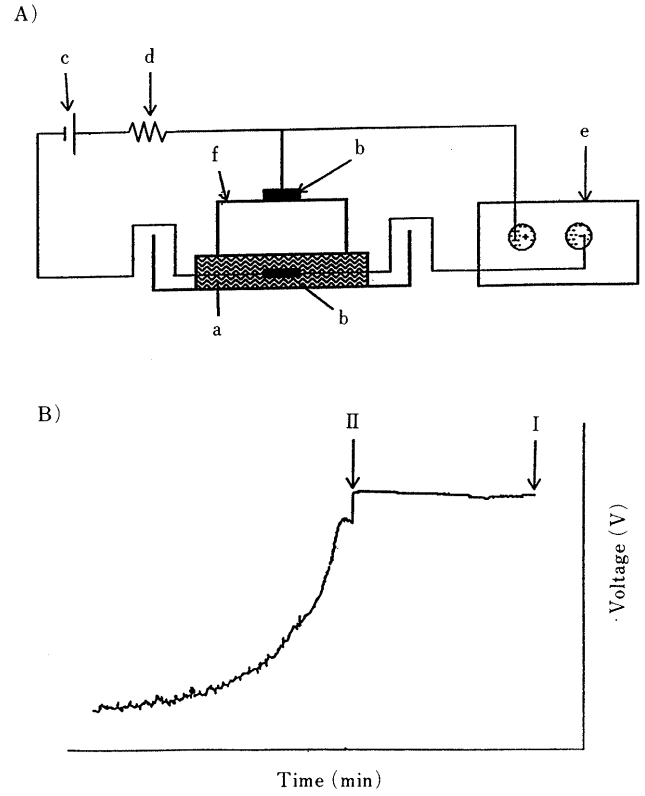

Fig. 2. Schematic Diagram of the Penetration Time Measuring Apparatus and Typical Recording

A) Apparatus; a, gauze filled with penetration fluid; b, electrode; c, battery (1.5 V); d, resistor (2 MΩ); e, voltmeter; f, sample tablet. B) Output chart; I, start point; II, end point.

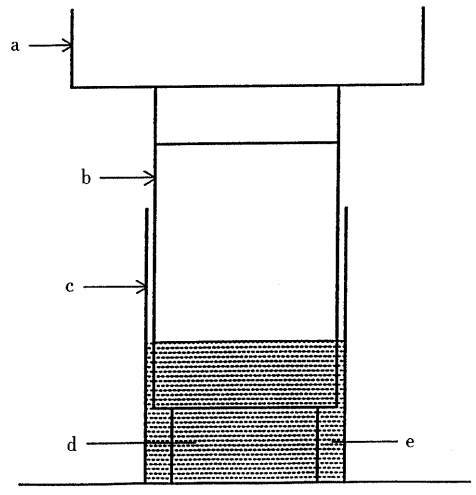

Fig. 3. Schematic Diagram of the Swelling Force Measuring Apparatus

a, load cell; b, piston; c, cylinder; d, sample tablet; e, fluid for swelling.

Tabletting All the tabletting experiments were performed using a reciprocating press (Autograph IS-5000, Shimadzu Seisakusyo) with a flat-faced punch and a die. Core tablets with diameters of 5, 6 and 7 mm, were compressed at the applied force of 400 kg/cm^2 and at the punch velocity of 10 mm/min. HCO–PEG granules were compressed to make disks with a diameter of 10 mm and various thickness under the same condition, and these were used for the water penetration study. The thickness of the disk was adjusted by altering the weight of granules. Dry-coated tablets were prepared using the press coating technique. A half amount of HCO–PEG granules was filled into the die to make a powder bed, then a core tablet was placed on the center of the powder bed. Next, the remaining half of the granules was filled in the die, and the contents were compressed at 600 kg/cm^2.

Dissolution Study Dissolution tests were performed according to the paddle method described in JP XII. A 900 ml of distilled water at 37 °C was used as the dissolution fluid, and the fluid was stirred with a paddle at 100 rpm. A sinker was applied to prevent the flotation of the tablet. The amount of the drug released was spectrophotometrically assayed at 280 nm.

Penetration Study Figure 2 is the schematic representation of the penetration testing apparatus used. A disk sample was placed on gauze. Before the initiation of the experiment, the top and bottom surfaces of the disk were connected with electrodes and charged at the voltage of 1.5 V. Immediately after the gauze was filled with water, the measurement was started. When water penetrated into the disk from the bottom and reached the top surface, and electric current flowed between two electrodes; consequently, the voltage sharply dropped. The change in voltage was monitored on a recorder as a function of time. Figure 2B shows the example of the output chart. The penetration time was regarded as the distance between I and II in Fig. 2. The determination was conducted at 24±2 °C and at 50±10% relative humidity.

Swelling Force Determination Figure 3 shows the schematic representation of the swelling force measuring apparatus used. A 500 mg of the disintegrant was compressed using a reciprocating press (Autograph IS-5000, Shimadzu Seisakusyo) with a flat-faced punch and a die with a diameter of 10 mm. Applied force and punch velocity were 1273 kg/cm^2 and 10 mm/min, respectively. The tablets prepared from various disintegrants were placed on the center of a cylinder. A piston attached on a tensile tester (Autograph AGS-100A; Shimadzu Seisakusyo) was placed on the surface of the tablet. A 5 ml of water was poured into the cylinder. Then, changes in the force were monitored on a recorder as a function of time. The maximum detected force was regarded as the swelling force. The determination was conducted at 24±2 °C.

Tablet Characteristics The weight, diameter and thickness of each tablet was determined using an ordinary balance and gages. The crushing strength of the disks from the compressed direction was determined after finishing the penetration experiments at a punch velocity of 1 mm/min using a tensile tester (Autograph AGS-100A; Shimadzu Seisakusyo).

Results and Discussion

Water Permeability of Outer Shell The formulae of the outer shell examined in the water penetration study are shown in Table I.

To determine the penetration rate constant of water on the outer shell, the granules of formula C-1 were compressed to make disks with varying thickness, and the penetration test was conducted.

The water penetration from a planar matrix system is known to obey the boundary retreat mechanism.[8] So, in this matrix system, the penetration distance from the surface after time t(X_t) is expressed as:

Table I. Formulation of Outer Shell

Ingredient	Formulations (w/w%)				
	C-1	C-2	C-3	C-4	C-5
HCO	78	63	58	48	38
PEG	20	35	40	50	60
St-Mg	2	2	2	2	2

$$X_t = K_p \cdot t^{1/2} \quad (1)$$

where K_p is the penetration rate constant. Under the given experimental condition, the penetration distance equals the thickness of disk (L), and the time required for water penetration from the bottom to the top of the disk corresponds to the penetration time (T_p) that represents the lag time of the dry-coated tablet. Therefore, the penetration rate constant (K_p) was rewritten as:

$$K_p = L/T_p^{1/2} \quad (2)$$

Figure 4 is a plot of disk thickness against the square root of penetration time. A linear relation was found between both parameters, indicating that the mechanism of water penetration obeys the boundary retreat theory. Then, the K_p value was calculated from the slope of the regression line according to Eq. 2. From the obtained K_p value, the lag time of the tablet with a 2 mm thick outer shell of formula C-1 (this is probably the maximum acceptable thickness for dry-coated tablets) was estimated to be about 20 h, which is long enough for an oral dosage form because the colon arrival time of a tablet in human is known to be within 20 h at the latest, as reported by Wilson *et al.*[9]

To examine the effect of the PEG content in the outer shell on the penetration rate, K_p values of the disks prepared from formulae C-2, C-3, C-4 and C-5 were also determined using the same technique. Figure 5 shows the change in K_p with PEG content. The observed K_p value increased linearly with increasing PEG content in the experimental range applied. The results shown in Figs. 4 and 5 indicated that T_p was controllable by altering the thickness and/or PEG content. So, the lag time of the dry-coated tablet can be estimated from the thickness (L) and PEG content (R) of the outer shell according to Eq. 3.

$$T_p^{1/2} = (-200 \cdot R + 214) \cdot L \quad (3)$$

In order to examine the effect of the pH and viscosity of the penetrating fluid, another set of experiments using the C-1 disk was performed using three test solutions, including the first fluid and second fluid described in JP XII and a highly viscous water (1.5% HPC-M® solution; 110 cps at 37 °C). The K_p values obtained are summarized in Table II. It was found that the K_p of a disk was hardly affected by either the pH or viscosity of penetrating fluid.

Table II. Penetration Rate Constant of Various Penetrating Media into Disk Prepared from C-1 Formulation

	Penetration rate constant K_p ($\times 10^{-3}$ cm/min$^{1/2}$)
Water	5.56±0.23
JP XII 1st fluid	5.34±0.19
JP XII 2nd fluid	5.24±0.13
Viscous water[a)]	5.33±0.17

a) Viscosity was 110 cps at 37°C determined with a viscometer (DVL-B; Tokyo Keiki).

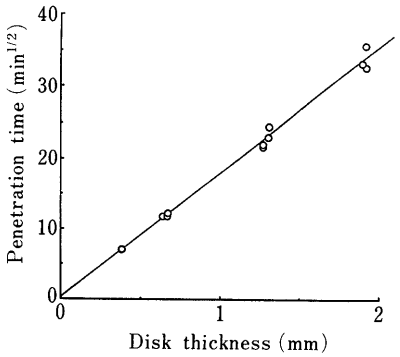

Fig. 4. Relation between Thickness of Disk and Penetration Time

Disks were prepared by varying the weight of the C-1 granules.

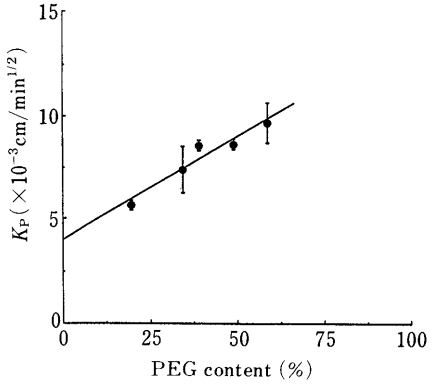

Fig. 5. Relation between Penetration Rate Constant and PEG Content in Disk

Disks were prepared from 100 mg of C-1, C-2, C-3, C-4 and C-5 granules. Each point represents mean±S.D. of three measurements.

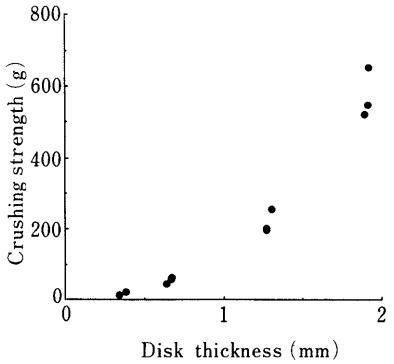

Fig. 6. Plot of Crushing Strength against Thickness of Disk

The crushing strength was determined after finishing penetration test. Disks were prepared by varying the weight of C-1 granules.

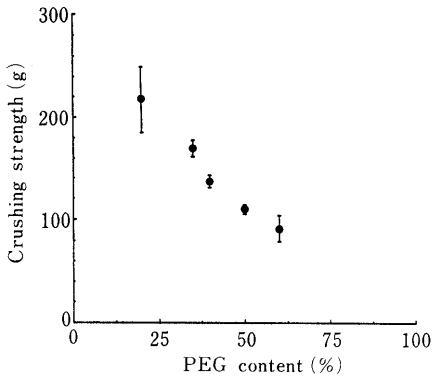

Fig. 7. Plot of Crushing Strength against PEG Content in Disk

The crushing strength was determined after finishing the penetration test. Disks were prepared from 100 mg of C-1, C-2, C-3, C-4 and C-5 granules. Each point represents mean±S.D. of three measurements.

Crushing Strength of the Outer Shell To achieve the pulsatile drug release, the tablet must break instantaneously after the outer fluid penetrates into the core tablet. The breaking force generated by the swelling of the disintegration agent is an important factor. To assess the force required to break the outer shell, the crushing strength (from the compressed direction) of disks was determined. Figure 6 shows a plot of the crushing strength of the disks of C-1 against the thickness. The crushing strength increased exponentially with increasing thickness. Even though 2 mm of disk thickness (the estimated lag time was 20 h) was applied, the crushing strength was less than 800 g. Figure 7 shows the change in crushing strength as a function of the PEG content of disks. The crushing strength decreased linearly with increasing PEG content. The observed decrease in crushing force was caused by the increase of porosity in the disks resulting from the leaching of PEG during the penetration study.

The crushing strength was increased by either increasing the thickness or decreasing the PEG content. From our experimental results, the force of 800 g was thought to be enough to break an outer shell. However, Ito *et al.* reported that the dividing strength of scored tablets prepared with various excipients was almost 1 kg.[10] So, 1 kg of the swelling force was more adequate as the minimum force required to break the outer shell.

Swelling Force of Disintegration Agents The swelling force of various disintegration agents was examined as a function of time. The force-time profiles of core tablets with five commercially available disintegration agents are shown in Fig. 8. Avicel® generated a higher swelling force than the others. However, Avicel® is not always suitable, because it is known to have high elasticity property,[11] and high elastic recovery after compression may cause cracks on the outer shell of the tablet. Kollidon CL® and Explotab® only showed a low swelling force, less than 1 kg. Cornstarch generated a high swelling force instantaneously, but this quickly decreased. The swelling force of ECG® exceeded 1 kg quickly and remained at a high level for many hours. From these results, ECG® was thought as an appropriate disintegration agent to be used for the core tablet.

Figure 9 shows the swelling behavior of ECG® in various media. As is clear from the figure, the swelling behavior of ECG® is not affected by the pH or viscosity of the medium.

Design of the Pulsatile Release Dry-Coated Tablet Through the above-mentioned fundamental studies, several types of dry-coated tablets of Isoniazid were prepared in order to find the desirable pulsatile release system. The candidate formulas from D-1 to D-11, which were compressed with varying tablet thicknesses or diameters, are summarized in Table III.

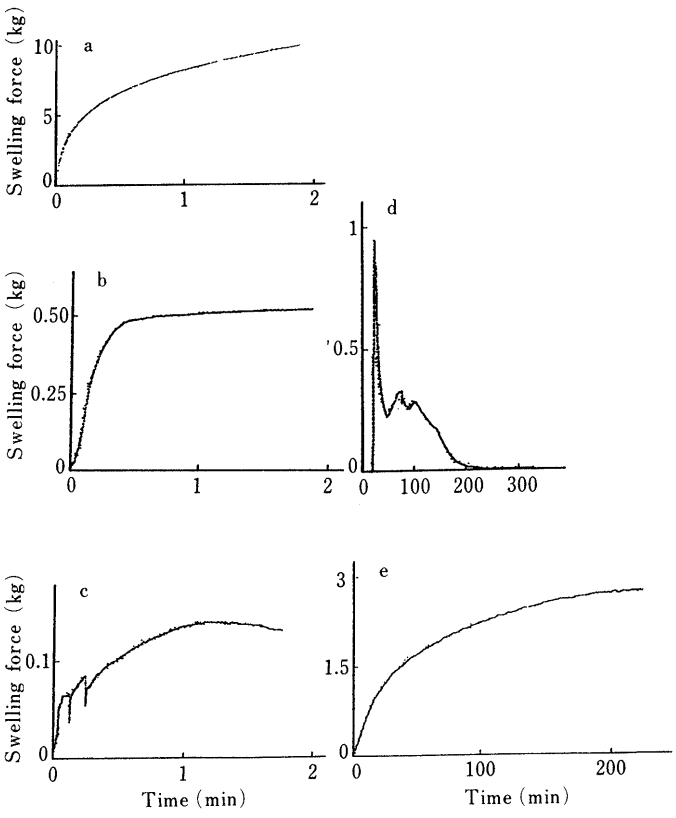

Fig. 8. Swelling Force of Various Disintegration Agents as Function of Time

a, Avicel®; b, Kollidon CL®; c, Explotab®; d, cornstarch; e, ECG®.

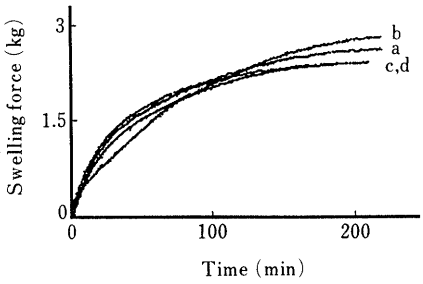

Fig. 9. Influence of Property of Fluid on Swelling Force of ECG®

Swelling fluid: a, water; b, JP XII 1st fluid; c, JP XII 2nd fluid; d, viscous water (110 cps at 37 °C).

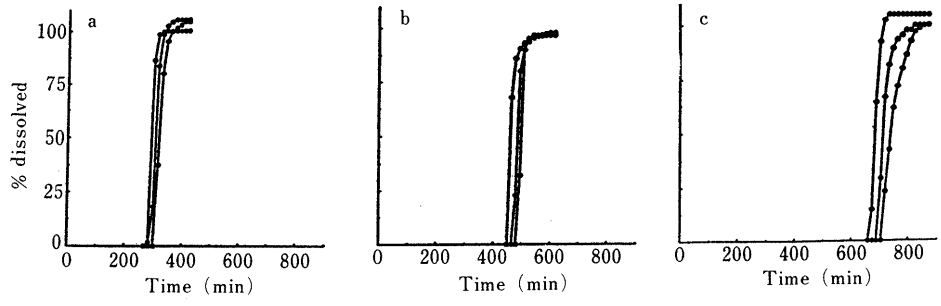

Fig. 10. Dissolution Behavior of Pulsatile Release Dry-Coated Tablets

The formulation of dry-coated tablet: a, D-1; b, D-2; c, D-3.

The typical dissolution behavior from the dry-coated tablets prepared (D-1, D-2 and D-3) were shown in Fig. 10. Even though only a small variation was observed, the lag time was delayed depending on the amount of PEG content and thickness of the outer shell, and the drug release after the lag time was considerably fast in all cases.

Figure 11 shows the relationship between the observed lag time in the dissolution test and the estimated lag time calculated from Eq. 3 for various dry-coated tablets with different compositions and thicknesses of the outer shell. A linear relation was found even though the slope was not equal to the unit. The major reason for the systematic difference found between observed and estimated values should be based on the difference in temperature at which the penetration and the dissolution study were performed, because the leaching of PEG can be significantly influenced by temperature. Nevertheless, this analytical result suggests that the *in vitro* lag time of pulsatile release dry-coated tablets can be estimated from the given formulation factor by adding a necessary correction term to Eq. 3.

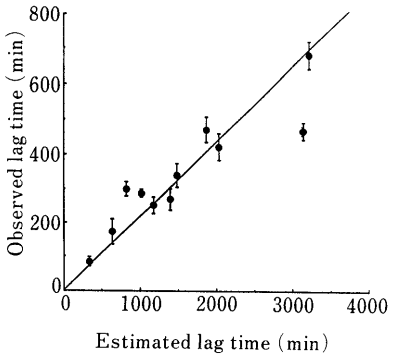

Fig. 11. Relation between Estimated Lag Time and Observed Lag Time of Various Isoniazid Dry-Coated Tablets

Each point represents mean ± S.D. of three measurements.

To examine the influence of physiological conditions after oral administration, dissolution tests using the D-3 formulation were performed at various paddle rotation speeds and dissolution media. It was found that the dissolution behavior for dry-coated tablets was not affected by the paddle rotation and/or dissolution medium, as shown in Fig. 12.

Conclusion

Through the present fundamental studies, it was shown that pulsatile drug release can be successfully achieved by introducing the concept of "time-controlled disintegration" to the conventional dry-coated tablet formulation. The important formulation factors necessary to realize an immediate release after a long lag time should be selection of the suitable thickness and composition of the outer shell and the disintegrant with enough swelling force to break the outer shell. Also, in the system using the HCO–PEG mixture for the outer shell, the *in vitro* lag time was predictable from the thickness and composition of outer shell using an empirical equation, even though the dimension of dry-coated tablets differed. All the information will be useful for designing a pulsatile release system which should enable us to achieve time-controlled or site-specific drug delivery in the gastrointestinal tract.

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TABLE III. Formulation of Isoniazid Dry-Coated Tablet

Ingredient	Formulations (mg/tablet)										
	D-1	D-2	D-3	D-4	D-5	D-6	D-7	D-8	D-9	D-10	D-11
Core tablet											
INZ	75	75	75	75	75	37.5	37.5	37.5	37.5	37.5	37.5
ECG	25	25	25	25	25	12.5	12.5	12.5	12.5	12.5	12.5
Outer shell											
HCO	195	390	352	332	340	117	156	195	234	312	390
PEG	50	100	40	60	50	30	40	50	60	80	100
St-Mg	5	10	8	8	10	3	4	5	6	8	10

Formulations from D-1 to D-5 consisted of a core tablet with a diameter of 7 mm and an outer shell with a diameter of 10 mm. Formulations from D-6 to D-9 consisted of a core tablet with a diameter of 5 mm and an outer shell with a diameter of 9 mm. Formulations D-10 and D-11 consisted of a core tablet with a diameter of 6 mm and an outer shell with a diameter of 10 mm.

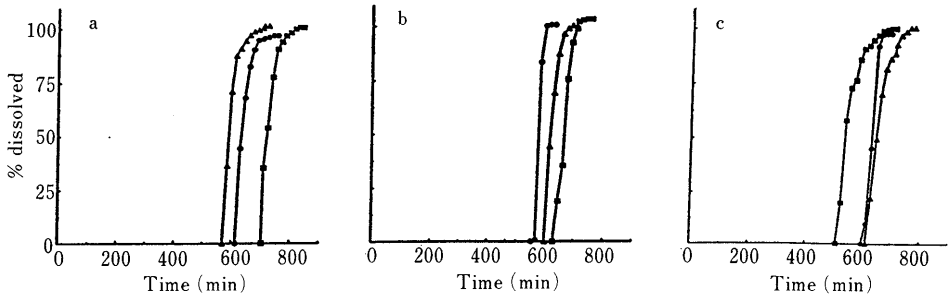

Fig. 12. Influence of Various Dissolution Test Fluids on Dissolution Behavior

Dry-coated tablets of D-3 were tested. Dissolution fluid: a, water; b, JP XII 1st fluid; c, JP XII 2nd fluid. Paddle rotation: ●, 50 rpm; ▲, 100 rpm; ■, 200 rpm.

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