Development of Dividable One-Step Dry-Coated Tablets (Dividable-OSDRC) and Their Evaluation as a New Platform for Controlled Drug Release

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Purpose. The purpose of this study is to develop novel dividable coated tablets that retain their characteristics even after they are divided.

Methods. We prepared dividable one-step dry-coated tablets (dividable-OSDRC) using our own manufacturing process with double structure punches. The release pattern of the dividable-OSDRC with hydroxypropyl methylcellulose (HPMC) or methacrylic acid copolymer LD (Eudragit) as an outer layer was investigated before and after the division, and dissolution profiles were statistically compared using difference factor f_1 and similarity factor f_2.

Results. The dividable-OSDRC with HPMC for sustained-release (compression pressure, 150 MPa; crashing strength, 6.1 N; friability, 0.05%; CV of divided tablet weight, 7.8%) showed statistically equivalent release patterns between the one-half and the whole (f_1, 13.9; f_2, 55.5) and between the one-half and the two-halves (5.5, 72.5). The surface area of the tablets affected the sustained-release profiles. Furthermore, the tablets made with Eudragit LD for timed-release (150 MPa, 12.8 N, 0.18%, 9.6%) also showed approximated release patterns before and after the division.

Conclusions. We proved that dividable-OSDRC maintain their release characteristics after they are divided. We conclude that the dividable-OSDRC could be used as a new platform for the controlled release of drugs.

KEY WORDS: compression-coated tablets; controlled release; dividable-OSDRC; one-step dry-coated tablets.

INTRODUCTION

Recently, studies have shown that it is possible to achieve effective medicinal effects and reduce the side effects of orally administered drugs by controlling the rate of drug release at the absorption site (i.e., the gastrointestinal tract). A dry-coated tablet is one of the most useful solid dosage forms that can be used for such controlled release systems giving a sustained-release pattern or a time-programmed pulsatile release pattern (1–9).

In practice, divided tablets are often given to match the drug kinetics to individual patients. Recently, Santen *et al.* (10) pointed out the problems of breaking difficulty, unequal parts, and a loss of mass for the administration of divided tablets to be dosed up or down. In contrast, Makino *et al.* (11) reported that the frequency of administration of divided tablets was increasing in the actual medical institutions to adjust the dosing schedule to individual patients. McEwen *et al.* (12) carried out to characterize the plasma level profile of verapamil as an antihypertensive calcium-channel-blocking agent under multiple-dose condition and to compare plasma levels after intact 240 mg tablets with those after the same total dose given as two halves of the same formulation. They reported the tablet retained its original sustained-release properties when the tablet was divided. Stockis *et al.* (13) reported that fractional dosing with a controlled-release scored tablet of isosorbide-5-mononitrate with highly reproducible divisibility allows achievement of lower peak concentrations and higher morning trough levels. However, neither conventional dry-coated tablets, enteric-coated tablets, nor sustained-release tablets with a coating layer should be divided, as they lose the original characteristics producing the release patterns. In addition, dividing conventional dry-coated tablets exposes the ingredients to light and/or humidity and may affect the taste of the tablet.

Dry-coated tablets having two cores surrounded completely by an outer layer might be a useful platform for the controlled release of drugs from dividable tablets. There has been, however, no method of manufacturing dry-coated tablets with double core. There are several difficulties even with the manufacturing of dry-coated tablets with a single core. The current manufacturing process requires core tablets prepared in advance. The core tablets are fed to each die of a rotary tableting machine for dry coating where the powder for the outer layer is fed previously and then compressed after feeding additional powder for the outer layer on the core. The core tablet supply system frequently produces non-core and off-center core tablets (14).

We previously reported a novel method of manufacturing dry-coated tablets (One-Step DRy-Coated tablets system, or OSDRC-system) that solves all the problems associated with the conventional approach (15–18). We applied the OSDRC-system to the preparation of novel dividable dry-coated tablets. The novel tablets, developed with the OSDRC-system as a base, are easily dividable dry-coated tablets having double core and are expected to continue the controlled release of drugs after they are divided, as their two cores are completely surrounded by the outer layer. One can prepare dry-coated tablets with double core in a single run with a rotary tableting machine without having to prepare core tablets beforehand. Furthermore, this manufacturing process has advantages in terms of selecting the core's shape and placing the cores in a suitable position (19).

The objectives of this study are to develop dividable-OSDRC for the pharmaceutical market and to evaluate the possibility of their application as a new platform for dividable controlled-release tablets similar to sustained-release and timed-release tables.

TECHNICAL VIEW OF THE MANUFACTURING PROCESS

Structure of the Novel Punch Used for the Manufacturing of Dividable-OSDRC

The double punch used for this system is shown in Fig. 1. The structure consists of a center punch whose tip is divided

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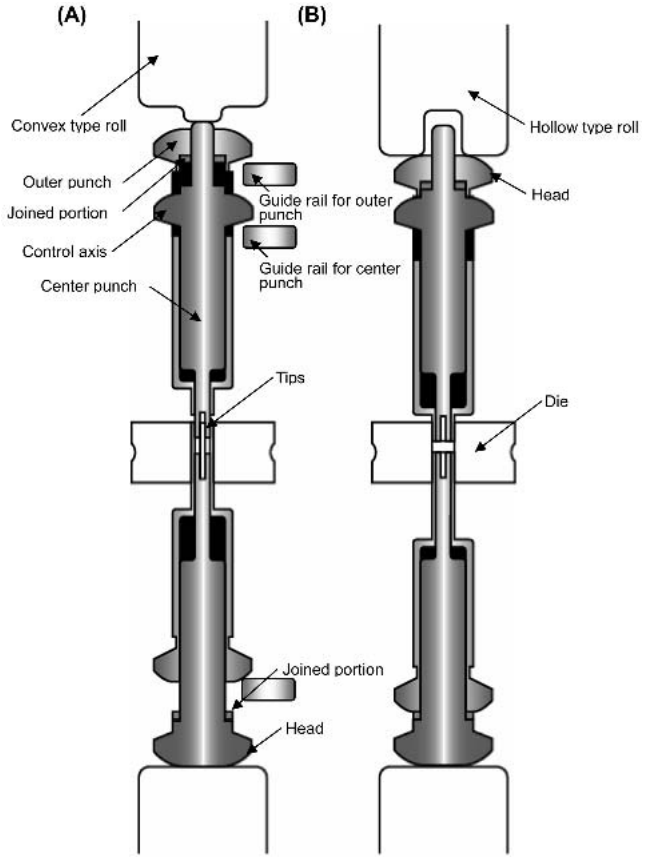

Fig. 1. Novel punches developed for the manufacturing process. (A) The punches for the first-outer layer or first-outer layer/core layer compression. (B) The punches for the second-outer layer compression (including the chore).

into two, like a fork, completely surrounded by an outer punch. The upper-center punch has two tips branched from the body. Its compression head protrudes from the upper-outer punch head. The upper-center punch moves freely in the body of the upper-outer punch, and its location is controlled by the control axis, which protrudes from the body of the upper-outer punch in contact with a guide rail.

A convex type roll presses only the head of the upper-center punch to compress the first-outer layers and their complexes with the core-layers (Fig. 1A). The second-outer layer surrounding the first-outer layer/core-layer complexes is formed by pressing only the head of the upper-outer punch with a hollow type roll (Fig. 1B). Because the upper-center punch and upper-outer punch are in fact joined, the compression pressure generated by the hollow type roll is transmitted to the upper-center punch as well as the upper-outer punch. The tips of the upper-center and upper-outer punches are adjusted to create a flat face. Namely, the upper-unified punches act as a normal punch.

As for the lower punches, two tips also branch from the body of the lower-center punch. Its compression head protrudes from the lower-outer punch head. However, the movement of the lower-center punch is controlled by the head itself differently from the upper punch, which is controlled by the control axis. The tips of the lower-center and lower-outer punches are also combined like the upper punches.

Manufacture and Characteristics of Dividable-OSDRC

The dividable-OSDRC can be assembled on the turntable of a rotary tableting machine. Because the manufacturing process does not require an external core tablet supply system, dry-coated tablets with co-locating double core can be easily and constantly produced (Fig. 2). Furthermore, the method has the advantage of allowing the selection of the core's shape and an arrangement suitable for division. This is because the shape and arrangement of the core depend upon shape of each tip of the double structure punch.

The dividable-OSDRC are prepared as follows. Step 1 (Fig. 2) shows the die and punches of the double structure, and step 2 through 4 depict the formation of the first-outer layers. The powder for the first-outer layers fills the two spaces made by the lower-center punch and the inside wall of the lower-outer punch. The tip of the lower-outer punch and the surface of the die are leveled flat under these conditions (step 2). Then, the powder is pre-compressed by the upper-center punch and lower-center punch (step 3). The powder not compressed by the center punches remains on the lower-outer punch. Therefore, a suction device is applied to remove it (step 4). Steps 5 through 8 depict the formation of two complexes of the first-outer layer/core layer. The two complexes of the first-outer layer/core layer are formed similar to the first-outer layer. Any powder not used for the core layers is also removed at this point (step 8).

Steps 9 through 13 depict the formation of dividable-OSDRC, which include the complexes of the first-outer layer/core layer. After sliding down the lower-outer punch (step 9), the powder for the second-outer layer fills the die (step 10). The complexes of the first-outer layer/core layer are pushed into the powder for the second-outer layer in the die (step 11). The space around the pre-compressed complexes of the first-outer layer/core layer is filled with the powder for the second-outer layer. The surplus powder for the second-outer layer is removed by the cutting-board, and the core layers are surrounded thoroughly (step 12).

During the last compression, the powder for the second-outer layer is compressed by the upper and lower punches together with two pre-compressed complexes. The final compression employs a simultaneous movement of the center and outer punches (step 13). The compressed dividable-OSDRC are ejected by the knock off plate and taken out from the tableting machine (step 14).

MATERIALS AND METHODS

Materials

The powders used for dividable-OSDRC were acetaminophen (Tyco Healthcare Co., Ltd., Tokyo, Japan) as a water-soluble drug, α-lactose monohydrate (Pharmatose 200M lactose; DMV Japan Co., Ltd., Osaka, Japan) as a diluent, hydroxypropyl methylcellulose (HPMC) with a viscosity of 6 cps (TC-5RW; Shinetsu Chemical Co., Ltd., Tokyo, Japan) as an sustained release agent, cross-linked carboxymethylcellulose sodium (AcDiSol; Asahi Chemical Industry Co., Ltd., Tokyo, Japan) as a disintegrant, methacrylic acid copolymer LD (Eudragit L 100-55; Higuchi Co., Ltd., Tokyo, Japan) as an enteric coating agent, triethyl citrate (SC-60; CBC Co., Ltd., Tokyo, Japan) as a plasticizer, magnesium aluminometasili-

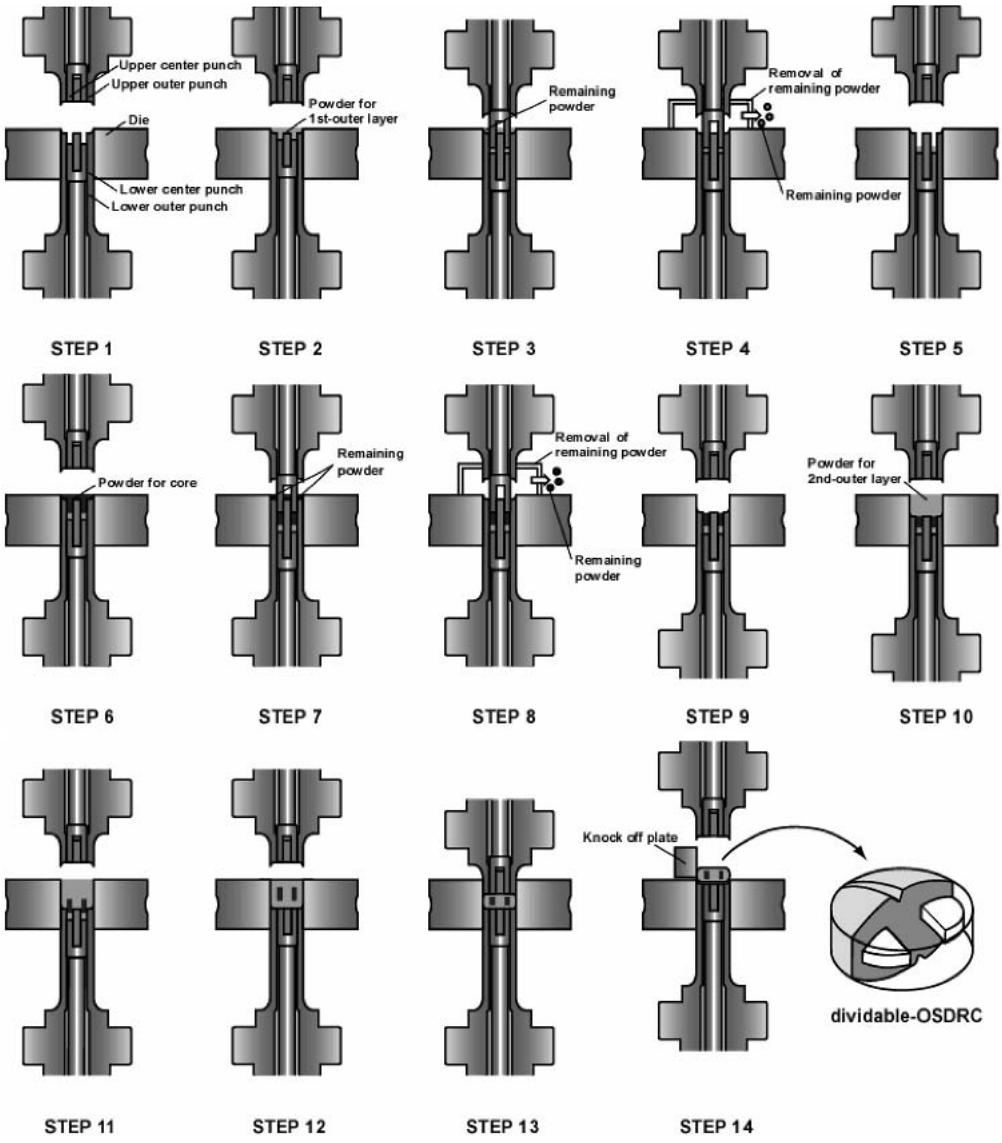

Fig. 2. Mechanism of manufacturing dividable-OSDRC.

cate (Neusilin-US2; Fuji Chemical Industry Co., Ltd., Toyama, Japan) as an absorbent of plasticizer, and magnesium stearate (Taihei Chemical Co., Ltd., Osaka, Japan) as a lubricant.

Preparation of Dividable-OSDRC

The powders for the dividable OSDRC with sustained-release and timed-release were mixed at ratios shown in Table I using a V type blender (Tsutsui Rikagaku Instrument Co., Ltd., Osaka, Japan). Acetaminophen was sieved into 60–180-μm fractions prior to the mixing. The triethyl citrate was used after absorption of the equivalent weight of magnesium aluminometasilicate.

The method used to produce the dividable-OSDRC is outlined in the section "Technical View of the Manufacturing Process." The method was developed for use with rotary-type tableting machine. In this study, however, we used a single set of model punches and dies to prepare dividable-OSDRC. The double punches consist of an upper-center punch with two-forked tips (tips of half-oblong: 6 × 4 mm), a lower-center punch with two-forked tips, an upper-outer punch (oblong: 16 × 6 mm), and a lower-outer punch. The final compression was at a fixed speed of 1 mm/min under 150 MPa, using a universal tension and compression tester (AG-I 20 kNT; Shimadzu Co., Kyoto, Japan) to obtain dividable-OSDRC weighing 240 mg (each core weight: 30 mg) and approximately 3.3-mm thick. The tablets were left at room temperature for 24 h in a desiccator with silica gel and then subjected to the following tests.

Measurement of Crushing Force

The tablets were subjected to the breaking test using a tablet hardness tester (TH-203; Toyama Kagaku, Osaka, Japan). The load was applied along the minor axis of the tablet to measure the maximum load as a crushing force at the tablet fracture.

Friability Tests of Dividable-OSDRC

Twenty polystyrene beads (Polystyrene beads; diameter of 6 mm; Wako Pure Chemical Industries, Osaka, Japan)

Table I. Ingredients of Dividable-OSDRC

Material (mg/tablet)	Core	Outer layer	Total
Dividable-OSDRC with HPMC			
Acetaminophen	48		
Lactose	11		
Magnesium stearate	1		60
Hydroxypropyl methylcellulose		179	
Magnesium stearate		1	180
			240
Dividable-OSDRC with Eudragit			
Acetaminophen	30		
Cross-linked carboxymethylcellulose sodium	29		
Magnesium stearate	1		60
Methacrylic acid copolymer LD		143	
Magnesium aluminometasilicate		18	
Triethyl citrate		18	
Magnesium stearate		1	180
			240

HPMC, hydroxypropyl methylcellulose.

were put into a drum with the samples of a friability tester (Electrolabo; EF-1W, Higuchi, Tokyo, Japan). The drum was rotated (25 rpm) for 4 min, and the decrease in weight of each tablet was measured to calculate the friability.

Dissolution Tests of Dividable-OSDRC

The pattern of drug release from the dividable-OSDRC was evaluated by conducting dissolution tests in compliance with the paddle method described in the *Japanese Pharmacopoeia XIII* (JP XIII). The samples were non-divided tablets (whole), one half of a tablet (divided one-half), and two separated halves of a tablet (divided two-half), and they were put into the sinkers described in JP XIII for the prevention of flotation or the adhesion of tablets to dissolution vessels. They were sunk in a test medium maintained at 37°C. The paddle rotation speed was set at 50 rpm.

The test media used for evaluation of the release pattern were purified water, No. 1 fluid (pH 1.2), and No. 2 fluid (pH 6.8) according to JP XIII. Fractions of the medium were sampled with the fraction collector of a dissolution tester (NTR-6100A; Toyamakagaku Co., Osaka, Japan), and the concentration of acetaminophen in the medium was measured using a spectrophotometer at a wavelength of 284 nm (UV-1700; Shimadzu Co., Kyoto, Japan). The mean value of three run was used for each dissolution rates.

Calculations of the Surface Area

Theoretical calculations of the surface areas of non-divided tablets (whole) and two divided halves of a tablet (divided two-half) with 3.3 mm of thickness were made with computer software (Tablet CAD, Saga Software, Reykjavik, Iceland).

Measurements of the Erosion Rate

Dividable-OSDRC (oblong: 16 × 6 mm) with no core were prepared by compressing 240 mg of the outer layer ingredients at 150 MPa with the universal tension and compression tester. Whole and divided two-half preparations were put into the sinkers in compliance with JP XIII. They were sunk in purified water as a dissolution medium at 37°C. The paddle rotation speed was set at 50 rpm. The samples were taken out of the dissolution medium at predetermined time points and then put in small glass bottles of known weight. The samples were dried at 70°C for 3 days and left at room temperature for 3 days in a desiccator with silica gel. The dried samples were weighed, and the change in the weight fraction of dividable-OSDRC was calculated.

Statistical Analysis

Difference factor f_1 and similarity factor f_2 were calculated using the following equations (20).

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \quad (1)$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where n is number of time points, R_t is the amount dissolved from the reference sample at time t, T_t is the amount dissolved from the test sample at time t, and w_t is an optional weight factor and was set to 1 in this experiment according to the FDA guidance.

Statistical differences in lag time were examined using a one-way analysis of variance (ANOVA) followed by a least significant difference test. The significance level was set at $p < 0.05$.

RESULTS AND DISCUSSION

Compression Characteristics of Dividable-OSDRC

The physical properties of dividable-OSDRC compressed at different pressures are summarized in Table II. An increase in the compression pressure from 50 to 150 MPa resulted in a slight increase in the crushing force at the score line and a decrease in friability of dividable-OSDRC prepared both with HPMC and with Eudragit LD. All of the samples were able to be divided by hand at the score line. The variation coefficients in weight between two halves with HPMC and with Eudragit LD were 7.8% and 9.6%, respec-

Table II. Compression Characteristics of Dividable-OSDRC

Sample	Compression pressure (MPa)	Crushing force of score line (N)	Friability (%)
OSDRC with HPMC (Whole)	50	2.3 ± 0.6	—
	100	3.3 ± 0.6	0.49 ± 0.15
	150	6.1 ± 0.4	0.05 ± 0.02
OSDRC with Eudragit (Whole)	50	2.3 ± 0.6	—
	100	10.5 ± 3.2	0.22 ± 0.10
	150	12.8 ± 2.8	0.18 ± 0.11

The mark (—) indicates not measured due to crushing. All tests were performed three times. HPMC, hydroxypropyl methylcellulose.

tively (n = 5). The friability of the dividable-OSDRC made at 50 MPa could not be measured because they were divided or disrupted during the friability test.

From the above results, we concluded that the dividable-OSDRC compressed at 100 and 150 MPa were suitable for studies to evaluate the drug release profile.

Evaluations of Drug Release from Dividable-OSDRC Using HPMC as Sustained-Release Tablets

The release profiles of acetaminophen from non-divided tablets (whole), one of their halves (divided one-half), and both halves (divided two-half) were evaluated in a dissolution test with purified water. The results are shown in Fig. 3. The dissolution of core-only tablets reached 100% within 40 min. On the other hand, all of the whole, divided one-half, and divided two-half samples showed delayed release profiles in comparison with the core-only tablet. All dividable-OSDRC clearly showed sustained-release patterns. We speculated that the release of the divided tablets was sustained by the outer layer, HPMC, which prevented direct exposure of the core to the dissolution medium.

Moore and Flanner (20) have reported the mathematical indices to define difference factor f_1 and similarity factor f_2 to compare the dissolution profiles. The factor f_1 is proportional to the average difference between the two profiles, whereas the factor f_2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time-points (21). In addition, Shah *et al.* (22) have reported the importance of condition to limit the number of sample points to no more than one, once any of the sample reaches 85% dissolution. We used the dissolution data at 0.67, 1.00, 1.33, 1.67, 2.00, and 2.33 h for dividable-OSDRC with HPMC. The f_1 and f_2 factors between the divided one-half and two-half preparations showed 5.5 and 72.5, respectively, as shown in Table III. Generally, the f_1 values 0–15 and f_2 values 50–100 ensure the sameness or the equivalence of two profiles (23). Based on the criteria, the drug release patterns of the divided one-half and two-half preparations were statistically the same. In contrast, the f_1 and f_2 values of one-half and two-half in relation to the whole were 13.9, 55.5, and 17.1, 50.3, respectively. The f_1 and f_2 values suggested that the drug release pattern of the one-half is statistically equivalent to that of the whole. Although the f_1 value of the two-half was marginally out of the range to ensure the statistical equivalence to the whole, the two-half and the whole also showed the approximated release patterns (Fig. 3).

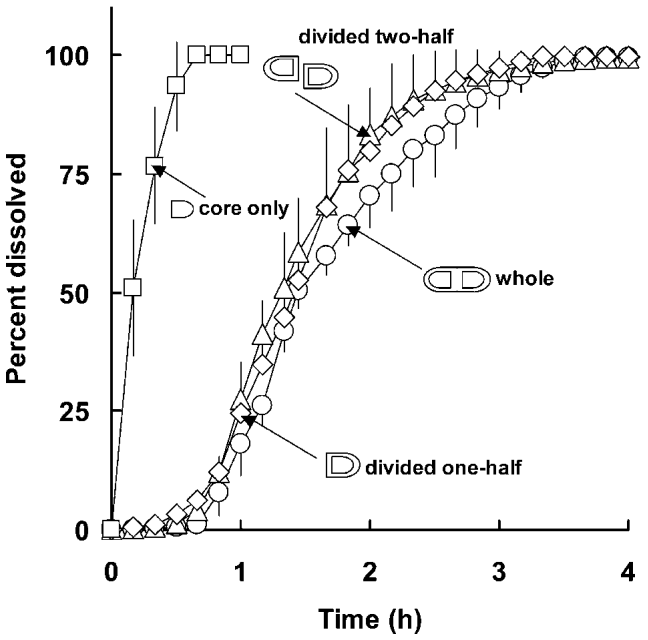

Fig. 3. Comparison of the release pattern of acetaminophen from the dividable-OSDRC samples consisting of an HPMC outer layer.

Table III. Statistical Test Results for the Difference Factor and the Similarly Factor

Samples	Difference factor (f_1)	Similarly factor (f_2)
Dissolution of dividable-OSDRC with HPMC		
One-half and two-half	5.5	72.5
Whole and one-half	13.9	55.5
Whole and two-half	17.1	50.3
Dissolution of dividable-OSDRC with Eudragit		
One-half and two-half	11.4	58.3
Whole and one-half	33.7	34.3
Whole and two-half	20.5	41.5
Erosion		
Whole and two-half	15.8	44.9

HPMC, hydroxypropyl methylcellulose.

The surface area of tablets is one of the factors that affect drug release from coated tablets, because the contact probability of outer layer with the medium depends on its surface area. On another hand, the outer layer thickness of divided tablets is also a key factor to affect the drug release pattern. We observed that the core in the divided tablet was completely enclosed by approximately 1-mm-thick outer layer. To test whether the surface area of the sample affected the release pattern, theoretical calculations of the surface areas of the tablets were made. It was confirmed that the divided tablets (362.9 mm^3) had a surface area that was approximately 13% larger than that of the intact dividable-OSDRC (320.0 mm^3).

Furthermore, it is likely that the rate of erosion of the outer layer, which would be closely linked to the release rate of the drug, also depends on the surface area. In order to verify this, the rate of erosion of both whole and divided tablets, both of which were prepared only with the powder for the outer layer, was evaluated in dissolution tests using weight change as an indicator. The results are shown in Fig. 4 and Table III. The changes in weights of the whole and divided tablets were different according to the results of f_1 (15.8) and f_2 (44.9) values. The change in weight of the whole tablet was smaller than that of the divided tablet, indicating slower erosion. Considering the above results, we concluded that the increase in the release rate of the divided one-half and two-half preparations was dependent on the increase in the surface area of the tablets. It is indicated that by choosing a tablet shape that gives almost the same surface area before and after the division, more similar release patterns before and after the division can be obtained.

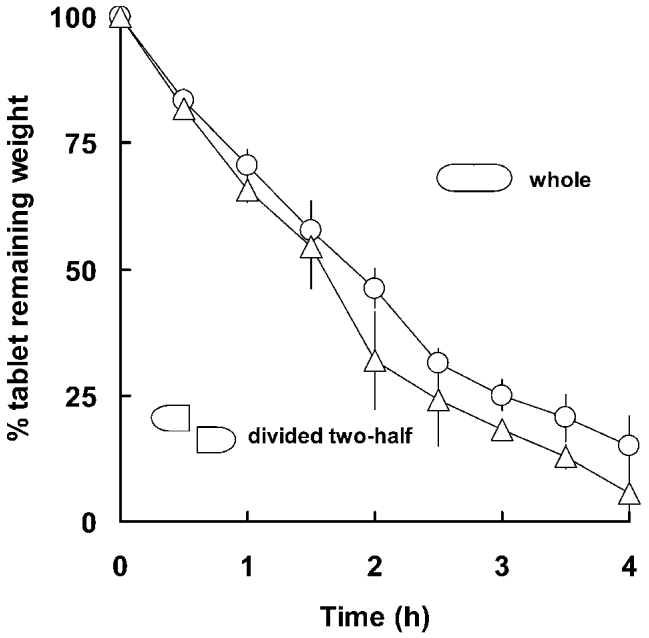

Fig. 4. Change in the weight of dividable-OSDRC and divided two-half consisting of HPMC without a core.

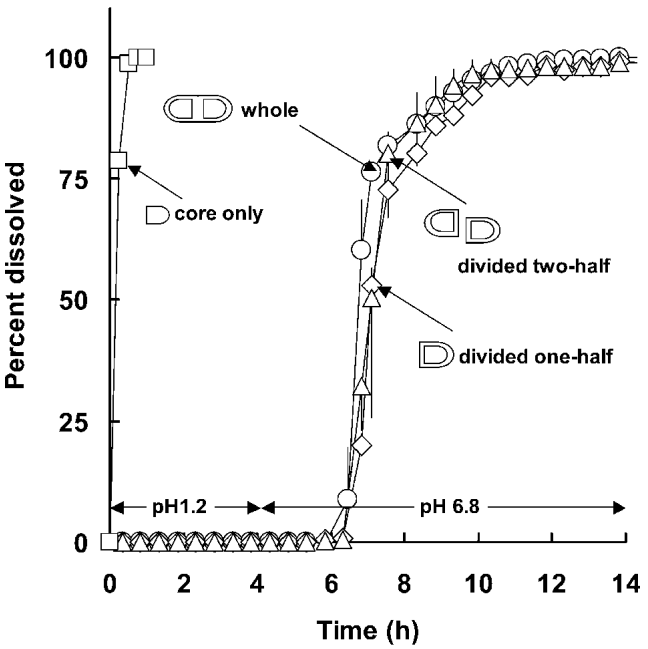

Fig. 5. Comparison of the release pattern of acetaminophen from the dividable-OSDRC samples consisting of a Eudragit outer layer.

Evaluations of Drug Release from Dividable-OSDRC Using Eudragit as Timed-Release Tablets

In order to evaluate the possibility of using dividable-OSDRC as timed-release tablets, tablets were prepared with an enteric coating agent (Eudragit) as an outer layer and their release pattern was evaluated. All of the whole, divided one-half, and divided two-half preparations were acid resistant, as no sample showed any release in 24 h in the test using No. 1 fluid (pH 1.2) complying with JP XIII (data not shown). It was successfully confirmed that each core of the dividable-OSDRC was completely surrounded by the outer layer of the enteric agent after the division of the tablets.

The samples left in the No. 1 fluid for 4 h were put in the No. 2 fluid (pH 6.8) to evaluate the release. The results are shown in Fig. 5. The point when 5% or more of the acetaminophen dissolved in the medium was defined as the end of the lag-time in this experiment. Each sample showed a rapid release after some lag-time, 6.5–6.7 h, which was statistically equivalent ($p < 0.05$) among the samples.

The whole, divided one-half, and divided two-half preparations showed almost the same dissolution profiles. We calculated f_1 and f_2 values using the dissolution data at 6.33, 6.83, 7.33, 7.83, and 8.33 h to examine the equivalency among the preparations. Although the divided one-half and divided two-half were statistically equivalent, the equivalency of the one-half and two-half in relation to the whole was not proved as shown in Table III. However, we considered that the tablets made with Eudragit for timed-release had practically the same release patterns before and after the division because the drug was released within a limited time span from the three preparations. Because the drug was released very rapidly after a long lag time (Fig. 5), a very slight variation of lag time would result in a large variation of released amount at a time.

The above results indicated that the dividable-OSDRC could create a lag time similar to timed-release tablets. We proved that the release pattern of the dividable-OSDRC did not change after the tablets were divided.

CONCLUSIONS

Dry-coated tablets having two cores were produced using a novel manufacturing method. Moreover, it was proved that the original characteristics of the drug release pattern did not change even after the tablets were divided.

The dividable-OSDRC enable us to control doses more precisely by dividing them even when they are dry-coated or enteric-coated. Furthermore, the dividable-OSDRC may reduce the number of tablets with different drug contents and will bring about a medical economical advantage.

Pharmaceutical formulators could use them as a new oral dosage form in the actual formulation process.

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