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Formulation study and drug release mechanism of a new theophylline sustained-release preparation

Tetsuo Hayashi [a,b,*], Hideyoshi Kanbe [a,b], Minoru Okada [a], Makoto Suzuki [a], Yasuo Ikeda [a], Yoichi Onuki [a], Tetsuo Kaneko [a], Takashi Sonobe [b]

[a] *Central Research Laboratories, SSP Co., Ltd., Nanpeidai 1143, Narita-shi, Chiba 286-1511, Japan*
[b] *School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka-shi, Shizuoka 422-8526, Japan*

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Abstract

Two matrix theophylline tablets with different release mechanisms were compared. Tablet A was a swelling/disintegration-type wax matrix made of hydrophobic wax granules, consisting of stearic acid, hydrogenated oil and glycerol esters of fatty acids, and hydrophilic polymer granules composed primarily of hydroxypropyl methylcellulose (HPMC). We named Tablet A the cluster tablet. Tablet B was a gel matrix made of hydrophobic ethylcellulose granules, consisting of ethylcellulose and hydrogenated oil, and hydrophilic polymer granules consisting of HPMC and hydroxylpropylmethylcellulose acetate succinate (HPMCAS).

The formulations were screened in vitro according to their dissolution characteristics. The drug release from each preparation was analyzed using release kinetics theories. In Tablet A, the value of the exponent(n) representing the apparent diffusion mechanism determined from the Korsmeyer–Peppas model equation was about 0.6 and was unlikely to be affected by the rotation speed. In Tablet B, the value of the exponent(n) by the Korsmeyer–Peppas model equation changed with the paddle rotation speed. These results suggested that the drug release mechanism of Tablet B is greatly affected by the extent of physical force in the gastrointestinal tract.

Keywords: Theophylline; Matrix tablet; Sustained-release; Release mechanism; Hydrophobic wax; Hydrophilic polymer

1. Introduction

Tablets are generally easier to take than capsules or granules, and are among the most widely used dosage forms. Also, sustained release technology of drugs has been developed recently to alleviate patient's burden and improve their QOL by reducing the dosing frequency.

Oral sustained-release preparations can be classified into multiple-unit preparations and single-unit preparations. Multiple-unit preparations distribute granules relatively widely in the digestive tract after

* Corresponding author. Tel.: +81 476 27 1511; fax: +81 476 26 7948.
E-mail address: Tetsuo.Hayashi@ssp.co.jp (T. Hayashi).

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administration and have been reported to be relatively unaffected by digestive tract activities, causing less variation in the results of pharmacokinetic studies (Bechgaard and Ladefoged, 1981; Davis et al., 1988; Efentakis and Koutlis, 2001; Sandberg et al., 1993). Multiple-unit preparations are often manufactured by coating spherical granules with a controlled release film, and a large quantity of organic solvent is used in the manufacturing process. Although there are water-based coating solutions for sustained-release processing (Frohoff-Hülsmann et al., 1999), they are mostly mixed solvents containing ethanol. Also, the coating of granules in a fluid bed coating machine has been reported to cause differences in the release characteristics of the active component between tablets prepared with a small scale experimental system and those prepared with a large scale manufacturing system, even with identical formulations because of differences in the drying/stirring efficiency and to be unsatisfactory in the release reproducibility, and the improvement of these things was reported (Aoki et al., 1998; Ohkuma et al., 1998).

As for single-unit preparations, tablets coated with a controlled release film (Marvola et al., 1985), tablets with a water-soluble polymer matrix (Madhusudan Rao et al., 2001; Rao et al., 2001), tablets with a wax matrix (Zhang and Schwartz, 2003) and tablets with hydrophobic polymer matrix (Katikaneni et al., 1995; Neau et al., 1999) are known. The release of the active components of single-unit preparations are more likely to be affected by meals and peristaltic activities than those of multi-unit preparations, and this is the primary cause of the variation of the results of the pharmacokinetic studies.

Theophylline has long been used as a treatment for diseases, including bronchial asthma. However, as its therapeutic concentration range is narrow, and as its absorption is prone to the effects of meals, the dosing management of the drug has been difficult.

The drug release rate is difficult to control in all existing sustained-release tablets. Moreover, as they are manufactured by a complicated process, the drug release rate is likely to vary among lots, and advanced technology is needed to ensure consistent quality. Drug absorption from a conventional matrix tablet is influenced heavily by its transition rate in the gastrointestinal tract, and accordingly, the bioavailability of conventional matrix tablets varies widely (Abrahamsson et al., 1998). It was reported that the multiple-unit dosage form can overcome this problem to a certain extent; however, it requires a sophisticated manufacturing technology (Li et al., 1988; Appelgren and Eskilson, 1990; Ohkuma et al., 1998). It is the purpose of this study to develop a new dosage form that overcomes these biological and technological problems.

A formulation study on the novel theophylline sustained-release preparation of the cluster tablet is hereby reported and its drug release mechanism will be discussed.

In this study, we prepared sustained-release granules consisting of a hydrophobic matrix base, and granules consisting of a hydrophilic matrix base using the ordinary granulation method, unlike the film-coating method using organic solvents, and mixed them at a particular ratio to control the release rate, and obtained sustained-release tablets with a satisfactorily reproducible release rate.

We analyzed the release mechanisim of two sustained-release tablets.

2. Experimental

2.1. Materials

Theophylline (Shiratori Pharmaceutical Co. Ltd.), lactose (200 M, Megre), hydroxypropylmethylcellulose (HPMC) 2208 (Metolose® 90SH viscosity 4000 mm^2/s, 15,000 mm^2/s, 100,000 mm^2/s; Shin-Etsu Chemical Co. Ltd.), hydroxypropylmethylcellulose (HPMC) 2910 (Metolose® 60SH viscosity 50 mm^2/s, Shin-Etsu Chemical Co. Ltd.), microcrystalline cellulose (Avicel® PH101, Asahi Kasei Corporation), stearic acid (NAA-174, NOF Corporation), hydrogenated oil (Lubriwax® 101, FREUND) and magnesium stearate (Taihei Chemical Industrial Co. Ltd.) were preparations conforming to the Japanese Pharmacopoeia (JPXIV). Ethylcellulose aqueous dispersion (Aquacoat®, Asahi Kasei Corporation) and hydroxypropylmethylcellulose acetate succinate (HPMCAS) (AQOAT®, Shin-Etsu Chemical Co. Ltd.) were products conforming to the Japanese Pharmaceutical Excipients. Glycerol esters of fatty acids (Exel84®, Kao Corporation, Myvacet®9–45k,

Koyo Mercantile Company Ltd.) were a product conforming to the Japan's Specifications and Standards for Food Additives. All other reagents were special grade commercial preparations.

2.2. Preparation of sustained-release tablets

2.2.1. Tablet A: tablets with a combination of hydrophobic wax granules and hydrophilic polymer granules-1

Preparation of hydrophobic wax granules: Hydrophobic wax granules were prepared by melting stearic acid (140 g), hydrogenated oil (130 g), and glycerol esters of fatty acids (130 g) by heating, adding them to theophylline (600 g) and kneading them, allowing the mixture to cool, and sizing it with a 16 mesh (1000 μm) sieve.

Preparation of hydrophilic polymer granules-1: Hydrophilic polymer granules-1 were prepared by mixing theophylline (600 g), HPMC2208 viscosity 4000 mm^2/s (50 g), and lactose (350 g), adding purified water, kneading the mixture, drying it, and sizing it with a 16 mesh (1000 μm) sieve. Table 1 summarizes the above formulations.

The above hydrophobic wax granules and hydrophilic polymer granules-1 were mixed at ratios of 10:90 to 90:10, then 3.4 mg of magnesium stearate was added, and tablets weighing 337 mg and 9 mm in diameter were prepared. Table 2 summarizes the above formulations.

In consideration of easy ingestion by patients, oblong tablets (13 mm in long diameter and 8 mm in short diameter) weighing 337 mg were prepared at a mixing ratio of A5 in the above formulations as samples for dissolution tests under various conditions.

Table 1
Formulations of theophylline granules of Tablet A

	Hydrophilic polymer granules-1 (g)	Hydrophobic wax granules (g)
Theophylline	600	600
Stearic acid	–	140
Hydrogenated oil	–	130
Glycerol esters of fatty acids	–	130
HPMC2208 (viscosity: 4000 mm^2/s)	50	–
Lactose	350	–
Total	1000	1000

Table 2
Mixing ratios of hydrophobic wax granules and hydrophilic polymer granules-1

Tablet	Hydrophobic wax granules	Hydrophilic polymer granules-1
A1	10	90
A2	20	80
A3	30	70
A4	40	60
A5	50	50
A6	60	40
A7	70	30
A8	80	20
A9	90	10

2.2.2. Tablet B: tablets with a combination of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2

Preparation of hydrophobic ethylcellulose granules: Hydrophobic ethylcellulose granules were prepared by mixing theophylline (600 g), microcrystalline cellulose (50 g), lactose (30 g), hydrogenated oil (150 g), and HPMC2208 viscosity 100,000 mm^2/s (50 g), adding a mixture of ethylcellulose aqueous dispersion (333.3 g) and glycerol esters of fatty acids (Myvacet® 9–45 K, 20 g), kneading the mixture, drying it and sizing it with a 16 mesh (1000 μm) sieve.

Preparation of hydrophilic polymer granules-2: Hydrophilic polymer granules-2 were prepared by mixing theophylline (600 g), microcrystalline cellulose (100 g), lactose (100 g), HPMC2208 viscosity 100,000 mm^2/s (150 g), and HPMCAS (50 g), adding 25% aqueous solution of ethanol (JP), kneading the mixture, allowing it to cool, and sizing it with a 16 mesh (1000 μm) sieve. Table 3 summarizes the above formulations.

The above hydrophobic ethylcellulose granules and hydrophilic polymer granules-2 were mixed at ratios of 40:60 to 60:40, then 3.4 mg of magnesium stearate was added and oblong tablets (13 mm in long diameter and 8 mm in short diameter) weighing 337 mg were prepared. Table 4 summarizes the above formulations. To examine the effect of the viscosity of HPMC, HPMC of varying viscosities was used for the preparation of the hydrophobic ethylcellulose granules and hydrophilic

Table 3
Formulations of theophylline granules of Tablet B

	Hydrophobic ethylcellulose granules (g)	Hydrophilic polymer granules-2 (g)
Theophylline	600	600
HPMC2208 (viscosity: 100,000 mm^2/s)	50	150
Microcrystalline cellulose	50	100
Lactose	30	100
Hydrogenated oil	150	–
Ethylcellulose aqueous dipersion (solid)	100	–
HPMCAS	–	50
Glycerol esters of fatty acids	20	–
Total	1000	1000

Table 4
Mixing ratios of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2

Tablet	Hydrophobic ethylcellulose granules	Hydrophilic polymer granules-2
B1	40	60
B2	50	50
B3	60	40

polymer granules-2. Table 5 summarizes the above formulations.

2.3. Dissolution tests

The in vitro dissolution tests of the tablets were performed under the conditions described in Sections 3.1 and 3.2 below, according to the dissolution test methods of the JPXIV. The release of theophylline was measured by the UV method at 272 nm.

Table 5
Viscosity of HPMC of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2

Tablet	Hydrophobic ethylcellulose granules (mm^2/s)	Hydrophilic polymer granules-2 (mm^2/s)
C1	50 (HPMC2910)	50 (HPMC2910)
C2	4000 (HPMC2208)	4000 (HPMC2208)
C3	100000 (HPMC2208)	100000 (HPMC2208)

2.3.1. Dissolution medium

Purified water, pH 6.8 (second fluid of the disintegration test method, JPXIV), and pH 7.5 (simulated intestinal fluid, KH_2PO_4/NaOH buffer). Dissolution characteristics of Tablets A and B were compared mainly based on data of dissolution in water. The other pH medium were used for confirmation purpose.

2.3.2. Stirring intensity

Paddle rotation speeds 50, 100 and 200 rpm.

3. Results and discussion

3.1. Screening of formulations of Tablet A using the dissolution test

The in vitro sustained release of theophylline from the tablets prepared as above was examined by performing dissolution tests under the following conditions. Conditions of dissolution tests: JP14, paddle method, 50 rpm, pH 6.8, dissolution medium volume 900 mL.

3.1.1. Dissolution tests of theophylline from tablets of a mixture of hydrophobic wax granules and hydrophilic polymer granules-1

Fig. 1 shows the results of dissolution tests of tablets prepared by changing the mixing ratio of hydrophobic wax granules and hydrophilic polymer granules-1 from 10:90 to 90:10.

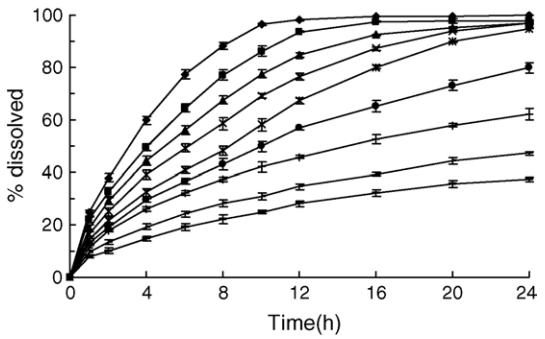

Fig. 1. Dissolution of theophylline from tablets with various mixing ratios of hydrophobic wax granules and hydrophilic polymer granules using the paddle method at a rotation speed at 50 rpm in JPXIV second fluid. Each result shows the mean ± S.D. ($n = 3$). (♦) A1; (■) A2; (▲) A3; (×) A4; (*) A5; (●) A6; (+) A7; (-) A8; (–) A9.

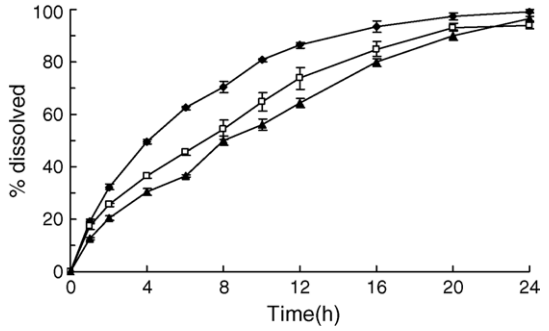

Fig. 2. Effect of viscosity of HPMC in hydrophilic polymer granules-1 on the dissolution of theophylline from Tablet A using the paddle method at a rotation speed at 50 rpm in simulated intestinal fluid (pH 7.5). Each result shows the mean ± S.D. ($n = 3$). (♦) 50 mm^2/s (HPMC2910); (□) 4000 mm^2/s (HPMC2208); (▲) 15,000 mm^2/s (HPMC2208).

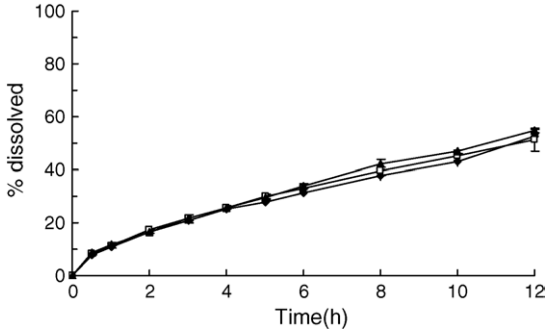

Fig. 3. Dissolution of theophylline from tablets with various mixing ratios of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2 using the paddle method at a rotation speed at 50 rpm in simulated intestinal fluid (pH 7.5). Each result shows the mean ± S.D. ($n = 3$) and error bars are in the symbols. (♦) B1; (□) B2; (▲) B3.

There have been reports of the matrix tablets consisting of hydrophobic and hydrophlilic polymers, but they also failed to continuously control the drug release rate (Kader and Jalil, 1998; Jovannvić et al., 1997). The release rate of theophylline was found to be controlled continuously over a long period by changing the mixing ratio of hydrophobic wax granules and hydrophilic polymer granules-1.

The purpose of the current study was to formulate once-a-day theophylline tablets, and the initial target of dissolution was 70% release in 12 h and more than 80% in 16 h.

3.1.2. Effects of the viscosity of HPMC in hydrophilic polymer granules-1 on the dissolution of Tablet A

Effects of the viscosity of HPMC in hydrophilic polymer granules-1 were examined using HPMC of varying viscosities. The dissolution test medium was pH 7.5. Fig. 2 shows the results of dissolution tests of tablets prepared by changing the viscosity of HPMC in hydrophilic polymer granules-1. The release slowed as the viscosity of HPMC increased.

3.2. Screening of formulations of Tablet B with dissolution tests

Effects of the mixing ratio of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2 on the theophylline release were examined. The dissolution test medium was pH 7.5. Fig. 3 shows the results of dissolution tests of tablets prepared by changing the mixing ratio of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2 from 40:60 to 60:40. The release of theophylline did not change with the mixing ratio of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2. In this formulation, the major component to form matrix is HPMC. And, the amount of HPMC in Tablet B is sufficiently formulated to maintain matrix in dissolution medium.

3.2.1. Effects of the viscosity of HPMC on the release of theophylline from Tablet B

Effects of changes in the viscosity of HPMC in hydrophobic ethylcellulose granules and hydrophilic polymer granules-2 on the results of dissolution tests were examined. The dissolution test medium was pH 7.5. Fig. 4 shows the results of dissolution tests of tablets prepared by changing the viscosity of HPMC in hydrophobic ethylcellulose granules and hydrophilic polymer granules-2. The release was delayed as the viscosity of HPMC increased. The release was slowest with the greatest viscosity of 100,000 mm^2/s. Compared with the release rate with a viscosity of 100,000 mm^2/s, wide differences were observed after 10 h with a viscosity of 4000 mm^2/s and from immediately after the beginning of dissolution tests with a viscosity of 50 mm^2/s.

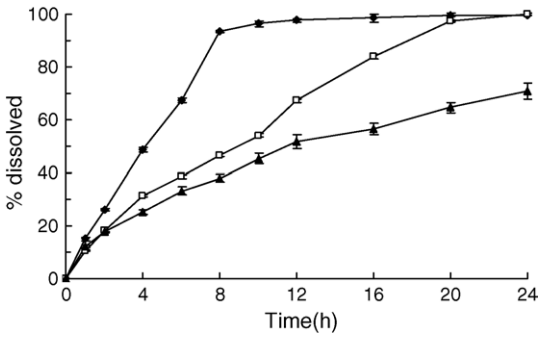

Fig. 4. Effect of the viscosity of HPMC in hydrophobic ethylcellulose granules and hydrophilic polymer granules-2 on the dissolution of theophylline from Tablet B using the paddle method at a rotation speed at 50 rpm in simulated intestinal fluid (pH 7.5). Each result shows the mean ± S.D. ($n = 3$). (♦) 50 mm^2/s (HPMC2910); (□) 4000 mm^2/s (HPMC2208); (▲) 15,000 mm^2/s (HPMC2208).

3.3. Analysis of the release pattern

Generally, zero order kinetics, first order kinetics, Hixson–Crowell, Higuchi and Korsmeyer–Peppas models were used for the analysis of the dissolution mechanism.

When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant.

The drug release patterns from Tablet A and Tablet B were analyzed.

The release of drugs from the matrix tablets can be analyzed by release kinetics theories (Hixson and Crowell, 1931; Higuchi, 1963; Gibaldi and Feldman, 1967; Korsmeyer et al., 1983; Costa and Sousa Lobo, 2001), as follows:

$$\text{zero order kinetics}: \quad F_t = K_0 t \tag{1}$$

where F_t represents the fraction of drug released in time t and K_0 the apparent release rate constant or zero order release constant.

$$\text{First order kinetics}: \quad \ln(1 - F) = -K_1 t \tag{2}$$

where F represents the fraction of drug released in time t and K_1 is the first order release constant.

$$\text{Higuchi model}: \quad F = K_2 t^{1/2} \tag{3}$$

where F represents the fraction of drug released in time t and K_2 is the Higuchi dissolution constant.

$$\text{Hixson–Crowell model}: \quad W_0^{1/3} - W_t^{1/3} = K_s t \tag{4}$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_s is a constant incorporating the surface volume relation. Dividing Eq. (4) by $W_0^{1/3}$ and simplifying:

$$(1 - F)^{1/3} = 1 - K_3 t \tag{4'}$$

where $F = 1 - (W_t/W_0)$ and F represents the drug dissolved fraction at time t and K_3 is the release constant. When this model is used, it is assumed that the release rate is limited by the drug particle dissolution rate and not by the diffusion that might occur through the polymeric matrix.

$$\text{Korsmeyer–Peppas model}: \quad F = K_4 t^n \tag{5}$$

where K_4 is a constant incorporating the structural and geometric characteristics of the drug dosage form, n is the release exponent (e.g. first order release when $n = 1$), indicative of the drug release mechanism and F represents the drug dissolved fraction at time t. This model is generally used to analyze the release of which mechanism is not well known or when more than one type of release phenomena are involved.

Analysis were performed by the above equations using water as the dissolution test medium.

Figs. 5 and 6 show the results of dissolution tests of Tablet A and Tablet B, which were oblong tablets

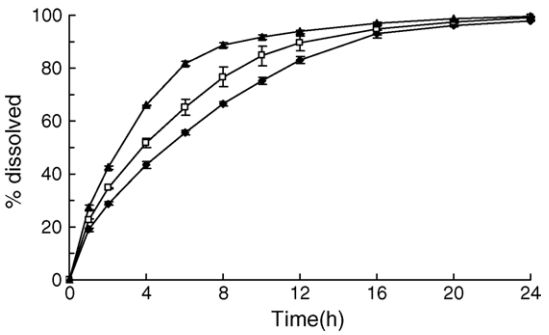

Fig. 5. Effect of paddle rotation speeds on the dissolution of theophylline from Tablet A using the paddle method in water. Each result shows the mean ± S.D. ($n = 3$). (♦) 50 rpm; (□) 100 rpm; (▲) 200 rpm.

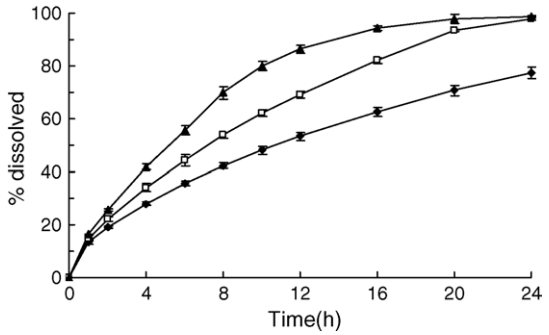

Fig. 6. Effect of paddle rotation speeds on the dissolution of theophylline from Tablet B using the paddle method in water. Each result shows the mean ± S.D. ($n = 3$). (♦) 50 rpm; (□) 100 rpm; (▲) 200 rpm.

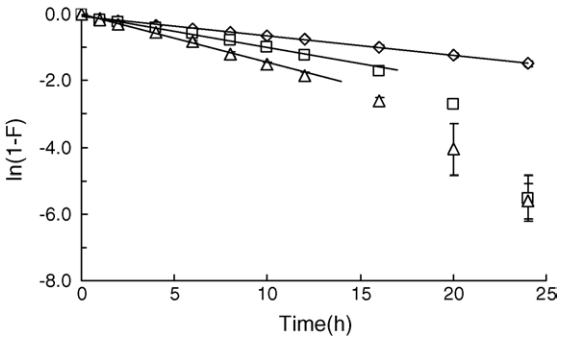

Fig. 8. Semilogarithmic plot of the unreleased fraction of theophylline of Tablet B as a function of time according to a first order kinetics model. Each result shows the mean ± S.D. ($n = 3$). (◇) 50 rpm; (□) 100 rpm; (△) 200 rpm.

13 mm in long diameter and 8 mm in short diameter, in water. Neither Tablet A nor Tablet B fit with Eq. (1) of zero order kinetics. Concerning Eqs. (2)–(5), regression analyses were performed in the ranges in which linearity was observed.

The first order kinetics model plot shows the relationship between the logarithm of the drug residual rate and time on the basis of Eq. (2). Figs. 7 and 8 show the results with Tablet A and Table B, respectively. Analyses were performed in the ranges in which linearity was maintained with both Tablet A and Tablet B. The theophylline release from both Tablet A and Tablet B was affected slightly by the paddle rotation speed. In Tablet A, satisfactory linearity was observed at 50 and 100 rpm throughout the test, and the release pattern was apparently linear release. At 200 rpm, satisfactory linearity was observed until after about 10 h, and the release pattern was linear, but the release thereafter did not fit with the equation.

In Tablet B, satisfactory linearity was observed at 50 rpm throughout the test. At 100 and 200 rpm, satisfactory linearity was observed until after about 10 h, but the release thereafter did not fit with the equation.

These results suggest that when the release from tablets is assumed to be linear, it was less affected by the paddle rotation speed in Tablet A.

A Higuchi model plot shows the relationship between the drug release rate and the square root of time on the basis of Eq. (3). Figs. 9 and 10 show the results with Tablet A and Table B, respectively.

Analyses were performed in the ranges in which linearity was maintained with both Tablet A and Tablet B. The release from both Tablet A and Tablet B was

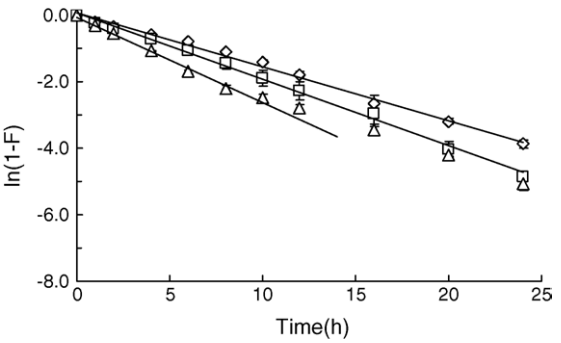

Fig. 7. Semilogarithmic plot of the unreleased fraction of theophylline of Tablet A as a function of time according to a first order kinetics model. Each result shows the mean ± S.D. ($n = 3$) and error bars are in the symbols. (◇) 50 rpm; (□) 100 rpm; (△) 200 rpm.

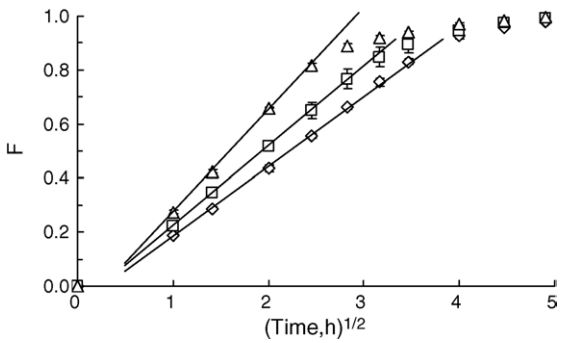

Fig. 9. A plot of the theophylline released from Tablet A as a function of time according to the Higuchi model. Each result shows the mean ± S.D. ($n = 3$). (◇) 50 rpm; (□) 100 rpm; (△) 200 rpm.

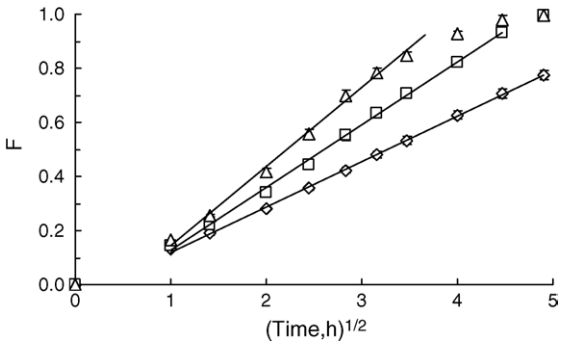

Fig. 10. A plot of the theophylline released from Tablet B as a function of time according to the Higuchi model. Each result shows the mean ± S.D. ($n = 3$). (◊) 50 rpm; (□) 100 rpm; (△) 200 rpm.

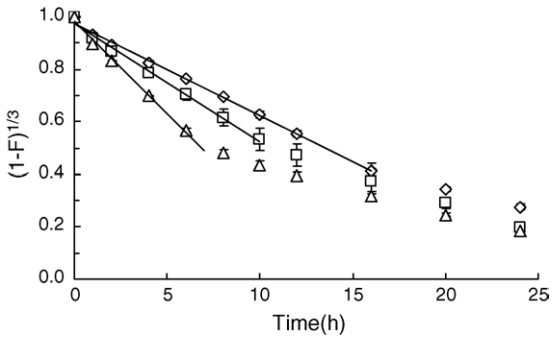

Fig. 11. A plot of the cubic root of unreleased fraction of theophylline from Tablet A as a function of time according to the Hixson–Crowell model. Each result shows the mean ± S.D. ($n = 3$). (◊) 50 rpm; (□) 100 rpm; (△) 200 rpm.

slightly affected by the paddle rotation speed, and the release from Tablet A was not linear throughout the test. The release fit with the Higuchi model equation of diffusion from the matrix until after about 10 h at 50 and 100 rpm and until after about 6 h at 200 rpm. The release from Tablet B showed satisfactory linearity at 50 and 100 rpm throughout the test, and it fit with the Higuchi model equation of diffusion from the matrix until after about 10 h at 200 rpm.

From these results, when the release of theophylline from tablets is assumed to be in accordance with the Higuchi model equation of diffusion from the matrix, the release was less affected by the paddle rotation speed, and the matrix was better maintained during the release in Tablet B.

The Hixson–Crowell model plot shows the relationship between the cubic root of the drug residual rate and time on the basis of Eq. (4). Figs. 11 and 12 show the results with Tablet A and Tablet B, respectively. Hixson and Crowell showed that the law of cubic root is valid in uniform particles. This equation is based on the assumption that the release occurs only in the vertical direction relative to the matrix surface, and that the release progresses with proportional decreases in all dimensions of the matrix, which maintains its shape.

Analyses were performed in the ranges in which linearly was maintained with both Tablet A and Tablet B. The release from Tablet A was not linear throughout the test at any rotation speed. The release was found to fit the cube root equation until after about 16 h at 50 rpm, until after about 10 h at 100 rpm and until after about 6 h at 200 rpm. Tablet B showed satisfactory linearity throughout the test (for about 24 h) at 50 rpm and until after about 20 h at 100 and 200 rpm.

From these results, when the release of theophylline from tablets was assumed to be in conformity to the equation of diffusion from the matrix by the Hixson–Crowell model, it was less affected by the paddle rotation speed, and the matrix was better maintained in Tablet B. Apparent release constants were determined based on Higuchi's and Hixson–Crowell's equations, respectively for the good fitting time frame.

Eq. (5) is a Korsmeyer–Peppas model equation concerning the diffusion mechanism, and it has been evaluated concerning pharmaceutical preparations of many matrix types. When both terms of Eq. (5) are converted to logarithms, the equation becomes $\ln F = \ln K_4 + n \ln t$, and the slope n can be determined

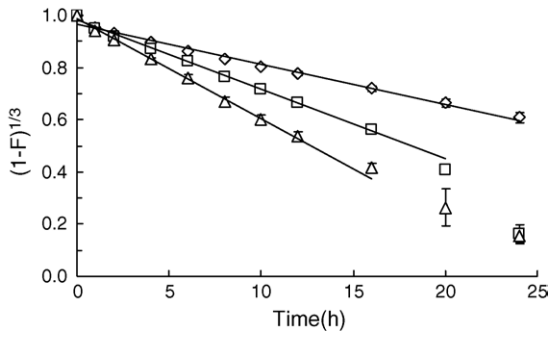

Fig. 12. A plot of the cubic root of unreleased fraction of theophylline from Tablet B as a function of time according to the Hixson–Crowell model. Each result shows the mean ± S.D. ($n = 3$). (◊) 50 rpm; (□) 100 rpm; (△) 200 rpm.

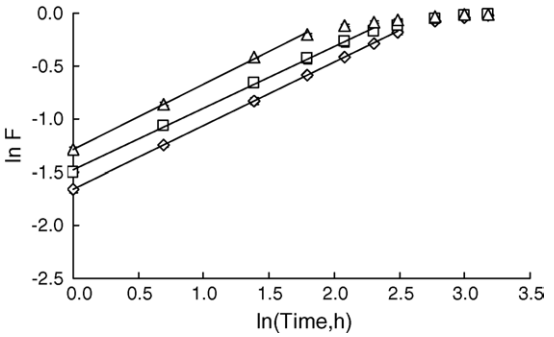

Fig. 13. A plot of the logarithm of theophylline released from Tablet A as a function of the logarithm of time according to the Korsmeyer–Peppas model. Each result shows the mean ± S.D. ($n = 3$) and error bars are in the symbols. (◊) 50 rpm; (□) 100 rpm; (△) 200 rpm.

by plotting the logarithm of the release rate against the logarithm of time. The exponent(n) determined by this equation suggests that columnar tablets show Fick's diffusion (Case-I transport) when $n = 0.45$, non-Fick type release (anomalous transport) when $0.45 < n < 0.89$, Case-II transport when $n = 0.89$, and super case-II transport when $n > 0.89$. Figs. 13 and 14 show the results in Tablet A and Tablet B, respectively.

From the results of analysis of the apparent diffusion pattern, the value of n, representing the diffusion pattern, was fixed in Tablet A, without being affected by the rotation speed. In Tablet B, the diffusion pattern was affected by the rotation speed, with n increasing

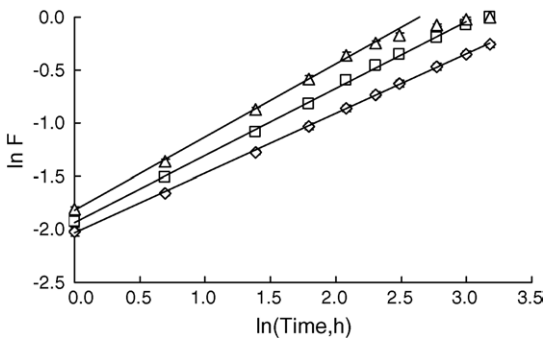

Fig. 14. A plot of the logarithm of theophylline released from Tablet B as a function of the logarithm of time according to the Korsmeyer–Peppas model. Each result shows the mean ± S.D. ($n = 3$) and error bars are in the symbols. (◊) 50 rpm; (□) 100 rpm; (△) 200 rpm.

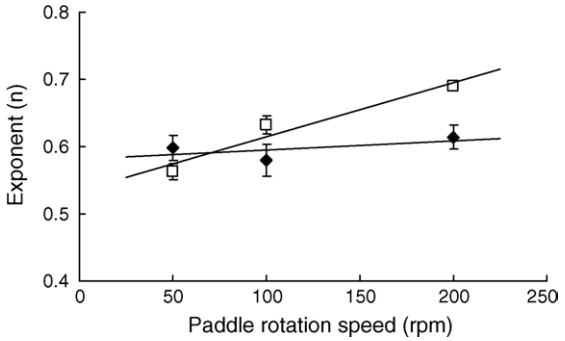

Fig. 15. The relation between the paddle rotation speed and the Korsmeyer–Peppas model's exponent n. Each result shows the mean ± S.D. ($n = 3$). (⧫) Tablet A; (□) Tablet B.

with the rotation speed (Fig. 15). This indicates that the gel matrix of HPMC is affected by the rotation speed, i.e. the stirring intensity, in Tablet B, resulting in differences in the diffusion pattern. Tables 6 and 7 summarize the kinetic constants and correlation coefficients of each analytical equation.

The visual observations Tablet A and Tablet B during dissolution test. When the paddle rotation speed increases, the disintegration occurs quickly in Tablet A. In the Korsmeyer–Peppas model, exponent(n) is about 0.6 and independent of the paddle rotation speed. This suggests that the drug release is not easily changed by physical agitation and probably even by peristaltic movement in the gastrointestinal tract. When the paddle rotation speed increases, the erosion of the gel matrix proceeds with Tablet B. The Korsmeyer–Peppas's exponent(n) was dependent on the paddle rotation speed. This suggests that the drug release can change easily due to physical agitation and probably peristaltic movement in the gastrointestinal tract.

The release rate constant of each mixture ratio was calculated from the rate constants of the hydrophobic wax tablets and of the hydrophilic polymer tablets prepared from granules-1. The release rate constant did not conform to the calculation. We speculated that this was because the release mechanisms differed between each other and the rate constant was not predictable, i.e. the hydrophobic wax tablets did not disintegrate, while the hydrophilic polymer tablets did.

Tablet B shows the gel matrix tablets, and the drug was released from the surface of the gel matrix. This conforms exactly to the assumption in the Higuchi

Table 6
Release rate constant of Tablets A and B

Tablet type	rpm	First order kinetics		Higuchi model		Hixson–Crowell model	
		K_1 (h^{-1})	r	K_2 ($h^{-1/2}$)	r	K_3 (h^{-1})	r
Tablet A	50	0.162	−0.9968	0.999	0.9995	0.035	−0.9985
	100	0.200	−0.9980	0.296	0.9999	0.045	−0.9964
	200	0.257	−0.9966	0.99	0.9997	0.070	−0.9972
Tablet B	50	0.059	−0.9982	0.168	0.9996	0.015	−0.9942
	100	0.098	−0.9984	0.232	0.9989	0.027	−0.9984
	200	0.144	−0.9965	0.293	0.9978	0.9988	−0.9988

Table 7
Fitting of release data to Korsmeyer–Peppas model

Tablet type	rpm	Release rate constant, K_4 (h^{-n})	Release exponent (n)	Correlation coefficient (r)
Tablet A	50	0.190	0.5983	0.9999
	100	0.229	0.5794	0.9994
	200	0.276	0.6143	0.9995
Tablet B	50	0.131	0.5630	0.9998
	100	0.144	0.6320	0.9994
	200	0.162	0.6898	0.9996

model. The Hixson–Crowell model is an equation of the dissolution mechanism that assumed a decrease in the surface area by dissolution in the sink condition.

It was thought that the gel matrix was eroded with the elapse of time, and the fragments of the matrix were discharged in the dissolution medium. It fitted the Hixson–Crowell model because the dissolution medium was apparently under the sink condition within the time period of observation.

4. Conclusions

Once-a-day type sustained-release matrix tablets of theophylline were evaluated by comparing two preparations with different release mechanisms. Both were matrix tablets prepared by tableting a mixture of hydrophobic matrix granules and hydrophilic matrix granules. Tablet A was a cluster tablet (swelling/disintegration-type matrix tablet), and Tablet B was a hydroxypropyl methylcellulose gel matrix tablet.

(1) In Tablet A, the theophylline release could be adjusted continuously by changing the mixing ratio of hydrophobic wax granules and hydrophilic polymer granules-1. The release mechanism of this tablet is provided by its wax matrix, and the release is considered to be controlled by gradual disintegration of the tablet with immersion of the dissolution medium into wax granules.
(2) In Tablet B, the drug release was found to be controlled by the gel formed by HPMC. Therefore, the release rate was changed by changing the viscosity of HPMC.
(3) The drug release from various tablets was analyzed according to release kinetics theories. In Tablet A, though the shape of tablet has changed, it showed a first order kinetics model. The value of exponent(n) of the apparent diffusion mechanism calculated by the Korsmeyer–Peppas model was unlikely to be affected by the paddle rotation speed, and was about 0.6.

In Tablet B, the drug release was slightly affected by the paddle rotation speed, but it was in conformity to the Higuchi model and Hixson–Crowell model. Also, the value of exponent(n) of the apparent diffusion mechanism calculated using the Korsmeyer–Peppas model was likely to be affected by the rotation speed.

(4) In this study, the release mechanism of Tablet A was the best, because when the paddle rotation increased, though the shape of the tablet changed, it showed first order kinetics. However, the drug release of Tablet B was affected by paddle rotation.

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