Application of Tumbling Melt Granulation (TMG) Method for Controlled Enteric-Release Beads by Coating Mixture of Hydrogenated Castor Oil and Higher Fatty Acid

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Controlled-release beads which can release drugs faster in the higher pH region (pH 5—7.5) than in the acidic region (pH 1—5) were prepared using the newly developed tumbling melt granulation (TMG) method, in which process a powdered meltable material was coated onto the core beads without use of any organic solvent. This function could be obtained by using a mixture of hydrogenated castor oil (HCO) and higher fatty acids as coating materials. Controlled-release beads containing various kinds of drugs were prepared. Use of stearic acid as a fatty acid resulted in excellent coating producibilities when the mixing ratio of stearic acid (X_{FA}) was less than 30%. The dissolution rates determined in purified water, 1st fluid, and 2nd fluid tended to increase with the increase of X_{FA}. This tendency was especially remarkable in the 2nd fluid. The effect of the carbon number (12—22) of the fatty acid was then determined. The permeability coefficient, P, calculated from the dissolution rate, decreased with the increase of carbon number. This seemed to be due to the difference of the release rate of fatty acid from the coating layer composed of HCO and fatty acid. Determination of the dependency of P value on the pH of the dissolution medium showed that the P values changed little in the acidic region (pH 1.2 to 5.0), but increased exponentially with an increase of pH over pH 5.5. Logarithm of relative P values (P_{pH}/P_w: P_w means the P values in purified water) plotted against pH were distributed on the same line irrespective of fatty acid. An empirical equation which predicts the dissolution rates in the enteric medium was proposed using this relationship.

Key words beads; tumbling melt granulation; wax; controlled-release; centrifugal fluidizing granulator; entero-soluble

In order to improve the compliance by reducing the administration frequency, or by achieving a reduction of side effects, sustained-release dosage forms have been widely investigated.[1,2] Sustained-release dosage forms should have not only a prolonged drug-releasing function, but should also assure good bioavailability. In many cases, however, the bioavailability is reduced greatly in sustained-release preparations. For instance, the formulation of isosorbite-5-nitrate which provided sustained-release over 14 h in an *in vitro* dissolution test showed a relative bioavailabilty of approximately 60% in humans. Such reduction could result from a decrease in drug absorption, a lowered rate of release due to fewer water-containing contents in the colon, or degradation of the drug by the acidity of gastric juice or micro-organisms in the lower gastrointestinal (GI) tracts.[3,4] To avoid a reduction in bioavailability, it was believed effective to give the preparation a function of faster releasing rate in the lower portion of GI tracts than in the upper.

Evans *et al.*[5] studied the variation of pH value in the GI tracts using pH-sensitive radiotelemetry capsules and reported that the mean pHs were 6.6 and 7.5 in the proximal small intestine and in the terminal ileum, respectively. Thus, a formulation designed to release drugs more rapidly in the pH range from 5 to 7.5 seemed reasonable to improve bioavailability of sustained-release formulation.

New pharmaceutical preparations with an additional function of bitter-taste masking[6,7] and controlled-release[2,8–11] have recently been studied. In a previous paper,[12] we reported a new method for preparing sustained-release beads which coated waxy materials without use of any solvents using a centrifugal fluidizing granulator. The coated layer obtained by this method showed pH-independent permeability.

To prepare beads capable of releasing drugs more rapidly with the increase of pH, especially in the range from 5 to 7.5 (here, we denote such function as controlled enteric-release function), we used a mixture of hydrogenated castor oil (HCO) and higher fatty acid in the coating layer. Fatty acids are good materials to use because their origin is a natural source. They also have the carboxyl group and thus their solubility increases with the increase of pH, especially in the range from 5 to 7.5. In this study the effect of the mixing ratio of fatty acid, fatty acid species, coating levels, drug species, and dissolution medium on the dissolution rate were investigated.

Experimental

Materials Isoniazid (ISA), theophylline (THEO) and salicylic acid (SA) used as model drugs were of JP grade. The original sources were as follows: ISA (Yuki Gosei Kogyo Co., Ltd., Tokyo, Japan), THEO and SA (Katayama Chemical, Osaka, Japan). These model drugs were used after grinding in a hammer mill. HCO and stearic acid were also of JP grade. Lauric acid, myristic acid, palmitic acid, and behenic acid were of JPCI-11 grade. HCO was used without grinding. Higher fatty acids were used after sieving with a 60 mesh sieve. The original sources were as follows: HCO (Kawaken Fine Chemical, Tokyo, Japan), and higher fatty acid (Katayama Chemical, Osaka, Japan).

Evaluation of Drug Properties Solubility of the Drugs: The solubilities of the three drugs (ISA, THEO, SA) were determined at 37 °C in purified water, the 1st fluid (pH 1.2) and the 2nd fluid (pH 6.8) described in the disintegration test of JP XIII. The drugs were suspended in the solvent and stirred occasionally during a 20 h period at 37 °C, then the suspensions were filtered using a membrane filter (pore size: 0.4 μm) and the filtrates were subjected to spectrophotometric assay.

Mean Particle Size of the Drugs: Laser granulometry (Granulometry model 715, Cilas Co., Ltd., France) was used for slightly water-soluble THEO and SA. The powdered drugs were dispersed in their saturated solutions and were applied to the granulometry. Optical micrographs were used for ISA because of its high water solubility.

True Density of the Drugs: The true density of drug powder was

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evaluated by an auto pycnometer (Auto Pycnometer 1320, Shimadzu, Kyoto, Japan).

Preparation of Spherical Beads For the preparation of spherical beads, a CF granulator (CF-360S: rotor diameter 360 mm, Freund Industrial Co., Ltd., Tokyo, Japan) was used in a wet powder coating according to the method reported previously.[13] One thousand grams of Nonpareil-103 (350—500 μm: Freund Industrial Co., Ltd., Japan) were used as a core material. Particles were placed on the rotor of the granulator. While spraying a binder solution containing sucrose, 2000 g of drug powder was gradually fed to the driving bed and adhered to the surface of the Nonpareil-103. The beads produced were dried overnight at 45 °C and sieved using 350 and 1000 μm sieves.

Preparation of Wax Coated Beads To prepare wax coated granules, the CF granulator was used as described.[12] Three hundred grams of spherical beads was placed in the CF granulator and heated up to the relevant temperature (Table 1). A mixture of HCO and fatty acid was gradually and continuously fed to the core beads while the bed temperature was maintained at the relevant temperature. Upon completion of the feeding, the coated beads were driven in the granulator for 5—10 min. Then the hot beads were removed and cooled at room temperature. Finally, single-core beads were obtained by sieving through 350 and 1000 μm sieves to remove agglomerates and non-adhering powder.

Evaluation of Coating Producibility The coating producibility was evaluated by the two values described earlier[12]: the recovery% of coating mass (Rec%) and the yield% of single core beads (Ysc%, fraction ranged from 350 to 1000 μm) against the charging amount of the core beads and the coated material. When both Rec% and Ysc% were over 93%, the producibility was considered to be excellent.

Dissolution Test A dissolution test was carried out according to the paddle method of JP XIII (37 °C, 100 rpm). The dissolution media used were the purified water, the 1st fluid (pH 1.2) and the 2nd fluid (pH 6.8) described in the disintegration test of JP XIII. To determine the exact dissolution rates in the pH range from 5.0 to 7.5, McIlvane buffers (pH 5.0, 5.5, 6.0, 6.5, 7.0, 7.5) were also used as dissolution media. Test samples containing 100 mg of drug were placed in a test vessel containing 900 ml of a dissolution medium and the concentration of drug in the sample solution was determined spectrophotometrically.

Calculation of Permeability Coefficient The permeability coefficient (P) was calculated from the dissolution curve as shown previously.[12] The mechanism by which release from capsule-type controlled release dosage forms coated with water insoluble polymers is diffusion through a continuous polymer phase in parallel with diffusion through aqueous pores.[14-17] The dissolution rate of a drug from coated beads in the steady state under the sink condition can be described by:

$$dQ/dt = A \cdot P_p \cdot C_i/l + A \cdot P_m \cdot C_i/l \quad (1)$$

where Q is the total amount of the drug released in the surrounding medium at time t, A is the surface area of the coated beads, P_p and P_m are the permeability coefficient in the aqueous phase and the polymer phase, respectively, C_i is the concentration of drug at the drug-layer interface, and l is the thickness of the coated layer. The permeability coefficient is written by:

$$P = P_p + P_m \quad (2)$$

At the beginning of the dissolution, a linear relationship between time and the released percent was obtained because a sufficient amount of the drug would be present to maintain saturation in the internal phase of the coated beads. Therefore, the zero order dissolution rate is given by:

$$dQ/dt = K = A \cdot P \cdot C_s/l \quad (3)$$

where K is the dissolution rate of the drug from the coated beads, and C_s is the solubility of the drug. The permeability coefficient was calculated by Eq. 3. The l was calculated using Madan's equation[18] as described.[12]

Scanning Electron Microscopic Observation The morphological change of the surface in the coated beads before and after the dissolution test was evaluated using a scanning electron microscope (JSM-T100 JEOL Co., Ltd., Japan).

Results and Discussion

Coating with Mixture of HCO and Higher Fatty Acid.

1) Effect of Mixing Ratio of Fatty Acid on Dissolution Behavior First, the TMG coating method using a mixture of HCO and fatty acid was applied to drugs having various physico-chemical properties. The coated beads were prepared by changing the mixing ratio of fatty acid in the coating layer (X_{FA}; $X_{FA} = W_{FA}/(W_{FA} + W_{HCO})$, where W_{FA} and W_{HCO} means the weight of fatty acid and HCO in the coating layer). The properties of the drugs chosen as model drugs are shown in Table 2.

In this case, stearic acid was used as a fatty acid. The coating producibilities were shown to be excellent when X_{FA} was less than 30%, and Rec% and Ysc% were more than 95%. However, when X_{FA} exceeded 30%, a serious agglomeration of beads occurred in the coating process.

The dissolution rates of the drugs were determined for 30% coated beads of which X_{FA} was 0, 10, or 30% in purified water, 1st fluid, and 2nd fluid. The dissolution profiles of THEO in purified water, the 1st fluid, and the 2nd fluid are shown in Fig. 1, and the representative dissolution profiles of ISA and SA in the 2nd fluid are shown in Fig. 2. The coating level in these fig-

Table 1. Coating Condition

Composition of coated material	Bed temperature (°C)
HCO	61—63
HCO : fatty acid = 9 : 1	52—57
HCO : fatty acid = 7 : 3	51—54

Table 2. Properties of Drugs

Drug	Particle size (μm)	True density (g/cm^3)	Solubility (mg/ml)		
			Purified water	1st fluid (pH 1.2)	2nd fluid (pH 6.8)
ISA	40	1.42	196	211	188
THEO	30	1.50	11	12	11
SA	27	1.44	2.9	2.3	6.2

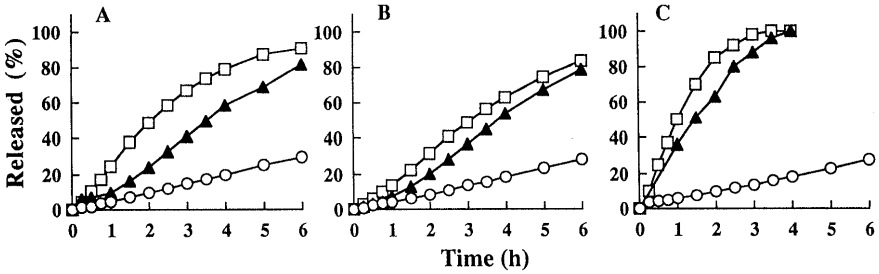

Fig. 1. Effect of Mixing Ratio of Stearic Acid on Dissolution Profile of THEO from Coated Beads

Dissolution medium: A, purified water; B, 1st fluid; C, 2nd fluid. X_{FA}: ○, 0%; ▲, 10%; □, 30%; coating level, 30%.

ures shows the weight percentage of the coated material against the core beads. The permeability coefficient P was calculated from the linear part of the dissolution curve (Table 3).

Comparison of the dissolution rate K among the drugs suggested that the rate was larger in the order of ISA > THEO > SA, and this order agreed with that of drug solubility. The permeability coefficients were fairly similar in THEO and SA, but smaller in ISA. The reduction of P values in ISA could be due to the same factors as described earlier[12]: 1) as the aqueous solubility increased, the partition of the drug on the surface of hydrophobic waxy materials decreased, and thus the gradient of the drug concentration in the coated layer decreased; 2) the activity coefficient of the saturated solution was lower in a soluble drug than that in a slightly soluble one; and 3) the viscosity of the inner saturated solution in the coated beads was higher in a soluble drug than in a slightly soluble one.

As shown in Fig. 1 and Table 3, the dissolution rates in all dissolution media tended to increase with increase in X_{FA}, irrespective of the drug. Also, the dissolution rates in the 2nd fluid greatly increased with the addition of stearic acid. However, the increase of X_{FA} from 10% to 30% hardly affected the dissolution rate in the 2nd fluid (Figs. 1, 2). This phenomenon suggested that the addition of 10% of stearic acid was enough to give the entero-soluble function to such beads.

According to Table 3, the P values in purified water and the 1st fluid enlarged only 3—5 fold with the addition of 10—30% of stearic acid compared with no addition, whereas it became 10—20 times larger in the 2nd fluid. This meant that the coating with a mixture of HCO and stearic acid provided the beads with the entero-soluble function.

As the entero-soluble function was sufficiently obtained by the addition of 10% of stearic acid, later studies were done using this mixing ratio.

2) Effect of Species of Fatty Acid on Dissolution Behavior The effect of the fatty acid species on the dissolution behavior was determined by coating THEO beads with the powdered mixtures of HCO and fatty acid of various carbon numbers (lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18), and behenic acid (C22)) with the coating levels of 10, 20, and 30%; and the dissolution test was then performed on the beads. THEO seemed to be suitable as a model drug, since its solubility hardly changed in the pH range from 1.2 to 7.5. The dissolution profiles in the cases of palmitic acid and behenic acid in purified water for instance, are shown in Fig. 3. Each dissolution curve was nearly zero order and the depressing ability of THEO release increased with increase in the coating level irrespective of fatty acid species.

The dissolution rates and permeability coefficients are evaluated and summarized in Table 4. The P values were decreased with the increase of coating level. The difference in P value between 20% and 30%, however, was not as large as that between 10% and 20%. This was the same tendency as noted previously,[12] namely, P values de-

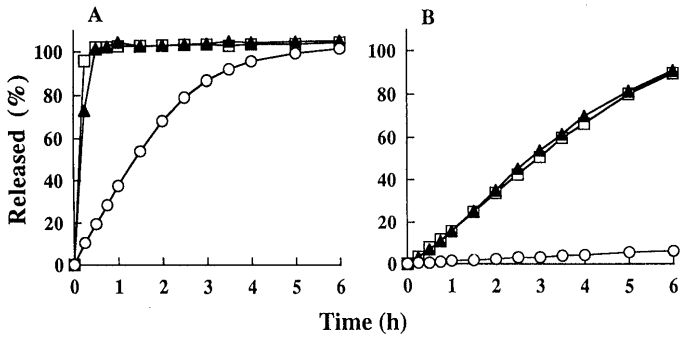

Fig. 2. Effect of Mixing Ratio of Stearic Acid on Dissolution Profiles of ISA and SA from Coated Beads in 2nd Fluid

A, ISA; B, SA; coating level, 30%. Symbols are the same as in Fig. 1.

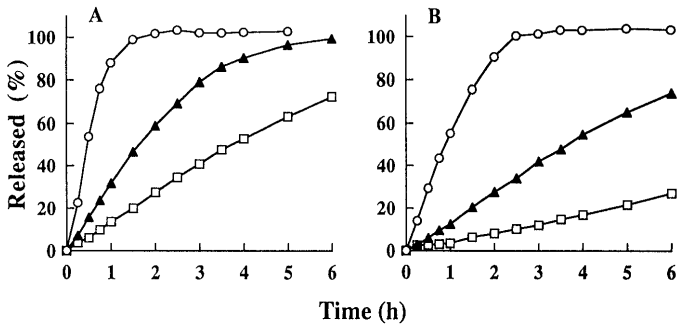

Fig. 3. Dissolution Profile of THEO from Beads Coated with Mixture of HCO and Fatty Acid

Fatty acid: A, palmitic acid; B, behenic acid. Coating level: ○, 10%; ▲, 20%; □, 30%. X_{FA}, 10%. The dissolution medium was purified water.

Table 3. Effect of Mixing Ratio of Stearic Acid on Release Rate (K) and Permeability Coefficient (P)

Drug	X_{FA} (%)	Purified water		1st fluid		2nd fluid	
		K (mg/h)	P ($\times 10^{-8}$ cm^2 s^{-1})	K (mg/h)	P ($\times 10^{-8}$ cm^2 s^{-1})	K (mg/h)	P ($\times 10^{-8}$ cm^2 s^{-1})
ISA	0	43.5	2.7	33.0	1.9	36.6	2.3
	10	50.8	2.9	41.0	2.2	(>300)	(>17.9)
	30	130.0	6.4	111.0	5.0	(>385)	(>19.5)
THEO	0	4.9	3.5	4.3	2.9	4.3	3.3
	10	14.2	13.1	13.2	11.5	37.5	35.9
	30	24.2	16.5	16.1	10.4	50.0	35.5
SA	0	0.8	2.8	0.9	3.9	1.0	1.7
	10	3.2	11.6	2.6	11.5	18.0	30.1
	30	2.8	10.4	2.5	11.9	17.0	29.5

Coating level, 30%; ( ), the dissolution rate was so high that the value is shown as a reference.

Table 4. Effect of Species of Fatty Acid on Release Rate (K) and Permeability Coefficient (P)

Dissolution medium	Fatty acid	Coating level 10% K (mg/h)	10% P ($\times 10^{-8}$ cm^2 s^{-1})	20% K (mg/h)	20% P ($\times 10^{-8}$ cm^2 s^{-1})	30% K (mg/h)	30% P ($\times 10^{-8}$ cm^2 s^{-1})
Purified water	C12	135.7	41.3	65.4	40.4	51.4	40.0
	C14	182.9	46.3	47.5	25.7	27.1	22.1
	C16	106.4	27.5	30.5	18.7	13.4	11.7
	C18	55.9	13.5	16.5	10.1	5.8	5.0
	C22	56.2	17.8	13.6	8.5	4.0	3.5
1st fluid	C12	188.7	54.1	96.5	55.3	54.6	40.0
	C14	186.3	44.4	58.5	29.8	25.2	19.3
	C16	122.0	29.7	31.1	17.9	9.6	7.9
	C18	73.7	16.8	12.9	7.4	4.8	3.9
	C22	48.5	14.5	13.8	8.1	3.8	3.2
2nd fluid	C12	150.8	47.6	121.0	76.4	87.7	70.7
	C14	184.0	48.3	76.9	43.2	43.4	36.6
	C16	166.7	44.7	61.7	39.2	29.5	26.7
	C18	113.2	28.3	36.3	22.9	10.9	9.7
	C22	61.3	20.1	16.9	10.9	7.4	6.9

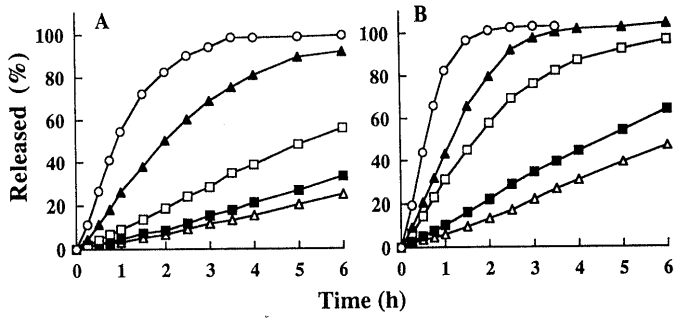

Fig. 4. pH Dependency of THEO Beads Coated with Mixture of HCO and Various Fatty Acids

Dissolution medium: A, 1st fluid; B, 2nd fluid. Fatty acid: ○, lauric acid; ▲, myristic acid; □, palmitic acid; ■, stearic acid; △, behenic acid. X_{FA}, 10%; coating level, 30%.

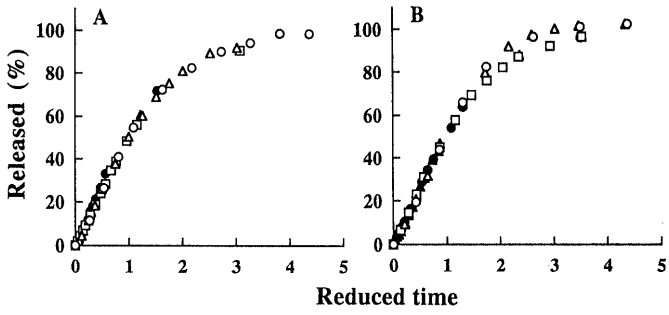

Fig. 5. Superposition of Dissolution Curves of THEO Beads Coated with Mixture of HCO and Fatty Acids

Dissolution medium: A, 1st fluid; B, 2nd fluid. Fatty acid: ○, lauric acid; ▲, myristic acid; □, palmitic acid; ■, stearic acid; △, behenic acid. X_{FA}, 10%; coating level, 30%.

creased with the increase of coating levels and attained constant values when the coating levels exceeded a certain value.

The dissolution rates of THEO from the beads coated with HCO and various fatty acids at the 30% coating level were determined in purified water, the 1st fluid, and the 2nd fluid, and are shown in Fig. 4 for the 1st and 2nd fluid as examples. At the same coating level, the dissolution was more prolonged with the increase in carbon number. The same tendency was shown in purified water (the dissolution profile is not shown).

The normalized dissolution curves are shown in Fig. 5 by replotting the dissolution rates of THEO against the reduced time (t/t_{50}) according to the method described.[12] The dissolution profiles of several fatty acids were superposed on the same line in each dissolution medium. Further, these normalized curves (A, B) were nearly superposed on the same curve irrespective of dissolution medium. The results suggested that the drug probably was released obeying the same mechanism and only the release rate differed. It was concluded that the drug release rate can be controlled by changing the species of fatty acid when this coating method is used.

The permeability coefficient P in each fatty acid was

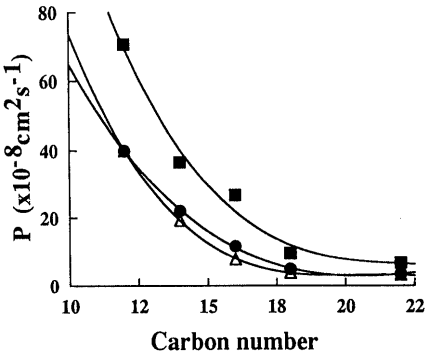

Fig. 6. Relationship between Carbon Number of Fatty Acid and Permeability Coefficient

Dissolution medium: ●, purified water; △, 1st fluid; ■, 2nd fluid. X_{FA}, 10%; coating level, 30%.

calculated and then plotted against the carbon number (Fig. 6); as shown, P decreased with the increase of carbon number of fatty acid in all the dissolution media. The reason for the difference in P values among the fatty acids was believed due to either the difference in the structure of the resultant layer or in fatty acid properties.

Kataoka and his colleagues[19] reported that the structure of coated membrane was different depending on the

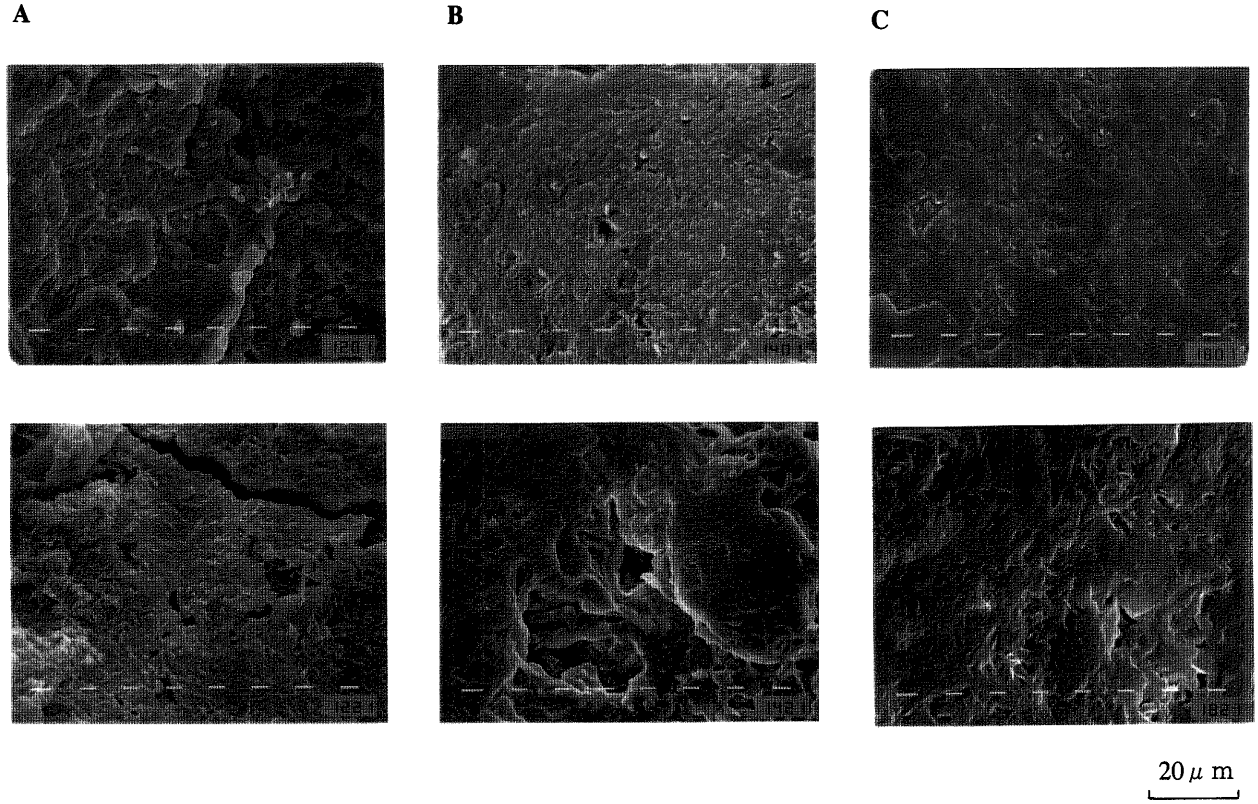

Fig. 7. SEM Microphotograph of Coated Beads' Surface before and after Dissolution Test

A, C14; B, C16; C, C18: upper side, before dissolution test; lower side, after dissolution test. X_{FA}, 10%; coating level, 30%.

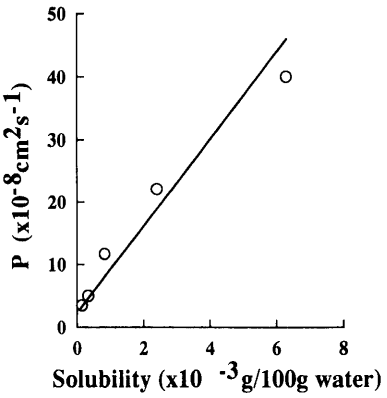

Fig. 8. Relationship between Solubility of Fatty Acid and Permeability Coefficient in Purified Water

X_{FA}, 10%; coating level, 30%.

mixing ratio of two fatty acids (palmitic acid, stearic acid) when these waxes were co-melted. Also, they concluded that the best membrane was formed when the mutual affinity between each fatty acid was maximum. The structure of the layer composed of HCO and fatty acid as in this study also seemed to be affected by the mutual affinity. Scanning electron microscope (SEM) observation of the surface of the coated beads, however, the difference of the structure was hardly observed among the coated beads.

In contrast, it was found that the appearance of the coating layer was altered during the dissolution test. SEM microphotographs of the surface of beads before and after the dissolution test are shown in Fig. 7. It was obvious that the cracks and holes on the coating layer were generated after the test; also, the smaller the carbon number, the more cracks and holes were visible. This suggested that some other physico-chemical properties of fatty acid might have an effect.

Thus, the relationship between the permeability coefficient and physicochemical properties of fatty acid such as molecular weight, melting point, and solubility were investigated. A good linearity was found between P value and the solubilities of fatty acids,[20] as shown in Fig. 8 for purified water.

These results suggested that the delay of the dissolution rate with the increase of fatty acid carbon number could be due to the fact that the coated layer became more porous because of the release of fatty acid from this layer.

Prediction of Dissolution Profile at Various pH Dissolution tests were performed in various pH media for the coated beads of which X_{FA} was 10%, and which had been prepared using a mixture of HCO and myristic acid (C14), palmitic acid (C16), or stearic acid (C18) as the coating layer. Representative dissolution profiles of the THEO from the coated beads with palmitic acid are shown in Fig. 9. The dissolution rates from pH 1.2 to 5.0 varied little; however, at pH higher than 5.5, these tended to increase with pH increase in all fatty acid species.

The permeability coefficients were calculated and plotted against the pH of the dissolution medium as shown in Fig. 10. The permeability coefficients of beads with a coating layer consisting only of HCO and not containing any fatty acid were unchanged in the pH range from 1.2 to 6.8, while those with the addition of C14, C16, or C18 were constant up to pH 5, and then remarkably increased at above pH 5.5. This seemed to be due to the increase in

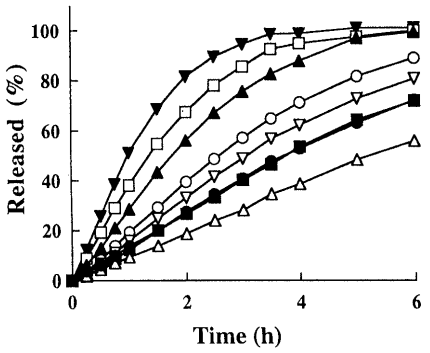

Fig. 9. Effect of pH on Dissolution Profile of 30% Coated THEO Beads with Mixture of HCO and Palmitic Acid

Dissolution medium: ●, purified water; △, pH 1.2; ■, pH 5.0; ▽, pH 5.5; ○, pH 6.0; ▲, pH 6.5; □, pH 7.0; ▼, pH 7.5. X_{FA}, 10%; coating level, 30%.

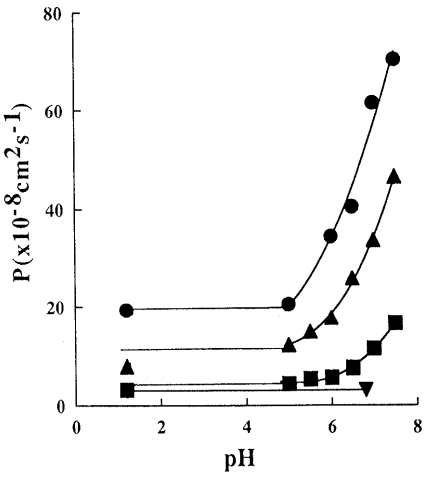

Fig. 10. Relationship between Permeability Coefficient and pH of Dissolution Media

●, C14; ▲, C16; ■, C18; ▼, HCO. X_{FA}, 10%, coating level, 30%.

solubility of fatty acid according to increase of pH.

The logarithm of the relative permeability coefficient P_R ($=P_{pH}/P_w$), which was denoted as the ratio of permeability coefficient in a certain pH medium (P_{pH}) against that in water (P_w), was then plotted against the pH of the dissolution medium (Fig. 11). The values fell approximately on the same line.

The relationship between P_R and pH of the dissolution medium was described as Eq. 4 by the least squares method.

$$\log(P_{pH}/P_w) = K_1 \cdot (pH - pH_0) = 0.226 \cdot (pH - 5.2) \quad (r = 0.975) \tag{4}$$

Substituting Eq. 4 into Eq. 3 gave Eq. 5. This Eq. 5 means that the dissolution rate at a certain pH medium K_{pH} can be calculated from A, l, P_w, and Cs.

$$K_{pH} = A/l \cdot P_w \cdot Cs \cdot \exp(2.303 \cdot 0.226(pH - 5.2)), \quad pH > 5.2 \tag{5}$$

In the case where the 2nd fluid was used for the dissolution medium, the dissolution rate K_{2nd} can be calculated as

$$K_{2nd} = A/l \cdot P_w \cdot Cs_{2nd} \cdot \exp(2.303 \cdot 0.226(6.8 - 5.2)) = 2.300 \cdot A/l \cdot P_w \cdot Cs_{2nd} = 2.300 \cdot K_w \cdot Cs_{2nd}/Cs_w \tag{6}$$

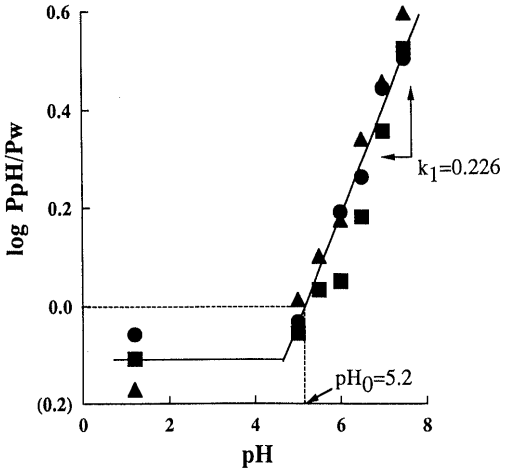

Fig. 11. Relationship between log P_{pH}/P_w and Permeability Coefficient

●, C14; ▲, C16; ■, C18.

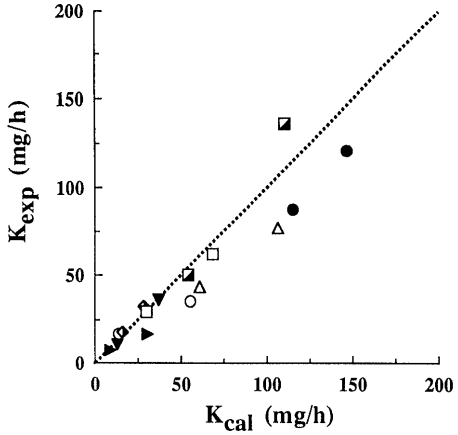

Fig. 12. Comparison of Dissolution Rate Estimated Experimentally with Calculated Dissolution Rate in 2nd Fluid

●, C12; △, C14; □, C16; ▼, C18; ▼, C22 (THEO; X_{FA}, 10%); ◩, C18 (THEO; X_{FA}, 30%): ◇, C18 (SA; X_{FA}, 10%); ○, C18 (SA; X_{FA}, 30%).

where Cs_{2nd} and Cs_w mean the solubilities of drugs in the 2nd fluid and purified water, respectively. Thus, K_{2nd}s were calculated for the beads shown in Tables 3 and 4, and then compared with the experimental ones. In Fig. 12, K_{exp}s estimated for the beads with coating levels of 20% and 30% are plotted against K_{cal}. K_{exp} were nearly distributed on the line of $K_{exp} = K_{cal}$ (shown by dotted line). Thus, K_{cal} and K_{exp} agreed fairly well regardless of the difference in fatty acid species (C12—C22), coating levels (20%, 30%), mixing ratio ($X_{FA} = 10\%$, 30%), or the drug species (THEO, SA).

When coating levels were 10%, the points were widely dispersed around the dotted line. This could be due to the fact that the dissolution rates in the 2nd fluid were too rapid to estimate precisely when the coating level was 10%.

The relationship shown in Fig. 12 suggested that the dissolution rate in the 2nd fluid can be roughly estimated using the rate determined in purified water (K_w), the solubility of drugs in purified water (Cs_w), and that in the 2nd fluid (Cs_{2nd}).

Thus, in conclusion, it was shown that the method has wide applicability and many advantages:

1) The manufacturing process is simple and safe because no use of solvent is necessary.

2) Producibility is excellent when the mixing ratio of fatty acid in the coating layer is less than 30%.

3) It can be applicable for drugs of various physicochemical properties.

4) The coated beads show the controlled enteric-release, thus the dissolution rate can be faster in the lower part of the GI tracts than in the upper part, and the lowering of bioavailability which is often generated in sustained release dosage forms can be avoided.

5) The dissolution rate can be adjusted by choosing an appropriate fatty acid species and coating level.

6) The dissolution rate in the neutral pH region can be estimated approximately from the solubility of the drug and its dissolution rate in purified water.

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