Application of Tumbling Melt Granulation (TMG) Method for Preparing Controlled Release Beads Coated with Hydrogenated Castor Oil

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The tumbling melt granulation (TMG) method by a centrifugal fluidizing granulator (CF) without any use of organic solvents was applied as a coating technique for preparing controlled-release spherical beads. The core beads containing four kinds of drugs with different solubilities: nicotinamide (NA), isoniazid (ISA), theophilline (THEO) and salicylic acid (SA), were driven in the CF and were previously heated at 61—63 °C before feeding powdered hydrogenated castor oil (HCO) to the CF. HCO was gradually fed and adhered on the surface of the core beads. At the bed temperature of 61—63 °C, about 20% of the HCO was presumed to have melted. After the adherence of HCO, the coated beads were cooled at room temperature and thus the controlled-release beads were obtained. The dissolution rates of these coated beads were determined by use of the JP paddle method. The rates seemed to increase with an increase in the solubility of the drug. To clarify the mechanism of drug transport through the coated layer of HCO, the superposition method was applied for the dissolution profile of the coated beads with various coating levels. Then, in each case of ISA, THEO, and SA, the dissolution curves were superposed completely, irrespective of their coating level. Permeability coefficients, *P* values of each drug calculated for various pH media, were coincident, irrespective of pH. These facts indicated that the limiting factor of the dissolution of HCO coated beads was diffusion, and that the permeability of the coated layer was pH independent. The equilibrium *P* values decreased with the increase in solubility of the drug. The partition coefficient between the layer surface and inner core medium, activity coefficient, viscosity, diffusion through waxy phase and so on, might be attributed to these phenomena.

Key words beads; tumbling melt granulation; wax; controlled release; centrifugal fluidizing granulator; release mechanism

For the control of the release rate of an active ingredient from controlled release dosage forms, waxy materials have often been used because they have a depressing ability against the drug permeation due to their hydrophobic properties. For instance, controlled release tablets have been formulated as matrix-types in which waxy materials, active ingredients and various additives were mixed and granulated by various methods such as spray-congealing[1] and melt granulation,[2] and then the granules were compressed into tablets. Indeed, many kinds of controlled release tablets are put to practical use.[3]

Recently, many researchers have insisted that multiple-unit dosage forms are more desirable for the oral controlled release dosage forms than single-unit dosage forms, since multiple-unit dosage forms such as granules, fine granules, or capsules filled with those granules tend to exhibit less variation in gastrointestinal transit times, especially in gastric emptying time. However, control of the release rate is more difficult in multiple dosage forms, due to their large specific surface area, than in single-unit dosage forms.[4-6]

The membrane coating method seems to be more advantageous than the matrix system for the accurate control of the release rate in multiple-unit dosage forms. Thus, many coating techniques, such as the method of spraying wax dissolved in an organic solvent[7,8] or that of feeding fine waxy powder with spraying aqueous–alcoholic ethylcellulose solution[9] were reported. The use of an organic solvent is not desirable, however, since it has risks of air-pollution, health hazard, explosion, high cost of manufacturing, and so on.

As methods without the use of an organic solvent, the spraying method of hot molten wax (hot-melt coating)[10] or an emulsion prepared with the use of a surfactant[11,12] have been described. However, these methods require complicated manufacturing equipment and in addition, agglomeration of granules tends to occur. Recently, the dry-blending method[13] and dry impact method[14] have been developed by using a newly developed granulating machine, but it has been difficult to obtain a uniform coating layer since the frictional heat derived from the mechanical impact is used to melt wax; thus, control of the coating temperature is difficult.

As a unique technique, a method using waxy seed materials was reported.[15] This seems to be very effective for masking the bitter taste of the granules,[16,17] but it has also been difficult to control the release rate of the drugs precisely.

We have been studying a new method for preparing controlled release beads to overcome the defects accompanying the ordinary methods mentioned above. We reported the tumbling melt granulation (TMG) method in the previous paper,[18] in which spherical core beads with smooth surface and narrow particle size distribution were prepared by use of a centrifugal fluidizing (CF) granulator without any solvents. The TMG method is classified as a layering method, and thus can be expected to be applied as a coating technique to precisely control the release rate of drugs from small spherical beads.

In this paper, the detailed preparation method and the results applied to drugs with different solubilities are described. Then, the mechanisms of transport of drugs through the waxy layer are discussed on the basis of a dissolution test of the coated beads prepared by this newly developed technique.

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Materials and Methods

Materials Nicotinamide (NA), isoniazid (ISA), theophilline (THEO), and salicylic acid (SA) used as model drugs were of JP grade. The original sources were as follows: NA and ISA (Yuki Gosei Kogyo Co., Ltd., Tokyo, Japan); and THEO and SA (Katayama Chemical, Osaka, Japan). These model drugs were used after grinding by a hammer mill. Hydrogenated castor oil (HCO) and stearic acid were of JP grade. Lauric acid was of JPCI-11 grade. HCO was used without grinding. Higher fatty acids were used after sieving with a 200 mesh screen. The original sources were as follows: HCO (Kawaken Fine Chemical, Tokyo, Japan); and higher fatty acids (Katayama Chemical, Osaka, Japan).

Thermal Analysis Thermal analysis was performed on a differential thermal analyzer (DTA-50, Shimadzu, Kyoto, Japan). The operation conditions were as follows: DTA, load of 15 mg; heating rate of 5 °C/min.

Solubilities of the Drugs The solubilities of the four drugs (NA, ISA, THEO, SA) were determined at 37 °C in purified water, the 1st fluid of the disintegration test of JP XIII (pH 1.2) and the 2nd fluid of the disintegration test of JP XIII (pH 6.8). The drugs were suspended in the solvent and these suspensions were occasionally stirred for 20 h 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.

Preparation of Spherical Core 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 wet powder coating method.[19] One thousand grams of nonpareil-103 (350—500 μm: Freund Industrial Co., Ltd., Tokyo, Japan) as a seed material was placed on the rotor of a CF granulator. While spraying a binder solution containing sucrose, 2000 g of the drug powders were gradually fed to the driving bed, which adhered to the surface of the nonpareil-103. The produced beads were dried in an air-forced oven overnight at 45 °C and sieved by use of 350 and 1000 μm sieves.

Preparation of HCO Coated Beads For the preparation of HCO coated beads, the CF granulator was used as shown previously.[18] Three hundred grams of spherical core beads was placed on the CF granulator and heated up to a bed temperature of 61—63 °C. The powder of HCO was gradually and continuously fed onto the core beads while the bed temperature was accurately maintained at 61—63 °C. After finishing the feeding of HCO, the coated beads were driven for 5—10 min. Then, the hot beads were taken out from the CF granulator and cooled at room temperature. Next single-core beads were obtained by sieving with 350 and 1000 μm sieves to remove the agglomerates and the non-adhering powder.

Evaluation of Coating Producibility The coating producibility was estimated in the same way, according to the granulatability in the TMG method shown in the previous paper,[18] as follows: 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%, we considered that the producibility was excellent.

Evaluation of Core Beads' Properties 1) Mean Particle Size: Mean particle size was determined by a computer-assisted color image analyzer (Olympus, Tokyo, Japan). The system consisted of a light microscope (SZH), a video camera, a computer connected to an image processor and TV monitor (TVIP-5100). Image enhancements and measurements were made using the system software (Image Command 5098).

2) Bulk Density of Core Beads: To a 100 ml graduated cylinder, each core bead was fed at a constant rate from the position of 2 cm above the top edge of the cylinder. Then, the weight of the powder was measured and bulk density was calculated.

Dissolution Test A dissolution test was carried out according to the paddle method of JP XIII (37 °C, 100 rpm). The dissolution mediums 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. The test samples containing 100 mg of drug were placed in a test vessel containing 900 ml of the dissolution medium. The concentration of drugs in the sample solution was determined spectrophotometrically.

Calculation of Permeability Coefficient There are some possible mechanisms by which release from capsule-type controlled release dosage forms coated with water insoluble polymers may occur. The mechanisms are as follows: A) diffusion through aqueous pores, B) diffusion through a continuous polymer phase, C) diffusion through a continuous polymer phase in parallel with diffusion through aqueous pores.[20-23]

In the case of A), the dissolution rate of a drug from coated beads in the steady state can be described by:

$$\frac{dQ}{dt}=\frac{A\cdot P_{\mathrm{p}}}{l}(C_{\mathrm{i}}-C_0) \tag{1}$$

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} is the permeability coefficient in the aqueous phase, C_{i} and C_0 are the concentrations of drug at the drug-layer interface and bulk solution, respectively, and l is the thickness of the coated layer. The permeability coefficient can be written as

$$P_{\mathrm{p}}=D_{\mathrm{p}}\cdot K'\cdot\frac{\varepsilon}{\tau} \tag{2}$$

where D_{p} is the diffusion coefficient through the aqueous pores, K' is the partition coefficient, ε is the porosity of the aqueous channels and τ is the tortuosity of the aqueous channels.

Under the sink condition ($C_{\mathrm{i}}\gg C_0$), Eq. 1 can be reduced to the following equation:

$$\frac{dQ}{dt}=\frac{A\cdot P_{\mathrm{p}}}{l}\cdot C_{\mathrm{i}} \tag{3}$$

On the other hand, if drugs are transported through a continuous polymer phase (in the case of B)), the dissolution rate is expressed by

$$\frac{dQ}{dt}=\frac{A\cdot P_{\mathrm{m}}}{l}\cdot C_{\mathrm{i}} \tag{4}$$

where P_{m} is the permeability coefficient in the polymer phase.

In the case of C), which is the most usual combination, the resultant permeability coefficient is written by

$$P=P_{\mathrm{p}}+P_{\mathrm{m}} \tag{5}$$

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 Eq. 6:

$$\frac{dQ}{dt}=K=\frac{A\cdot P}{l}\cdot C_{\mathrm{s}} \tag{6}$$

where K is the dissolution rate of the drug from the coated beads, C_{s} is the solubility of the drug. The permeability coefficient was calculated by Eq. 6.

The l was calculated using Madan's equation[24]:

$$l=\frac{W_{\mathrm{w}}}{W-W_{\mathrm{w}}}\cdot\frac{d_1}{d_2}\cdot\frac{D_{\mathrm{m}}}{6} \tag{7}$$

where W is the weight of coated beads, W_{w} is the weight of the coating material, d_1 is the bulk density of the core beads, d_2 is the apparent density of the coating material and D_{m} is the mean diameter of the core beads.

Results and Discussion

Optimum Conditions for Wax Coating 1) Wax Coating by Use of HCO: In pharmaceutical studies using the CF granulator, we found that powdered fine waxy material adhered onto the core granules by raising the preparing bed temperature over its melting point. This phenomenon led to the development of a new pharmaceutical technology of less time-consuming waxy coating without the use of any solvents for preparing a controlled-release formulation. Thus, we investigated the effect of the preparing bed temperature in detail to find out the optimum operating condition for this method.

It was found that Rec%, Ysc%, and sphericity were the highest when the bed temperature was maintained at 61—63 °C in the coating of HCO on nonpareil particles. The accurate control of bed temperature ranging from 61—63 °C, that should be an optimum condition, was

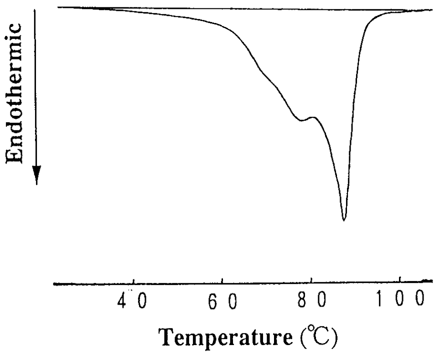


Fig. 1. Thermal Analysis (DTA) of HCO

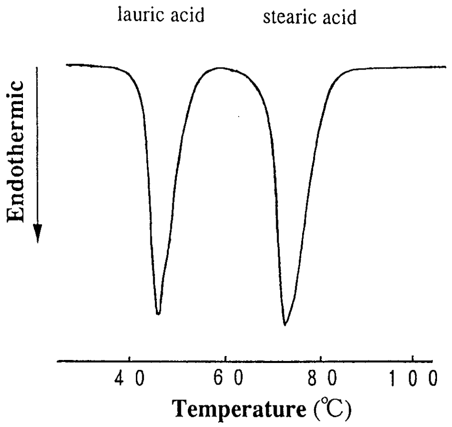


Fig. 2. Thermal Analysis (DTA) of Lauric Acid and Stearic Acid

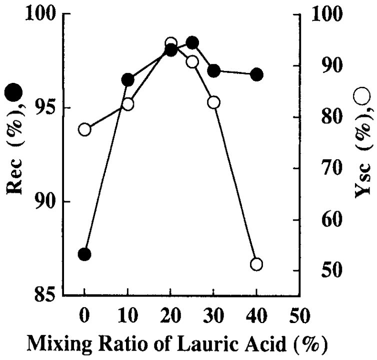


Fig. 3. Effect of Mixing Ratio of Lauric Acid in Mixture of Two Fatty Acids on Coating Producibility

●, Rec% (recovery percentage); ○, Ysc% (yield of single core beads); Seed material, nonpareil (710—840 μm); Meltable material, lauric acid (mp 44 °C); Non-meltable material, stearic acid (mp 70 °C); Bed temperature, 50 °C; Adhering level of powdered mixture of lauric acid and stearic acid against nonpareil, 30%.

essential for the HCO coating. When the operating temperature was lower than 61 °C, both the Rec% and Ysc% were low. The reason for this was that a part of the fed powdered HCO was removed from the CF granulator due to blowing slit air, without adhering onto the core beads. In contrast, when the temperature was higher than 63 °C, Rec% was fairly high, but serious agglomeration of beads occurred, and consequently the Ysc% was greatly decreased.

To determine the physical state of the waxy material at the temperature which gave the best condition for the wax coating, thermal analysis of HCO was performed and the result is shown in Fig. 1.

As can be seen in Fig. 1, the HCO gave a very broad endothermic pattern. This reveals that the origin of HCO was the natural source, and HCO is a mixture of various triglycerides with different melting points. From the DTA curve, it was presumed that about a 20% portion of the HCO might melt at the operating temperature (63 °C). Thus, the temperature at which about 20% of waxy materials melted seemed to be the optimum condition for the coating operation.

2) Determination of Optimum Condition for Wax Coating by Use of Two Different Fatty Acids: To certify the above presumption that the bed temperature at which about 20% of the waxy materials were melted seemed to be the optimum condition for the coating operation, we attempted coating with a mixture of two waxy materials. Lauric acid (mp 44 °C) and stearic acid (mp 69—70 °C) were used as waxy materials, the melting points of which could be clearly distinguished and were expected not to overlap with each other at all, as shown in Fig. 2.

Rec% and Ysc% at a 50 °C bed temperature, where lauric acid had completely melted while stearic acid was expected not to have melted at all, are plotted against the mixing ratio of lauric acid in the coating materials consisting of lauric acid and stearic acid, as shown in Fig. 3.

Rec% was more than 95% when the mixing ratio of lauric acid was higher than 10%, and exhibited a maximum at around 20 to 25% of the mixing ratio, while it was reduced when the mixing ratio was less than 10%. This should be due to the fact that stearic acid could not adhere to the core with a smaller mixing ratio of lauric acid acting as a binder since stearic acid did not melt at 50 °C and could consequently be exhausted from the duct. When lauric acid was increased to more than 25%, Rec% was reduced a little. It reflected that some of the wax was adhered to the stator and could not be recovered.

Ysc% exhibited a maximum when the lauric acid percent was around 20%. This indicated that a part of the added stearic acid was exhausted without adhering onto the beads when the mixing ratio of lauric acid was less than 20%, while agglomeration occurred at more than 20%. Thus, it was considered that the bed temperature at which 20% of the waxy material melted was preferable for the wax coating.

Preparation of Controlled Release Beads for Various Kinds of Drugs To clarify the applicability of this method as a controlled release coating technique, it was applied to four drugs: NA, ISA, THEO and SA, which have widely different solubilities. The spherical core beads containing NA, ISA, and SA were prepared by the wet powder coating method using a sucrose ethanol–aqueous solution as a binder, as described in the previous paper.[19] In the case of THEO, spherical beads were not obtained by the same condition as the other drugs. However, 5% of sucrose was added to the THEO powder and mixed well before the wet powder coating. This mixture was fed to the seed materials with spraying the sucrose ethanol–aqueous solution, as mentioned above. Thus, spherical beads of THEO could be obtained. In all of the drugs, the Ysc% was more than 95%, as shown in Table 1.

On the core beads prepared as above, HCO was coated. Both the Rec% and Ysc% were more than 94% in all the

Table 1. Coating Producibility of Core Beads and Coated Beads

	Core beads					Coated beads		
Drug	Rec% (%)	Ysc% (%)	Content of drug (%)	Mean particle size (μm)	Bulk density (g/cm^3)	Coating level (%)	Rec% (%)	Ysc% (%)
NA	97.2	96.5	60.5	629	1.56	100	98.1	94.4
ISA	96.9	96.3	60.5	624	1.58	80	98.8	96.7
THEO	96.5	96.4	51.6	643	1.61	50	98.5	96.2
SA	96.8	96.8	62.5	629	1.60	30	98.3	94.8

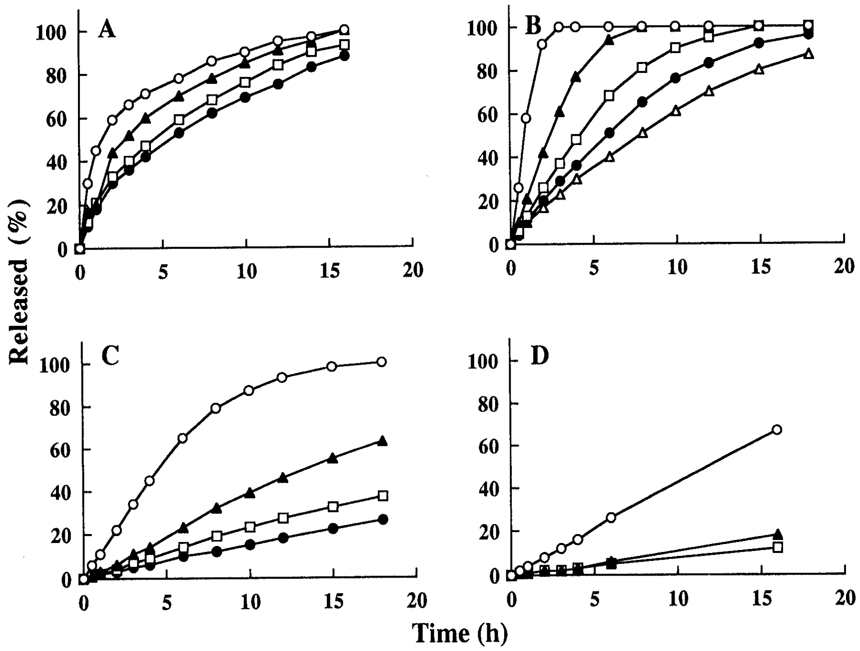


Fig. 4. Dissolution Profiles of HCO Coated Beads with Various Coating Levels Containing 4 Kinds of Drugs

A, NA: ○, 40%; ▲, 60%; □, 80%; ●, 100%; B, ISA: ○, 30%; ▲, 40%; □, 50%; ●, 60%; △, 80%; C, THEO: ○, 20%; ▲, 30%; □, 40%; ●, 50%; D, SA: ○, 10%; ▲, 20%; □, 30%. The dissolution medium was the purified water (paddle method, 37°C, 100 rpm).

drugs, as shown in Table 1. Thus, it was concluded that the coating method was applicable for the drugs with widely different solubilities.

Dissolution Behavior of Each Drug from HCO Coated Beads 1) Dissolution Behavior of HCO Coated Beads in Purified Water: The released percent of each drug from the coated beads with various coating levels was determined in purified water and shown in Fig. 4. The coating level shows the weight percentage of the coated HCO against the core beads. As shown in Fig. 4, the drug release rates decreased as the coating level of HCO increased in all cases. Comparing the dissolution rate at the same coating level, it was lower as the solubility decreased. It should be emphasized that this method depressed the dissolution rate very effectively since it was found that even the dissolution rate of such a highly water-soluble drug as NA could be depressed. Therefore, this coating method is very useful for preparing controlled release beads.

2) Dissolution Mechanism of HCO Coated Beads: To clarify the dissolution mechanism using the superposition technique,[22)] released percents were re-plotted against reduced time $T_r(=T/T_{50})$, as shown in Fig. 5, where T means the dissolution time and T_{50} means the dissolution time when half of the drug was released. In the case of ISA, THEO, and SA, the released percents against T_r were superposed in the same curve, and the released percents increased almost linearly until about 60% or 70% of the drug was released. This means that the releasing mechanisms were almost the same among these three drugs.

However, the releasing patterns of NA differed among them. In the cases of NA, the extent of superposition was not as good as those of the other three. When the coating level was more than 80%, rather good agreement was observed, but the curves deviated downwards at 40% and 60% coating levels. In addition, the zero order region until 60% of drug released was hardly observed in NA. The released amount per unit time decreased as dissolution time proceeded, and the superposed curve seemed to be the first order rate process.

As to the reason why the dissolution curve was not superposed in 40% and 60% of the coating levels of NA beads, the explosion of a part of the coated beads due to high osmotic pressure might be concerned in the early dissolution process when water permeated into the inner core, at which time dissolving of freely soluble NA in the permeated water occurred.

According to the diffusion theory, the dissolution rate

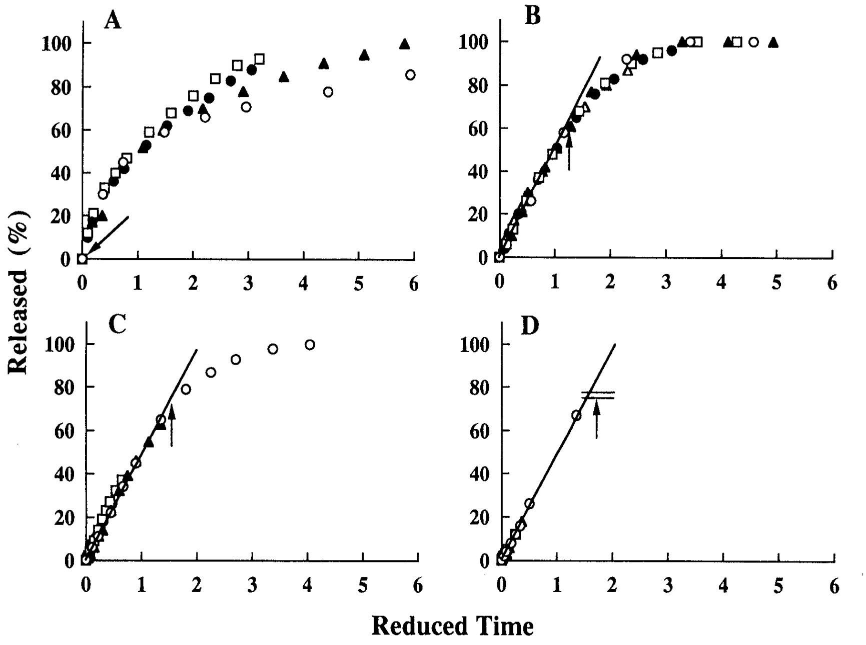


Fig. 5. Superposition of Dissolution Curves of HCO Coated Beads

A, NA; B, ISA; C, THEO; D, SA: Reduced time, T_r ($=T/T_{50}$). Symbols are the same as those in Fig. 4. The arrow indicates the experimental turning point.

Table 2. Comparison of Turning Point Determined Experimentally with Calculated Turning Point

Drug	V_0 (cm^3)	Calculated T.P. (%)	Experimental T.P. (%)
NA	1.30×10^{-4}	0	≒0
ISA	1.27×10^{-4}	80	60
THEO	1.39×10^{-4}	98	70
SA	1.30×10^{-4}	100	>70

could be expressed as follows:

$$-dm/dt=k_0 \quad (m_t>C_s\cdot V_0)$$

$$-dm/dt=k_t\cdot m_t \quad (m_t<C_s\cdot V_0)$$

where k_0 and k_t are dissolution rate constants, m_t is the amount of drug remaining in the core beads at time t, C_s is the solubility of the drug, and V_0 means the inner volume of empty coated beads after all of the drugs are released from the coated beads. V_0 could be calculated on the basis of mean particle size of the core beads. Then, the released percent where the dissolution rate changed from the zero order rate to a declining rate, namely, the calculated turning point, could be estimated. For instance, in the case of ISA, as shown in Table 1, the mean particle size of the core beads was 624 μm, thus V_0 can be calculated as 1.27×10^{-4} cm^3. Using this V_0, the bulk density of spherical core beads (1.58 g/cm^3), together with the ISA content in the core beads (60.5%), the amount of ISA per one core bead was calculated as follows: 1.27×10^{-4} (V_0) $\times$ 1.58 (bulk density) $\times$ 0.605 (ISA content). Then, by dividing the solubility of ISA in water (196 mg/ml), as shown in Table 3, by the amount of ISA per core bead obtained, the calculated turning point of the dissolution curve was approximately 80%. In such a way, turning points were calculated for other drugs and are shown in Table 2.

From the superposed curve shown in Fig. 5, the experimental turning point where the plots deviated from the linear curve was detected (pointed out by arrow) and is shown in Table 2, compared with the calculated values described above. As shown, the experimental values were rather lower than the calculated ones, but the order of the turning point was NA<ISA<THEO<SA and agreed completely with the calculated order. The lower values obtained by the experiment might be due to the fact that the diffusion pathway through the coated layer may be narrowed as time proceeded due to the filling of some pores by small particles or the swelling of the HCO layer by being in contact with water for a long period.

In any event, the result in Table 2 suggests that the dissolution rate of the drug through the coated layer could be controlled mainly by diffusion through the small water channels existing in the layer.

pH Dependency of Dissolution Rate The effect of the pH values of the dissolution medium was investigated by the use of purified water, the 1st, and the 2nd fluids of the disintegration test of JP XIII for ISA, THEO, and SA, which showed zero order dissolution behavior. These dissolution profiles from each drug's beads at the relevant coating level are shown in Fig. 6. From these results, the zero order dissolution rate constants were calculated (Table 3). As shown, the dissolution rate constant was larger in order of 1st fluid > water > 2nd fluid in ISA, nearly equal among the three media in THEO, and in the order of 2nd fluid > water > 1st fluid in SA. The order of the dissolution rate constants at the relevant pH in each case was coincident with that of the solubilities of each drug at the relevant pH. Thus, the pH of the dissolution medium seemed not to have much effect on the properties of the HCO layer.

Estimation of Permeability Coefficient 1) Relationship between Permeability Coefficient and Thickness of Coated

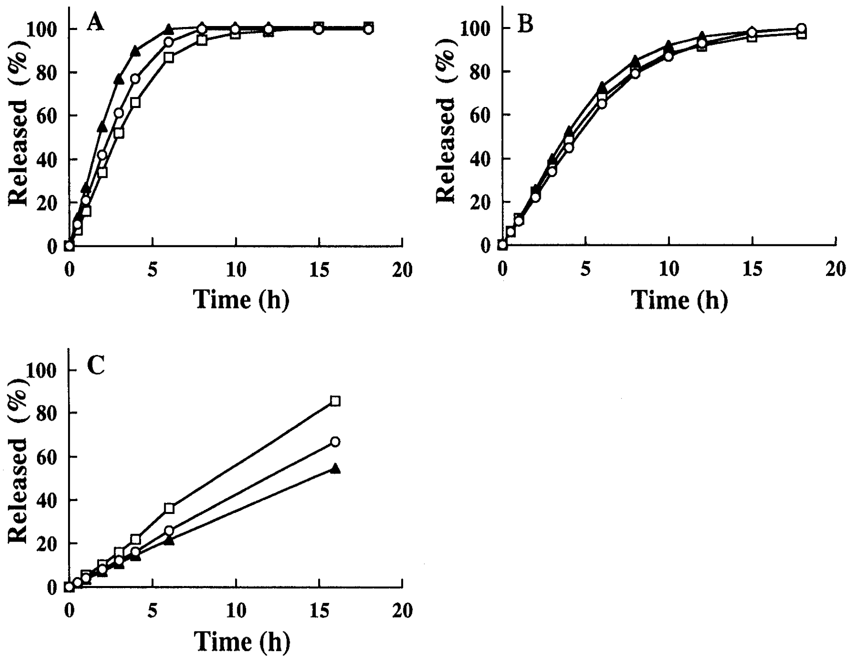


Fig. 6. Influence of Dissolution Medium pH on Dissolution Rate of HCO Coated Beads

A, ISA 40% coating level; B, THEO 20% coating level; C, SA 10% coating level: ○, purified water; ▲, 1st fluid; □, 2nd fluid.

Table 3. Zero Order Dissolution Rate Constant in Various pH Media

Drug	Dissolution medium	Solubility (mg/ml)	Dissolution rate (mg/h)						
			10%	20%	30%	40%	50%	60%	80%
ISA	pH 1.2	211			192	66	28	16	11
	Ph 6.8	188			36	17	11	8.6	5.7
	Water	196			57	21	12	8.6	6.4
THEO	pH 1.2	12		13	3.5	1.5	1.5		
	pH 6.8	11		12	3.2	1.8	1.3		
	Water	11		11	3.8	1.8	1.3		
SA	pH 1.2	2.3	4.2	1.1	0.77				
	pH 6.8	6.2	5.7	2.1	1.00				
	Water	2.9	3.4	1.1	0.86				

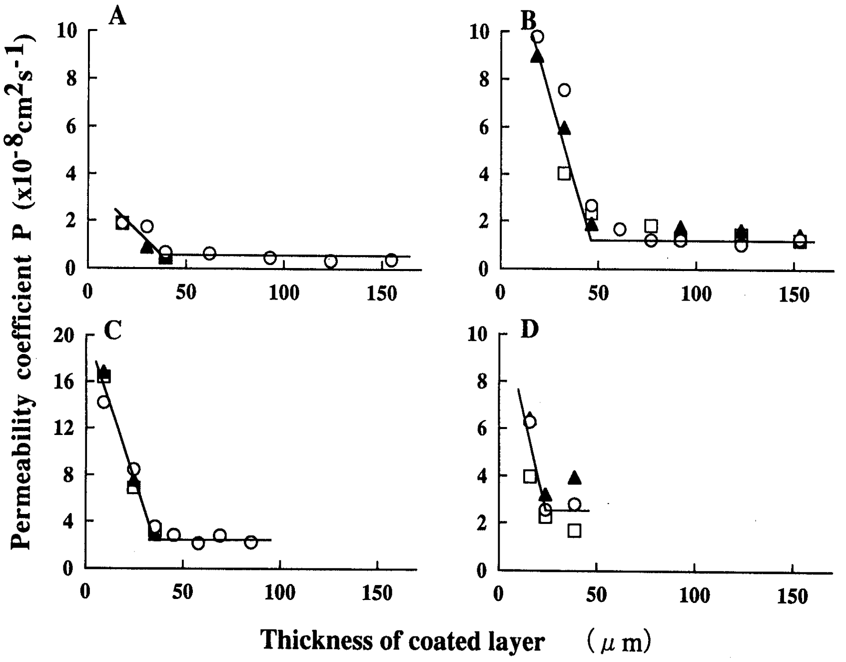
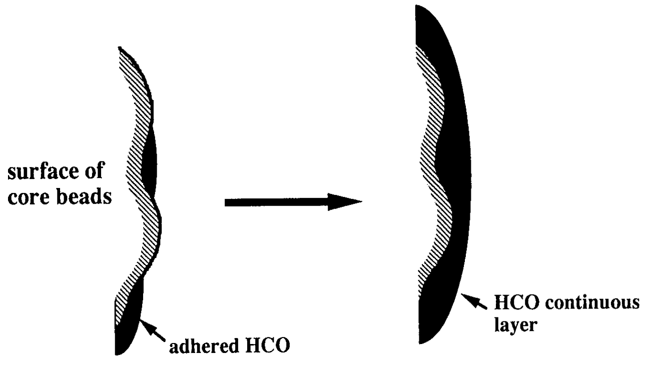


Fig. 7. Influence of Thickness of Coated Beads on Permeability Coefficient *P*

A, NA; B, ISA; C, THEO; D, SA: ○, purified water; ▲, 1st fluid; □, 2nd fluid.



(A) early stage (B) equilibrium stage

Fig. 8. Schematic Representation of HCO Coating Process

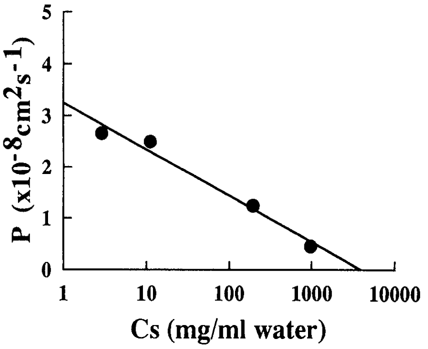


Fig. 9. Relationship between Solubility of Drugs and Permeability Coefficient *P*

C_s, saturated concentration of each drug.

Layer: The permeability coefficient (*P*) of each drug in purified water was calculated according to the method mentioned in the experiment. The *P* values obtained were plotted against the thickness of the coated layer in Fig. 7A to D. In all drugs, the *P* values decreased with an increase in the thickness up to certain thickness (NA, ISA, THEO: 40 μm; SA: 25 μm) and then reached an equilibrium stage. With regard to the pH dependency of permeation through the coated layer with HCO, the *P* values were almost not changed among in the 1st fluid, 2nd fluid, and purified water. Thus, the permeation through the coated layer with HCO was pH independent.

The reason the *P* values decreased with the coating level is presumably as follows: the surface of the core beads was not smooth but considerably rough under microscopic observation. Therefore, the HCO which adhered at an early stage of the coating process might be used to fill in the small holes or cracks on the surface of the core beads. Consequently, the HCO layer was discontinuous and thus did not act efficiently as a release depressing layer. When the coating level increased sufficiently, the layer became continuous and then served a release depressing function (schematically shown in Fig. 8).

2) Relationship between Permeability Coefficient and Solubility of Drug: The equilibrium *P* values obtained at the sufficient coating level were plotted against the solubilities of each drug. As shown in Fig. 9, *P* value decreased with an increase in solubility.

The reason *P* values were higher as the aqueous solubilities of drug decreased could not be clarified, but presumably multiple factors which could be concerned are: 1) As the aqueous solubility decreased, the partition of the drug on the surface of the hydrophobic waxy materials increased, and thus the gradient of the drug concentration in the coated layer increased; 2) the activity coefficient of the saturated solution is higher in a slightly soluble drug than that in a soluble one; 3) the viscosity of the inner saturated solution in the coated beads is lower in a slightly soluble drug than that in a soluble one; and 4) a part of the drug might also have been transported through the continuous phase of the wax layer in a slightly soluble drug.[22] To identify the contribution of each factor, further studies are necessary.

From this study it was found that the controlled-release beads coated with waxy material could be prepared by the TMG method without using any solvents. The layer formed with HCO had sufficient release depressing function and pH independency for permeation. These results suggest that waxy coating by the TMG method is an excellent coating method.

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