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Complexation of Aspirin with Potato Starch and Improvement of Dissolution Rate by Dry Mixing

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Dry mixing of aspirin with potato starch in a centrifugal rotating mixer produced a novel powder, composed of potato starch particles with an aspirin layer adhering on their surfaces. Friction and collision which occurred in the dry mixing process micronized and spread aspirin over the potato starch surfaces, forming a thin aspirin layer. The powder gave a higher rate of aspirin dissolution than a physical mixture. It was suggested from powder X-ray diffractometry, differential scanning calorimetry, and contact angle measurements that the improvement of dissolution rate was caused by an increase in wettability and an increase in the available surface area of aspirin.

Keywords——aspirin; potato starch; mixing; dissolution rate; dissolution improvement; complexation; powder

Introduction

Phenomena seen in dry mixing processes of a drug, diluent, lubricant and other components are important in the manufacture of solid pharmaceuticals. For example, it is well known that when magnesium stearate is used as a lubricant, the crushing strength, disintegration time, and drug-release properties of tablets are dependent on the method, duration and degree of mixing. These phenomena were explained in terms of the formation of a hydrophobic lubricant film on particle surfaces during the mixing.[1)]

Recently, specific mixed states produced by dry mixing of fine and coarse particles were reported. When large differences in particle size and particle interaction existed between the two types of particles, fine particles adhered to coarse particle surfaces and specific mixed states were obtained.[2)] One of the specific mixed states called an 'ordered mixture' or 'interactive mixture'[3)] was suggested to have potential advantages for the manufacture of tablets and granules. Powder segregation which may occur during mechanical processing (flow, fluidization or vibration) is one of the important problems in a situation where even minor changes in the degree of powder mixing could have a significant influence on the qualities of pharmaceuticals. Ordered mixture showed no significant segregation tendency under any conditions when fine particles adhered to coarse particle surfaces with an interparticle force strong enough to prevent the breakdown of ordered units.[4)] Further, the drug release pattern from matrixes prepared by dispersing the ordered mixture (which was composed of drug particles and water-soluble polymer particles) in a wax differed greatly from those from matrixes prepared by dispersing drug and polymer particles separately.[5)] A dry-coating method of particles was recently developed by utilizing ordered mixture formation.[6)] Furthermore, the phenomenon could be regarded as a new method for surface

modification. The wettability of coarse particles was changed by modifying their surfaces with fine particles.[7]

Microscopic mixed states of components are important in the design of solid pharmaceuticals. However, the details of the phenomena observed in dry mixing remain obscure. Much work needs to be carried out on such phenomena to improve the manufacture of high-quality pharmaceuticals. In this paper, the preparation of complex powders by dry mixing of a diluent and a drug in a centrifugal rotating mixer and the drug-release properties of the powders obtained are described.

Experimental

Materials——Potato starch was used as a core particle. The potato starch was fractionated by sieving and the size fraction less than 63 μm was used in the mixing experiments. Two potato starch samples different in water content were prepared to examine the effect of the water content on drug adhesion to potato starch. The dry potato starch was prepared by drying potato starch in an oven at 105 ± 2 °C for more than 6 h and was stored over silica gel in a desiccator. The wet potato starch was prepared by storing potato starch over a saturated ammonium sulfate solution for several days and kept in a sealed bottle until it was used. For determining the water content of the potato starches, the following procedure was employed. About 0.5 g of the potato starch was accurately weighed and dried in a drying chamber at 105 ± 2 °C for 5—8 h. After drying, it was allowed to cool over silica gel in a desiccator to room temperature, and reweighed accurately. The procedure was repeated until constant weight was indicated. Water content was calculated from the loss in weight.

Aspirin (Mitsui Pharmaceuticals Inc., Tokyo, Japan) was used as a model drug. The particle size of aspirin was reduced to less than 10 μm by crushing with a mill (Jet Mill; Freund Industrial Co., Ltd., Tokyo, Japan).

The other chemicals used were of analytical reagent grade.

Complexation of Potato Starch and Drug——A centrifugal rotating mixer (Mechano-mill; Okada Seiko Co., Ltd., Tokyo, Japan), shown in Fig. 1, was used for dry mixing of potato starch and drug. The vessel and the disc plate were made of stainless steel. Potato starch and aspirin were preliminarily mixed in a beaker with a spatula. The mixer was charged with 30 g of the mixed powder, containing 5—15% aspirin, and rotated at 1000 rpm for 20—60 min. Mixing was facilitated by using ten stainless steel balls of 6.3 mm in diameter. Owing to the centrifugal force caused by the rotation of the disc plate, the particles rose and fell along the inner surface of the vessel. After mixing, free aspirin particles which did not adhere to the starch surfaces were removed by sieving with a 37 μm sieve. Physical mixtures used for comparison were gently prepared by hand with a mortar and a pestle to minimize particle destruction.

Aspirin content of the resultant powder was measured spectrophotometrically. The mixed powders were dissolved in ethyl alcohol. The solution and diluent particles were then separated by filtration with a 0.6 μm membrane filter (Millipore filter BDWP 02500; Millipore Co., Ltd., U.S.A.). The absorbance of the filtrate was determined at 278 nm.

The shape and surface appearance of mixed powders were observed with a scanning electron microscope (SEM, JSM-T20; JEOL, Tokyo, Japan). Crystallinity and crystalline state of aspirin contained in mixed powders were evaluated with an X-ray diffractometer (Gigerflex-2012; Rigaku Denki Co., Ltd., Tokyo, Japan) and a differential scanning calorimeter (DSC, AZ-type; Rigaku Denki Co., Ltd., Tokyo, Japan). Contact angle was measured to estimate the wettability of mixed powders by the medium used in the dissolution test. Contact angle, θ, was calculated by means of the following equation from the height, h, and the width, r, of a droplet which was placed on a tablet.[8]

$$\tan(\theta/2)=2h/r$$

Tablets were prepared by introducing manually about 500 mg of the mixed powder into a die of a compression device

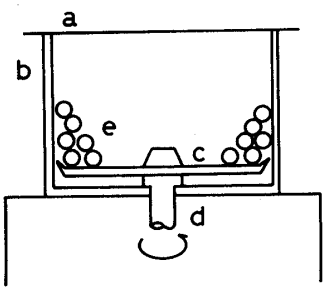

Fig. 1. Diagram of a Centrifugal Rotating Mixer Used for Complexation

a, lid; b, vessel; c, disc plate; d, rotating shaft; e, powder.

and compressing it with a hydraulic press. The contact angle of a droplet on a tablet generally decreases with time in a biphasic manner, with an initial fast decrease caused by spreading of the liquid followed by a slower decrease caused by the penetration of the liquid into the tablet. In this study, a contact angle at time 0, θ_0, and an apparent contact angle obtained by extrapolating the straight line in the plot of θ *vs.* time to time 0, θ_e, were used to estimate the wettability.

Dissolution Test——The dissolution of the drug was studied in a manner similar to the paddle method described in JP X. A given weight of the powder sample was dispersed into 600 ml of a dissolution medium maintained at 37 ± 0.5 °C in a vessel. The weight of drug dispersed into the dissolution medium was chosen to be less than 1/10 of the drug solubility to maintain a sink condition during the dissolution test. The dispersion was agitated with a paddle at a constant rate of 100 rpm. The vessel was equipped with a plastic cover to prevent water evaporation during the test period. Without stopping the agitation, aliquots of the dispersion were withdrawn with syringes at appropriate time intervals, and immediately filtered through a 0.6 μm membrane filter to remove the diluent particles. The concentration was determined by measuring the absorbance at 298 nm with an ultraviolet (UV) spectrophotometer after the aspirin had been hydrolyzed with a 0.5% sodium hydroxide aqueous solution. Simulated gastric fluid (pH 1.2) for the disintegration test, as described in JP X, was used as the dissolution medium. It contained 0.05% (v/v) of a nonionic surfactant, polyoxyethylene sorbitan monooleate (Kanto Chemical Co., Inc., Tokyo, Japan), to disperse the particles homogeneously. Each experiment was performed in triplicate, and mean values are reported. Reproducibility was adequate.

Results and Discussion

The mixing of aspirin and potato starch with a centrifugal rotating mixer produced an interesting powder. Scanning electron micrographs of the resultant powder particles are shown in Fig. 2. After mixing for 20 min, aspirin particles adhered to the surfaces of dry potato starch (water content 1.7%), and an ordered mixture was formed (Fig. 2a). The number of aspirin particles adhering to the starch surfaces decreased on further mixing, and the new surfaces (Fig. 2b) were observed after mixing for 60 min. They were different from those (Fig. 2c) obtained by treating potato starch alone for 60 min. Aspirin was spread over a fraction of the starch surface in a thin layer by mixing for 60 min. The powder prepared in this study differed from ordered mixtures in its structure. The drug spreads on the diluent particle surface in the former, but simply adheres on the excipient surface as intact particles in the latter.

The aspirin layer was considered to be formed as follows. Aspirin particles simply adhered to the starch surfaces within a few minutes in the first stage of mixing. The interparticulate force which was responsible for ordered mixture formation is presumably the electric charge interaction caused by triboelectrification, as reported by Staniforth and Rees,[9] since the mixer used in this study could produce stronger friction than conventional mixing equipment such as a Y-cone mixer. The aspirin particles which adhered on the starch surfaces were micronized by the friction and by collision with other particles and the inner surface of the vessel, and the micronized particles adhered to the surfaces of potato starch particles again. Then, the surfaces of micronized aspirin particles were softened by the temperature increase owing to collision and friction, and stuck to each other, forming the aspirin layers.

Potato starch powders usually contain some water. The effect of water content of potato starch powders on the formation of aspirin layers was studied. Figure 2d shows the particles prepared by mixing aspirin with a potato starch powder of 15.4% water content for 20 min. The aspirin layers are apparent in Fig. 2d, though layer formation was not observed on mixing with potato starch powder of 1.7% water content for 20 min (Fig. 2a). Though Stephenson and Thiel reported that the water content of the powders did not affect their ability to form an ordered mixture,[10] the water content of potato starch did affect the formation of aspirin layers in this study. The effect of water content on the aspirin adhesion is summarized in Table I. The amount of aspirin which adhered to starch surfaces increased with an increase in water content at every amount of aspirin added, *e.g.* 5.1% for 1.9% water content and 5.5% for 16.5% water content at 10% aspirin added. This result indicated that the water content of

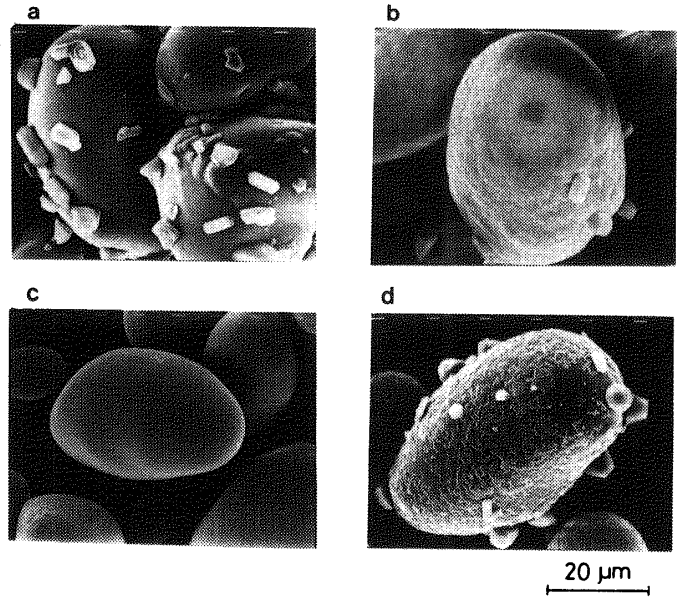

Fig. 2. Scanning Electron Micrographs of Complex Powders and Potato Starch

a, a complex powder prepared by mixing 10% aspirin with dry potato starch for 20 min; b, a complex powder prepared by mixing 10% aspirin with dry potato starch for 60 min; c, a potato starch treated for 60 min without aspirin; d, a complex powder prepared by mixing 10% aspirin with wet potato starch for 20 min.

TABLE I. Effect of Water Content of Potato Starch on Coating

Aspirin added (%)	Water content (%)	Aspirin content (%)
5	1.2	2.1
	14.3	3.5
10	1.9	5.1
	16.5	5.5
15	2.1	5.9
	13.5	6.4

Mixed for 60 min at 1000 rpm.

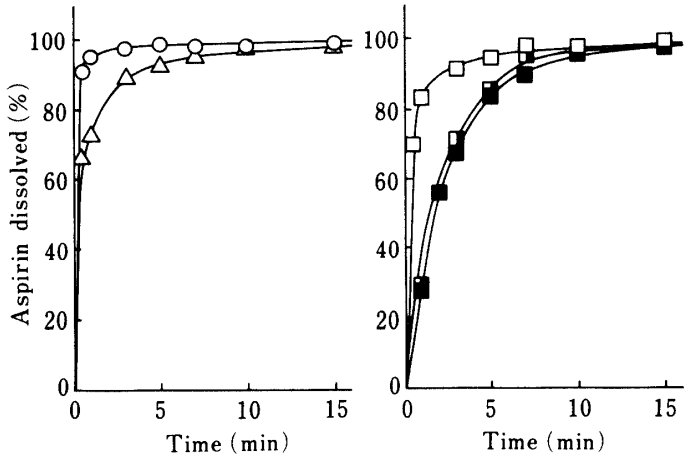

Fig. 3. Effect of Complexation on Aspirin Dissolution

○, complex powder (aspirin content 5.6%); △, aspirin powder crushed with a jet mill; □, physical mixture (aspirin content 5%); ■, physical mixture (aspirin content 25%); ◨, physical mixture (aspirin content 50%).

larger particles affects the adhesion of the aspirin particles to them.

Dissolution profiles of aspirin are illustrated in Fig. 3. Complexation with potato starch clearly accelerated aspirin dissolution (Fig. 3a). Though about 90% of the drug dissolved from aspirin powder in 5 min, more than 90% dissolved from the complex powder (aspirin content 5.6%) within 30 s.

Improvement of the drug dissolution rate by the mixing of a drug with a diluent has been

reported by three groups of investigators. Ampolsuk *et al.* demonstrated that drugs (digoxin and hydrocortisone) were spread over the diluent surface by frictional force in a mortar and pestle, and the resultant triturations showed high dissolution rates.[11] McGinity *et al.*[12] and Nyström *et al.*[13] reported separately that ordered mixtures prepared by mixing griseofulvin and other large particles with an industrial mixer gave high dissolution rates. Improvement of the drug dissolution rate by the formation of ordered mixture, where fine drug particles adhered to larger excipient particles, was proved by Nyström and Westerberg to be caused by an increase in the surface area exposed to the dissolution medium.[13a] Deaggregation of drug particles during the mixing process, owing to their adhesion to the excipient particle surface, would be responsible for this increase in the available surface area. However, no explanation for the improvement of drug dissolution by the trituration was offered by Ampolsuk *et al.*

Change in the wettability is responsible for the acceleration of drug dissolution. It is well known that drug release from less-wettable pharmaceuticals is generally slow. In this study, the dispersibilities of sample powders in the dissolution medium were not distinguishable from each other in the dissolution test. But, complexation and mixing of a hydrophobic powder with a hydrophilic powder might have changed the apparent dispersibility of the hydrophobic powder in the dissolution medium and thus might have affected the drug dissolution. Therefore, aspirin dissolution from physical mixtures was investigated and the contact angle of the sample powder against the dissolution medium was measured as an index of dispersibility.

The time courses of aspirin dissolution from the physical mixtures with potato starch are shown in Fig. 3b. In fact, physical mixing improved aspirin dissolution, but aspirin dissolution from the physical mixtures containing 50 and 75% potato starch was slower than that from the aspirin powder, and that from the physical mixture of 95% potato starch was as fast as from the aspirin powder and slower than from the complex powder. Further improvement was not achieved by the addition of more than 95% starch. Improvement of the drug dissolution rate by the physical mixing is presumably caused by the increase in the surface area exposed to the dissolution medium in the same manner as in ordered mixtures, because the number of agglomerates of aspirin particles decreased with increase of the percentage of starch added, and agglomerates did not exist in the physical mixture containing 95% starch.

The values of contact angle of the sample powder against the dissolution medium are summarized in Table II. Excepting aspirin, the extrapolated contact angles for other powders could not be measured owing to the rapid expansion of the droplet and the explosive swelling of potato starch. The contact angles at time 0 for potato starch, aspirin and the complex

TABLE II. Effect of Treatment with a Centrifugal Rotating Mixer on Wettability of Powders

Sample	Contact angle (°)	
	Time 0	Extrapolated
Potato starch	24.8±3.0	n.d.
Aspirin	52.1±1.5	42.8±2.1
Complex powder[a]	40.3±4.6	n.d.
Physical mixture		
Aspirin 3%	30.1±4.6	n.d.
Aspirin 5%	40.0±5.5	n.d.
Aspirin 10%	45.4±2.0	n.d.

n.d.: not detectable. *a*) Mixed for 60 min at 1000 rpm. Aspirin content was 4.2%.

powder containing 4.2% aspirin were 24.8, 52.1, and 40.3°, respectively. This suggested that the complexation of aspirin with potato starch improved the wettability and dispersibility of aspirin. Physical mixing also improved the wettability. The contact angle at time 0 increased with the aspirin content: 30.1, 40.4 and 45.4° for 3, 5 and 10% aspirin, respectively. The contact angle at time 0 for the physical mixture containing 5% aspirin was nearly equal to that for the complex powder composed of 4.2% aspirin and potato starch.

As described here, the improvement in the wettability by complexation and physical mixing was clearly shown by the contact angle measurements. However, the improvement in drug dissolution rate caused by the complexation would not be due solely to the change in wettability, because the contact angle data did not explain why the complexation improved the drug dissolution rate more effectively than physical mixing.

Change in crystalline state was suspected as a cause of the improvement of the dissolution rate. It plays an important role in drug dissolution; for example, Yamamoto *et al.* reported that the faster dissolution rate of a ground mixture of phenytoin and microcrystalline cellulose was due mainly to the transition of the drug from the crystalline state to the amorphous state.[14]

Melting points of aspirin in the powders are listed in Table III. Aspirin adhering to the diluent surfaces showed a lowered melting point (from 137.5 to 133.9 °C). However, aspirin which was physically mixed with starch melted at 133.7 °C. The difference between the two values is very small. Moreover, such remarkable changes as an appearance of a new peak[15] or

Table III. Effect of Treatment with a Centrifugal Rotating Mixer on Aspirin Melting

Sample	Melting point[a] (°C)
Aspirin	137.5
Complex powder[b]	133.9
Physical mixture[c]	133.7

a) Measured by DSC. *b*) Mixed for 60 min at 1000 rpm. Aspirin content was 5.6%. *c*) Aspirin content was 5.0%.

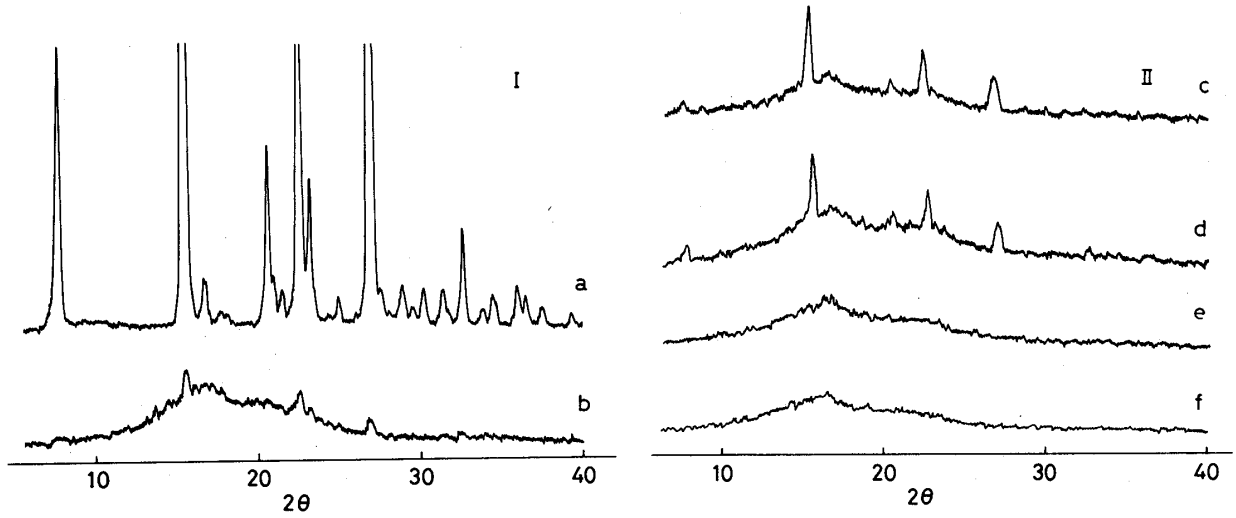

Fig. 4. Powder X-Ray Diffractograms of Aspirin, a Complex Powder, and Physical Mixtures

I) a, aspirin; b, a complex powder (aspirin content 4.2%). II) Physical mixtures: c, aspirin content 10%; d, 5%; e, 1%; f, 0%.

splitting of the peak[16] could not be found in the thermogram of the complex powder. The drop of melting point presumably arose from the change in heat conductivity which was caused by the presence of potato starch particles.

Powder X-ray diffraction profiles of the complex powder (aspirin content 4.2%), the aspirin powder and the physical mixtures of aspirin with potato starch are shown in Fig. 4. Clear peaks owing to aspirin appeared at 15.6, 22.6 and 27.0° (2θ) in the X-ray diffraction diagram of the complex powder. A broad peak in the region from 10 to 28° was due to potato starch. Though the peaks owing to aspirin were not found in the diagram of a physical mixture containing 1% starch, the peaks (which were proportional to the aspirin content) were observed for the physical mixtures containing 5 and 10% starch. As compared with the peaks shown in the X-ray diffraction diagram of the physical mixtures, a decrease in the peak intensity was apparent in the case of the complex powder. Further, a peak at 7.8° was not found in the X-ray diffraction profiles of the complex powder though it was observed in that of the physical mixture of 5% aspirin. These changes suggest that a portion of the aspirin which adhered on the potato starch surfaces was in the amorphous state.

As described above, clear evidence for a change in crystalline state by complexation was not obtained by X-ray diffractometry and differential scanning calorimetry. However, the aspirin treated with potato starch had been subjected to physical forces such as shear stress and impact force. It is well known that physical force disturbs the crystal lattice and structure of a solid, and trends to cause a transformation from a crystalline to an amorphous state.[17]

Consequently, the improvement in the dissolution rate by the complexation of aspirin with potato starch is concluded to have been caused by (1) the increase in the wettability of aspirin resulting from the presence of a hydrophilic material, potato starch, and (2) the increase in the surface area available for dissolution. The increase in the surface area exposed to the dissolution medium was shown by scanning electron microscopy. The friction and collision during the mixing in the centrifugal rotating mixer micronized and spread the aspirin on the diluent surface, and the surface area of aspirin adhering on the starch surface as a layer would be greater than that in the physical mixtures. The transition of a portion of the aspirin from the crystalline state to the amorphous state would also have played an effective role in improving drug dissolution.

The technique suggested in this study should be useful to manufacture pharmaceuticals of high quality. It can be used as a means to enhance the dissolution of less-soluble drugs. Further, the complex powder has an advantage over the ordered mixture in that it more readily remains homogeneous, *i.e.*, the complex powder should be more resistant to segregation than the ordered mixture, since the drug in the complex powder system tightly adheres to coarse particles as a layer, while the ordered mixture depends for its formation only on the interparticle force existing between coarse and fine particles.

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References

1) *a*) K. S. Murthy and J. C. Samyn, *J. Pharm. Sci.*, **66**, 1215 (1977); *b*) C. F. Lerk, G. K. Bolhuis, A. J. Smallenbroek, and K. Zuurman, *Pharm. Acta Helv.*, **57**, 282 (1982).
2) J. A. Hersey, *Powder Technol.*, **11**, 41 (1975).
3) H. Egermann, *Powder Technol.*, **36**, 117 (1983).
4) J. N. Staniforth and J. E. Rees, *J. Pharm. Pharmacol.*, **34**, 700 (1982).
5) H. Emori, T. Ishizaka, and M. Koishi, *J. Pharm. Sci.*, **73**, 910 (1984).
6) *a*) T. Ishizaka, M. Yamada, K. Yano, and M. Koishi, *Yakuzaigaku*, **45**, 193 (1985); *b*) A. Nakagawa, T. Ishizaka, K. Yano, and M. Koishi, *ibid.*, **45**, 254 (1985).
7) M. Koishi, T. Ishizaka, and H. Suzuki, *J. Pharmacabio-Dyn.*, **7**, s-21 (1980).
8) J. Kimura, T. Ito, and M. Koishi, *Shikizai Kyokai-shi*, **50**, 431 (1977).

9) J. N. Staniforth and J. E. Rees, *J. Pharm. Pharmacol.*, **34**, 69 (1982).
10) P. L. Stephenson and W. J. Thiel, *Powder Technol.*, **25**, 115 (1980).
11) C. Ampolsuk, J. V. Mauro, A. A. Nyhuis, N. Shah, and C. I. Jarowski, *J. Pharm. Sci.*, **63**, 117 (1974).
12) J. W. McGinity, Chi-Tze Ku, R. Bodmeier, and M. R. Harris, *Drug Devel. Indust. Pharm.*, **11**, 891 (1985).
13) *a*) C. Nyström and M. Westerberg, *J. Pharm. Pharmacol.*, **38**, 161 (1986); *b*) M. Westerberg, B. Jonsson, and C. Nyström, *Int. J. Pharm.*, **28**, 23 (1986).
14) K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, *J. Pharm. Sci.*, **65**, 1484 (1976).
15) Y. Nakai, K. Yamamoto, K. Terada, and J. Ichikawa, *Chem. Pharm. Bull.*, **32**, 4566 (1984).
16) N. Kaneniwa, A. Ikekawa, and M. Sumi, *Chem. Pharm. Bull.*, **26**, 2734 (1978).
17) T. Kubo, "Yukibutsu No Mekanokemisutori," Sougou Gijutsu Shuppan, Tokyo, 1985, pp. 165—179.