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Tableting of Coated Particles. I. Small Particle Size Chitosan as an Agent Protecting Coating Membrane from Mechanical Damage of Compression Force

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Formulation of sustained release tablets containing coated particles whose coating membrane is not damaged during compression was studied and several kinds of chitosan of different particle size were evaluated as protective agents for the membrane. Comparison was made with the dissolution rate of the coated particles. Ethylcellulose or ethylcellulose/hydroxypropylcellulose was chosen as a coating agent. When the coated particles were compressed with the small particle size chitosan (Marine Chito), the coating membrane was not ruptured, and the protective effect was not influenced by the compression pressure. Both the Eudragit RS-coated particles and the tablets manufactured by compressing the coated particles with Marine Chito were orally administered to dogs, and the plasma theophylline levels of the two dosage forms were compared to determine the drug release characteristics in the gastrointestinal tract. It was found that the plasma concentration–time curve of the tablets coincided with that of the coated particles, and the compressed tablet would disintegrate instantly and redisperse into many particles in the body after oral administration.

Key words tableting; coated particle; dissolution rate; disintegration; plasma concentration–time curve; bioavailability parameter

Compressed tablets, which contain a multiparticulate system, are becoming increasingly more in demand than hard gelatin capsules because of their lower production cost and ease in swallowing. When formulating sustained release tablets containing coated microcapsules, it is desirable to produce those which disintegrate into many subunits instantly after ingestion, thus maintaining the characteristics of the coated particles. However, it is often pointed out that drug release of such tablets may be faster or slower than the original microcapsules because of the rupture of the coating membrane or the formation of non-disintegrating tablets.

To prevent undesirable drug release properties of such tablets, the phenomena and mechanism involved during the compression of microcapsules have been the subject of numerous publications during the last four decades.[1] It has also been demonstrated that microcrystalline cellulose (Avicel) was the most effective agent among other pharmaceutical excipients in preventing the rupture of the coating membrane.[2] However, the effect was still not sufficient, and other techniques, such as applying a protective coating or addition of both waxy materials and plastically deformable excipients, have actually been employed.[3]

The purpose of our study was to find suitable protective agents to compress the coated particles into tablets which redispersed into many subunits while maintaining the advantageous functions of the original particles. It is desirable that the protective agents have the following properties: (i) that they be widely used in the pharmaceutical industry, and (ii) that they can be used without any complicated procedures.

Chitosan is easily prepared from chitin, which is widely distributed in nature, by partial *N*-deacetylation with alkali. Chitosan has been examined and used for various medical and pharmaceutical purposes.[4] For example, it has been examined as a new vehicle for sustained-release preparations,[4a,b] and also reported as a vehicle for direct compression.[4c] Despite these applications, there are no reports concerning utilization of chitosan as a protective agent for the coating membrane.

The suitability of chitosan as a protective agent was examined in this study. The integrity of the coating membrane after tableting was measured by comparing the dissolution rate of tablets with that of uncompressed coated particles. Theophylline was used as a model drug.

Experimental

Materials Anhydrous theophylline (Tokyo Kasei Kogyo Co., Tokyo, Japan) was of JP grade, and was used after sieving with 140 and 282 mesh screen (105—53 μm). Microcrystalline cellulose (Avicel PH102, Asahi Chemical Industry Co., Tokyo), ethylcellulose (EC; Ethocel standard premium, 10 cP, Dow Chemical Co., U.S.A.), hydroxypropylcellulose (HPC-SL; Nippon Soda Co., Tokyo), and aminoalkyl methacrylate copolymer RS (Eudragit RS, Röhm Pharma, Germany) were all of JP grade. Chitosans (P-45, Negami Chemical Industrial Co., Tokyo; 90L KTCA-6, Katokichi Co., Kagawa, Japan; Marine Chito 80MD-F10, Fuji Bouseki, Tokyo) were used as received. All other solvents and chemicals were of reagent grade.

Coating of Theophylline The fine particles of theophylline (105—53 μm) were coated by spraying with an aqueous ethanolic solution of EC (concentration: 5% EC and 80% ethanol) or EC–HPC (concentration: 4% EC, 1% HPC, and 80% ethanol) using a fluidized-bed system (GPCG-1, Glatt, Germany). The coating level was 40% based on the percent weight increase. The coating conditions were as follows: spray air pressure, 2 kg/cm^2; inlet air temperature, 43—47 °C; outlet air temperature, 32—38 °C; and spraying rate of coating solution, 2.5—4 g/min. The yield was 86%, and 90% of the coated particles had particle sizes of from 42 to 75 μm.

Tableting Before tableting, the coated particles were blended with additives in a polyethylene bag. About 200 mg of the powder mixture was compressed into a tablet using a tableting machine (Autograph IS-5000, Shimadzu Co., Kyoto, Japan) with a 10 mm flat face punch. The compressing rate was fixed at 10 mm/s, and the compression pressure applied was varied from 12.5 to 125 MPa.

Dissolution Test A dissolution test was performed according to the JP XII paddle method in 900 ml of water at 37 °C with constant stirring at 100 rpm. Aliquots were removed at appropriate intervals and assayed with a spectrophotometer (UV-160, Shimadzu Co., Kyoto, Japan, wave-

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length 242 and 360 nm) to determine the theophylline concentration.

***In Vivo* Study, Assay for Plasma Concentration of Theophylline and Pharmacokinetic Analysis** Because the dissolution rate of the EC-coated theophylline particles was very slow, it was feared that the difference in plasma concentration of the particles and tablets could not be detected. To avoid such difficulty, coating particles which had a moderate release rate were desirable. Eudragit RS was therefore chosen as the coating membrane for *in vivo* study instead of EC. The control mechanisms of the release rate of both membranes were the same. The fine theophylline particles were coated with Eudragit RS by spraying an aqueous ethanolic solution using a fluidized-bed system (GPCG-1). The coated particles (TH granules) and the tablets compressed with Marine Chito were used for the *in vivo* bioavailability study.

Four male beagle dogs weighing 10—12 kg were fasted overnight and used for the experiment. They were fasted until the end of the experiment, but were allowed free access to water. The experimental conditions of the crossover study were as follows: 1) TH granules, 2) two tablets which contained TH granules. Each dosage form (dose: 100 mg/dog) was administered with 50 ml of water. Blood samples were taken with heparinized syringes at appropriate intervals and were immediately centrifuged to separate plasma. The plasma samples were kept frozen until assayed.

The plasma concentration of theophylline was determined by HPLC under the following conditions: column, TSK-GEL ODS-120T (Toso, Tokyo); mobile phase, 0.01 M acetic acid/acetonitrile (100 : 5, v/v); flow rate, 0.5 ml/min; column temperature, 40 °C; wavelength, 273 nm.

The maximum plasma concentration (C_{max}) and the time to reach the C_{max} (T_{max}) were read from the plasma concentration–time curves. The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal method. The mean residence time (MRT) was calculated by moment analysis.

Results and Discussion

Influence of Compression of EC-Coated Theophylline Particles on Drug Release Characteristics The theophylline particles were coated with an aqueous ethanolic solution of EC and then compressed into tablets.

Figure 1 shows the comparison of the dissolution profiles of the EC-coated theophylline particles and the compressed tablet (without any additives). The dissolution rate from the coated particles was quite slow due to the excellent barrier function of EC-membrane, whereas the dissolution rate from the tablet was considerably faster. It is notable that increment in the dissolution rate was only observed at the early stage of the dissolution test. These results appeared to indicate that some part of the coating membrane had been ruptured during the compression process.

Effect of Avicel PH102 on Mechanical Damage of Coating Membrane Avicel, more than other excipients, is known to be very effective in protecting a coating membrane from damage caused by mechanical force during compression.[2] This protective efficiency of Avicel PH102 against mechanical damage to the membrane of the EC-coated theophylline particles was therefore investigated.

Figure 2 is a comparison of the dissolution profiles of the coated particles and tablets compressed with Avicel PH102 (coated particles/Avicel ratio; 5/5) under different compression pressure. The dissolution rate slightly increased even at low pressure (12.5 MPa) and the tablets were too soft to allow handling. At higher pressure, the dissolution rate of the tablet became faster and the coating membrane might have been ruptured by mechanical force. From these results, it was concluded that Avicel PH102 was not suitable as a protective agent for tableting of EC-coated theophylline particles.

Protective Effect of Chitosan Figure 3 shows the protective efficiency of various kinds of chitosan in preventing rupture of the coating membrane during compression (coated particles/chitosan ratio: 5/5; compression pressure: 62.5 MPa). The mean particle size (mass median diameter) of Chitosan/P-45 and Chitosan/90L KTCA-6 were 60 and 210 μm, respectively. Marine Chito was porous fine beads with a pore size of 0.2 to 0.3 μm and a mean particle size of 6 μm. When the coated particles were compressed with chitosans of larger particle size (P-45, 90L KTCA-6), the dissolution rate

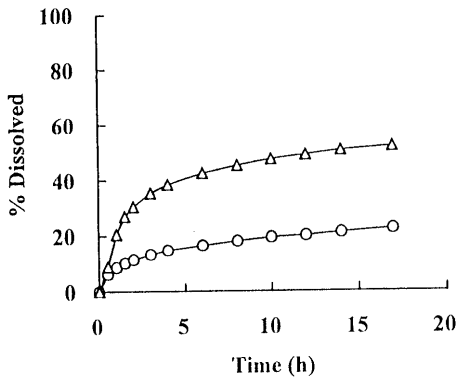

Fig. 1. Dissolution Profiles of EC-Coated Theophylline Particles and Compressed Tablets

○, coated particles; △, compressed tablets.

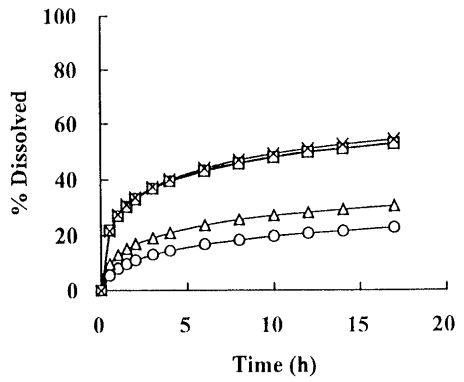

Fig. 2. Dissolution Profiles of EC-Coated Theophylline Particles and Tablets Compressed with Avicel PH102 under Different Pressures

Coated particles/Avicel PH102 ratio: 5/5. ○, coated particles; △, 12.5 MPa; □, 62.5 MPa; ×, 125 MPa.

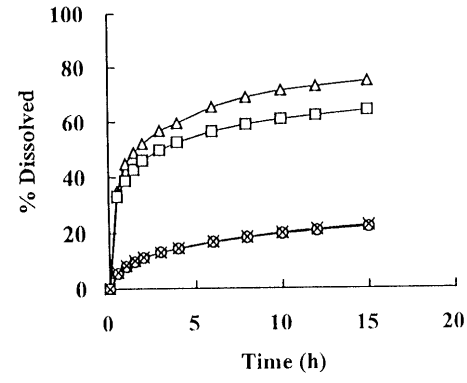

Fig. 3. Effect of Various Kinds of Chitosan on Dissolution Rate of Tablets Containing EC-Coated Theophylline Particles

Coated particles/chitosan ratio: 5/5, compression pressure: 62.5 MPa. ○, coated particles; △, chitosan (P-45); □, chitosan (90 L); ×, Marine Chito.

became faster than that of the original particles. It was obvious that they had no ability to protect the coating membrane from mechanical damage by the compression force.

On the other hand, when the smaller particle size chitosan (Marine Chito) was used, the dissolution rate was almost the same as that of the original particles. This meant that when the coated particles were compressed together with Marine Chito under pressure at 62.5 MPa, the coating membrane was not ruptured.

Figure 4 shows the influence of compression pressure on the protective efficiency of Marine Chito (coated particles/Marine Chito ratio: 5/5). In contrast to Avicel, the dissolution rates of tablets compressed with Marine Chito were almost the same as that of the coated particles, that is, the protective ability of Marine Chito to prevent rupture of the coating membrane was not influenced by the compression pressure.

Smaller tablets might be preferable for patients, especially for the aged and children. Considering the tablet size, a smaller amount of additives for protecting the coated particles was desirable. Influence of the quantity of Marine Chito added was then investigated. As shown in Fig. 5, when the concentration of Marine Chito was 10% (coated particles/Marine Chito ratio: 9/1), the dissolution rate became slightly faster, but when the concentration was more than 30% (coated particles/Marine Chito ratio: 7/3), the quantity of Marine Chito did not affect the tablet dissolution rate.

It was thus concluded that Marine Chito was an excellent protective agent for the EC-coated theophylline particles compressed into tablets to combat damage to the coating membrane. Particle size of the additives might play an important role in protecting the membrane from rupture during the compression process. Small particles of Marine Chito (mean particle size: 6 μm) could cover the surface of the coated particles and perhaps prevent direct contact among the latter. Mixing the coated particles with Marine Chito might give the mixture better compression characteristics to prevent rupture of the coating membrane. Figure 6A shows compression characteristics of the powder mixture of the coated particles and the additives. This mixture showed a different profile than other powder mixtures. The slope of the compression force–porosity curve of the tablets containing Marine Chito was more gentle than that of other additives, so that tablets containing the small particle size additives (Marine Chito) were believed to be compressed plastically without any fragmentation, with Marine Chito acting as a cushion. As a result, no rupture of the coating membrane occurred. The larger particle size additives might be more fragile, and the slope at the lower compression force level became steeper. When the coated particles were compressed with such additives, both the coated particles and the additives might fragment, and the compression force would be transmitted directly to the coated particles. This might be one reason why Marine Chito had

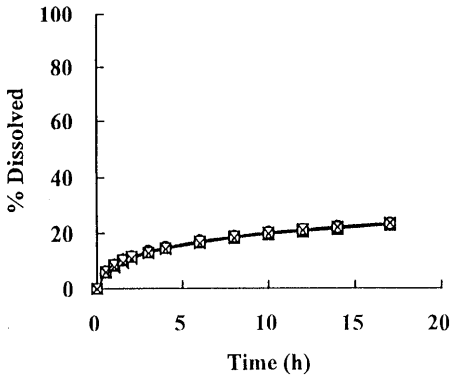

Fig. 4. Effect of Compression Pressure on Dissolution Rate of Tablets Containing EC-Coated Theophylline Particles with Marine Chito

Coated particles/Marine Chito ratio: 5/5. ○, coated particles; △, 12.5 MPa; □, 62.5 MPa; ×, 125 MPa.

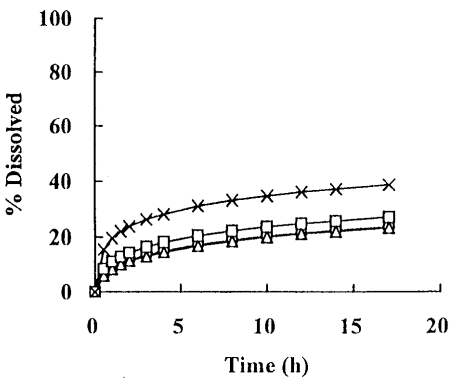

Fig. 5. Influence of Coated Particle/Marine Chito Ratio on Dissolution Rate of Tablets Containing EC-Coated Theophylline Particles

Compression pressure: 62.5 MPa. ○, coated particles; △, 5/5; □, 7/3; ×, 9/1.

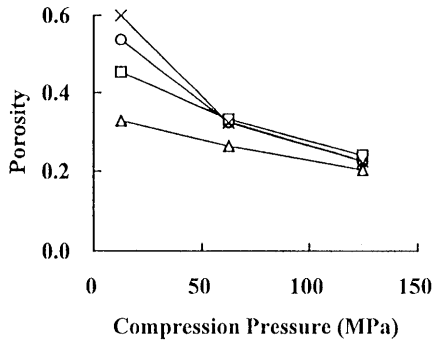

Fig. 6A. Effect of Compression Pressure on Porosity of Tablets Containing EC-Coated Theophylline Particles with Various Excipients

Coated particles/excipients ratio: 5/5. ○, Avicel PH102; △, Marine Chito; □, chitosan (P-45); ×, chitosan (90 L).

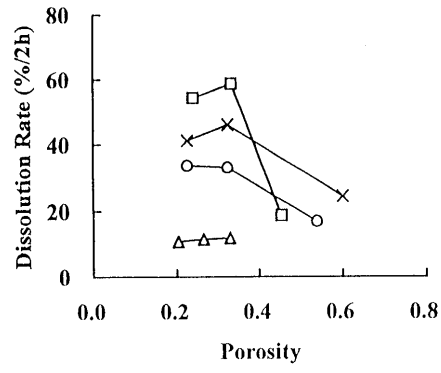

Fig. 6B. Effect of Porosity on Dissolution Rate of Tablets Containing EC-Coated Theophylline Particles with Various Excipients

Coated particles/excipients ratio: 5/5. ○, Avicel PH102; △, Marine Chito; □, chitosan (P-45); ×, chitosan (90 L).

good protective ability, although the mechanism involved is not yet clear. Figure 6B shows the relationship between the porosity and the dissolution rate of each tablet. Avicel and large particle size chitosans had almost the same profiles. The dissolution rate became faster with decreasing porosity, meaning that the fragmentation of the coated particles might occur as the compression progressed, and the coating membrane would be ruptured. The dissolution rate of the tablet made from Marine Chito, on the other hand, was little influenced by porosity.

The protective ability of Marine Chito on other coating membranes was then investigated. The EC–HPC membrane was chosen as the model of a nondisintegrating tablets. Tablets containing EC-coated theophylline particles disintegrated instantly, but EC–HPC coated theophylline particles created a matrix by compression and the matrix-tablets did not disintegrate without disintegrants.

Figure 7A shows the dissolution profiles of the EC–HPC coated theophylline particles and tablets (coated particles/Marine Chito ratio: 5/5). Tablets containing the coated particles and Marine Chito disintegrated instantly (less than 5 min) and showed excellent dissolution profiles under various compression forces. The period required for 50% release of the coated particles and the tablets compressed with Marine Chito or Avicel was 51, 53, and 25 min, respectively; the disintegration time of the tablets with either substance was almost the same (less than 5 min).

Figure 7B also shows the influence of the concentration of Marine Chito on the dissolution rate of the compressed tablets containing EC–HPC coated particles. The dissolution rate of the tablet containing the coated particles alone was slower than that of the original particles, as the tablet did not disintegrate. But for tablets compressed with Marine Chito, just 10% of Marine Chito (coated particles/Marine Chito ratio: 9/1) was sufficient to prevent the rupture of the coating membrane.

The lowest amount of Marine Chito required to protect the EC coated particles and the EC–HPC coated particles from compression force damage was 30 and 10%, respectively. Factors of compression speed, the hardness or the size of the coated particles might affect rupture of the coating membrane during compression, and the difference between the lowest amount for EC membrane and EC–HPC membrane might be attributed to the difference in film toughness or film thickness.

Thus, for both the disintegrating tablets and the nondisintegrating tablets, Marine Chito was very efficient in protecting the coating membrane from compression damage.

***In Vivo* Study** The *in vivo* drug release characteristics of tablets containing the coated particles were investigated by comparing the plasma concentration of theophylline after oral administration to beagle dogs to that of the

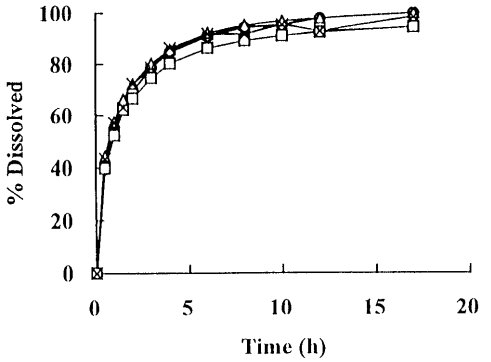

Fig. 7A. Effect of Compression Pressure on Dissolution Rate of Tablets Containing EC/HPC-Coated Theophylline Powder with Marine Chito

Coated particles/Marine Chito ratio: 5/5. ○, coated particles; △, 12.5 MPa; □, 62.5 MPa; ×, 125 MPa.

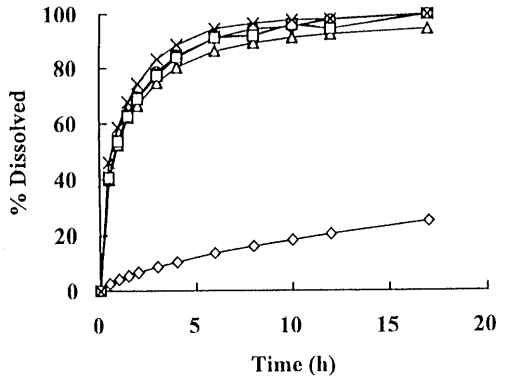

Fig. 7B. Influence of Coated Particles/Marine Chito Ratio on Dissolution Rate of Tablets Containing EC/HPC-Coated Theophylline Particles

Compression pressure: 62.5 MPa. ○, coated particles; △, 5/5; □, 7/3; ×, 9/1; ◇, 10/0.

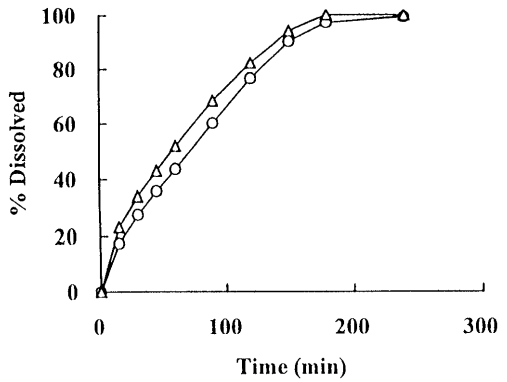

Fig. 8A. Dissolution Profiles of Eudragit-Coated Theophylline Particles and Tablets Compressed with Marine Chito

Coated particles/Marine Chito ratio: 5/5, compression pressure: 62.5 MPa. ○, coated particles; △, tablets.

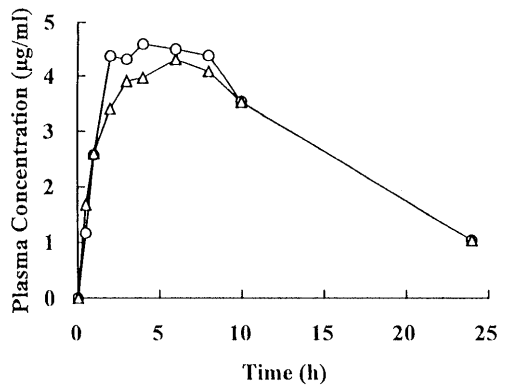

Fig. 8B. Plasma Concentration–Time Curves of Theophylline in Dogs after Oral Administration of Eudragit-Coated Theophylline Particles and Tablets

○, coated particles; △, tablets.

Table 1. Pharmacokinetic Parameters of Theophylline after Oral Administration in Dogs

	C_{max} (μg/ml)	T_{max} (h)	AUC (μg·h/ml)	MRT (h)
Granules	5.21±0.71	4.50±1.11	71.49±13.22	8.91±0.74
Tablets	5.23±0.99	4.13±2.01	68.45±14.18	8.96±0.45

original Eudragit-coated particles. Before administration to dogs, the dissolution profiles of both dosage forms were examined. As shown in Fig. 8A, the dissolution rate of the tablet was almost the same as the original particles and no rupture of the coating membrane was observed *in vitro*. Figure 8B shows the plasma concentration of theophylline after oral administration of both dosage forms, and Table 1 shows pharmacokinetic parameters. The T_{max} and C_{max} of tablets coincided with that of the coated particles. There were no differences in AUC and MRT in the two dosage forms. These results suggested that the tablets containing the Eudragit-coated theophylline particles and Marine Chito disintegrated quickly and redispersed into the original particles in the gastrointestinal tract after oral administration, and that there might be no rupture of the coating membrane.

In conclusion, the small particle size chitosan, *i.e.*, Marine Chito, is a very useful excipient to protect the coating membrane from mechanical damage of the compression force during tableting. The effect of Marine Chito might be superior to Avicel PH102 which has previously been thought to be the most effective excipient. The protecting mechanism of Marine Chito has not yet been identified, but the particle size has to be an important factor, and studies focusing on this aspect will be continued.

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