Studies on Internal Structure of Tablets. III.[1] Manufacturing of Tablets Containing Microcapsules[2]

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The aim of this study was to establish the best manufacturing conditions for preparation by the direct compression method of tablets which contain microcapsules having a minimal destruction rate of the coating wall, show the same dissolution pattern as microcapsules, and have enough mechanical strength for practical use, and to elucidate the internal structure of the tablets under the best manufacturing conditions. Degree of destruction of the microcapsule wall was evaluated by the dissolution rate of the medicine in the microcapsules. To learn the mechanical strength of tablets, the crushing strength and friability were measured; their internal structure was analyzed by the porosity and pore size distribution.

The best manufacturing conditions for the tablets were thus determined, and it was clarified by analysis of the internal structure that these conditions are markedly affected by the flowability of prescribed powders and the packing state at compression.

Keywords direct compression method; tablet; microcapsule; microcapsule wall; crushing strength; friability; porosity; pore size distribution; packing state

There are reports about tablets which contain microcapsules to control the release of a medicine, stabilize a medicine or mask an unpleasant taste.[3–9] However, Nixon *et al.*[5] reported that the compression pressure at tableting destroyed the microcapsule wall thereby decreasing the usefulness as a microcapsule, and Hasegawa *et al.*[7] suggested recently that the rate of destruction of the microcapsule wall was affected by the kinds of excipients.

The authors aimed at determining the best manufacturing conditions for the preparation by direct compression method of tablets which contain microcapsules having a minimal destruction rate of the coating wall, show the same dissolution pattern as microcapsules, and have sufficient mechanical strength for practical use. The effects of particle size of the excipient and microcapsules, and the quantity of microcapsules, on the rate of destruction of the microcapsule wall were also studied, and the relation between this rate of destruction and the internal tablet structure was elucidated.

Experimental

Material and Physical Properties of Powder Aspirin microcapsules (AMC) containing 90.1±1% aspirin were purchased as a microcapsule model from Rhone-Poulenc Sante Co., France. AMC was sieved through mesh to fractions of 24—32, 32—50 and 50—100 mesh. The microcrystalline cellulose (MCC) used as the excipient was Avicel® PH 101, PH 301, PH 302 and M-06 obtained from Asahi Kasei Kogyo Co., Tokyo. MCC-L was a fraction passed through 80—150 mesh of PH 302, MCC-M was a fraction through 200—400 mesh of PH 301 and MCC-S was a fraction through 400 mesh of M-06. Hydroxypropyl starch (HPS) used as the disintegrator was obtained from Freund Industries Co., Ltd., Tokyo, and was passed through a 200 mesh sieve. Silicon dioxide (Aerosil® 200) used as the lubricant was purchased from Aerosil Nippon Co., Tokyo.

The particle sizes of the classified AMC, MCC and HPS measured by the air permeability method and the densities measured with an Air Comparison Pycnometer (Toshiba–Beckman Co., Ltd., Model 930) are shown in Table I. The angles of repose of the powders were measure with a Konishi angle of repose meter (Konishi Seisakusho Co., Ltd., Model FK). Measurement was repeated 5 times for each kind of powder, and the mean value and standard deviation were determined.

Measurement of Physical Properties and Mechanical Strength of Tablets Tableting: AMC and various powder mixtures were compressed at varying pressures of 200—1000 kg/cm^2 into tablets of 400 mg each by the direct compression method, using a tableting machine (Nichiei Seiko Co., Tokyo, Type UPF-6) with a single flat punch of 1 cm^2 cross section and equipped with a strain gauge.

Formability: When 50 tablets were made under the same conditions of AMC particle size and amount and compression pressure, if more than half of them were not formed, the condition was an impractical one.

Crushing Strength: The crushing strength of 10 tablets of each kind was measured with a hardness tester (Kiya Seisakusho Co., Tokyo).

Friability: The friability was determined by the method of Funakoshi *et al.*[11] using 20 tablets of each kind.

Porosity: The porosity of 10 tablets of each kind was determined by measuring weight, diameter and thickness, using each density of powder shown in Table I.

Disintegration Time: The disintegration time was determined by the JP XI method. Pure water was used as the disintegration medium.

Mean Pore Diameter of Tablets: The mean pore diameter of tablets was measured from the penetration curve by the method described in a previous paper.[12] The measurement apparatus was a porosimeter (Aminco, motor driven 15000 psi). The contact angle of mercury on the tablets was regarded as 130°.[13]

Evaluation of the Destruction of AMC Considering that the microcapsule wall of ethylcellulose is also destroyed when AMC particles are destroyed by the compression, and that the exposured surface area of aspirin increases, which accelerates the dissolution rate of aspirin from the tablets containing AMC, the following experiments were made. The dissolution rate of aspirin from 3 tablets was compared with that from the AMC particles contained in the 3 tablets, and determined by the paddle

TABLE I. Particle Diameters and Densities of Used Powders

	AMC			MCC				HPS	Aerosil® 200
	L	M	S	L	M	S	PH101		
Particle diameter (μm)	146.6 (±5.3)[a]	130.6 (±3.6)	107.5 (±3.7)	13.9 (±1.7)	11.3 (±1.8)	8.8 (±1.1)	7.5 (±1.3)	12.9 (±1.4)	0.012[10]
Density (g/ml)	1.40 (±0.012)			1.58 (±0.005)				1.47 (±0.005)	2.2[10]

a) ±S.D., $n=3$.

method of the JP XI dissolution test. This dissolution test was carried out by the flow method and absorbance at 275 nm was measured with a UV spectrophotometer (Hitachi, U-3200). One thousand ml of No. 2 medium (pH 6.8) in the JP XI disintegration test was used as the dissolution medium. The slope of absorbances from the start of the dissolution test up to 10 min was determined as the dissolution rate.

Results and Discussion

Compression of AMC Figures 1 and 2 respectively show the porosity and mean pore diameter of tablets obtained by the compression of AMC-M at varying pressure. Both the porosity and the mean pore diameter markedly decreased up to 1000 kg/cm^2 of compression pressure. This result suggests that the packing caused by the movement, deformation and destruction of AMC particles significantly advanced at up to 1000kg/cm^2 of pressure. This speculation could not be confirmed with the dissolution rate of aspirin, because AMC particles have high formability and a tablet of AMC particles does not disintegrate.

Tableting of Prepared Powder The mixing ratios of MCC, HPS and Aerosil used as the excipient, disintegrator and lubricant, respectively, were as stated in the following experiments. Tablets desired for the dissolution test experiment were required to have a very short disintegration time so as not to affect the dissolution rate of aspirin. Then, varying amounts of HPS were added to MCC which has high formability, and each powder was tableted at a compression pressure of 1000 kg/cm^2. Figure 3 shows the disintegration time in these tablets, and it is observed that those containing more than 20% of HPS disintegrate within 1 min.

Figure 4 shows the angle of repose for the mixture of 20% of HPS containing MCC and Aerosil in varying ratios. MCC seemed to have a low flowability because of the shape and size of the powder particle.[12] The angle of repose reached minimum at the mixing ratio of 20% of HPS, 78% of MCC and 2% of Aerosil, and the flowability was best at this ratio.

Based on these results, each powder was prepared as follows: 20% of HPS, 2% of Aerosil and 78% of a mixture of MCC and AMC, and these powders were compressed into tablets of 400 mg each under 200, 400, 600, 800 and 1000 kg/cm^2 of compression pressure. The formability of these tablets is shown in Table II; it was reduced with smaller particle size of AMC, larger amount of AMC and lower compression pressure.

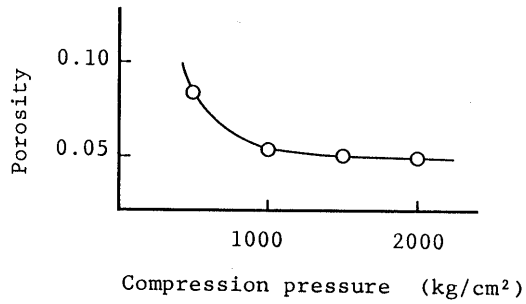

Fig. 1. Effect of Compression Pressure on Porosity of Tablets Composed of AMC Particles

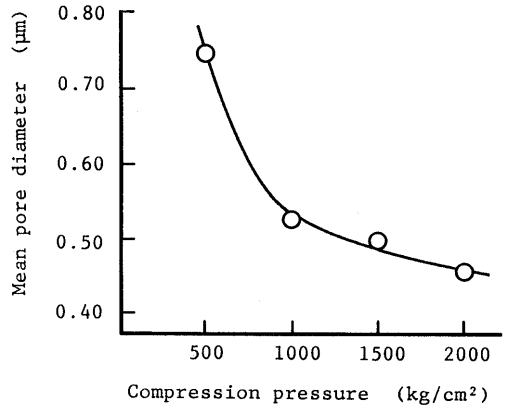

Fig. 2. Effect of Compression Pressure on Mean Pore Diameter of Tablets Composed of AMC Particles

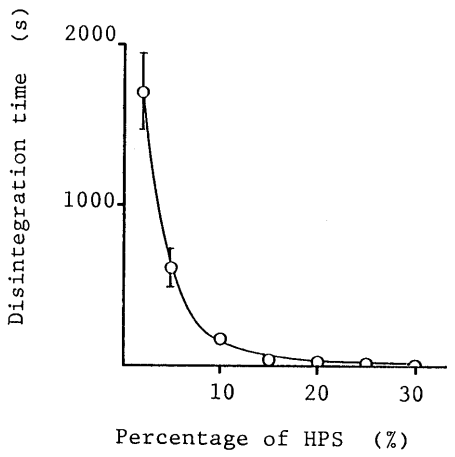

Fig. 3. Effect of Amount of HPS on Disintegration Time of Tablets Composed of MCC and HPS

Each point represents the mean ± S.D. for 6 tablets.

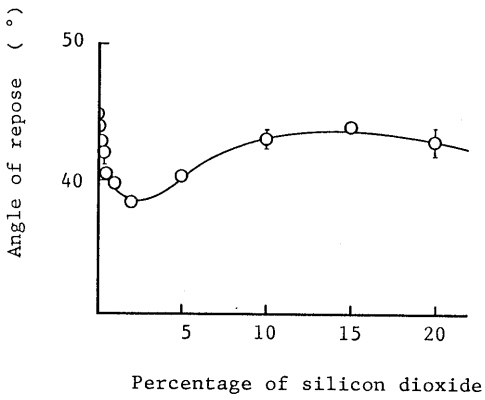

Fig. 4. Effect of Amount of Silicon Dioxide on Angle of Repose of Powder Composed of 20% HPS, 80% MCC and Silicon Dioxide Combined

Each point represents the mean ± S.D. obtained from 5 experiments.

Table II. Formability of Tablets

Compression pressure (kg/cm^2)	AMC														
	L (24—32 mesh)					M (32—50 mesh) AMC concn. (%)					S (50—100 mesh)				
	15	30	45	60	78	15	30	45	60	78	15	30	45	60	78
200	○	○	○	○	●	○	○	○	○	●	○	○	○	●	●
400	○	○	○	○	●	○	○	○	○	●	○	○	○	○	●
600	○	○	○	○	○	○	○	○	○	●	○	○	○	○	●
800	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●
1000	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●

○, formed. ●, not formed.

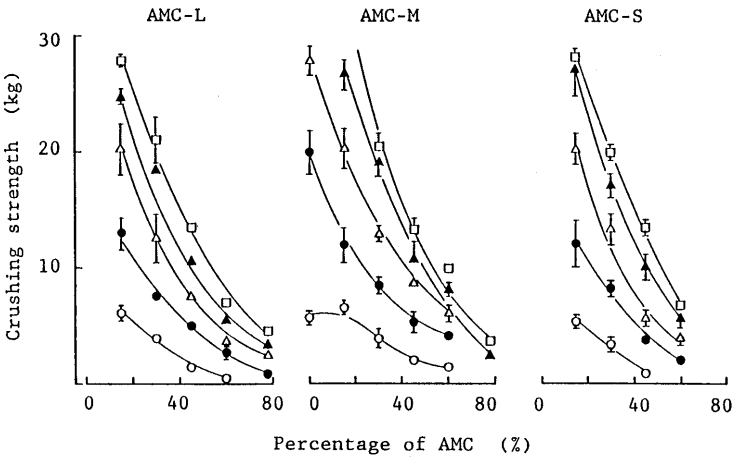

Fig. 5. Effect of Amount of AMC on Crushing Strength of Tablets Containing Different Particle Sizes of AMC Compressed under Different Pressures
Compression pressure (kg/cm^2): ○, 200; ●, 400; △, 600; ▲, 800; □, 1000. Each point represents the mean±S.D. for 10 tablets.

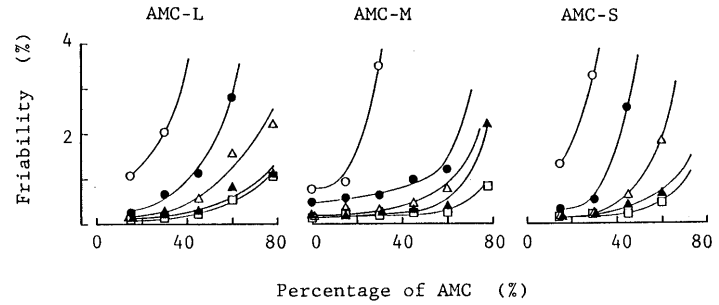

Fig. 6. Effect of Amount of AMC on Friability of Tablets Containing Different Sizes of AMC Compressed under Different Pressures
Compression pressure (kg/cm^2): ○, 200; ●, 400; △, 600; ▲, 800; □, 1000.

Mechanical Strength of Tablets The crushing strength and the friability of the tablets which could be formed in Table II are shown in Figs. 5 and 6, respectively. With the larger amount of AMC and lower compression pressure, the crushing strength decreased, friability increased, and the mechanical strength of tablets lowered. This suggests that the amount of MCC which forms the twined structure[12] in the tablet decreases when the amount of AMC increases, and then the formability and mechanical strength of the tablets are reduced. As for the particle size of AMC, AMC-S showed the lowest mechanical strength, but the difference between AMC-L and AMC-M was not clear.

Destruction of AMC Particles The dissolution rates of aspirin from AMC-L, M and S particles in varying amounts of AMC are shown in Fig. 7. A high linearity was observed for all three particle sizes of AMC, and the smaller the size, the larger was the dissolution rate. The dissolution rate appeared to increase as the specific surface area increased with the smaller particle size of AMC.

The dissolution rates of aspirin from tablets tableted at a compression pressure of 1000 kg/cm^2 using MCC (PH 101) in varying particle sizes and amounts of AMC are shown in Fig. 8. The vertical axis shows the increased percentage of the dissolution rate of aspirin from three tablets against that from AMC shown in Fig. 7. That is to say, when a plot is 0% in this figure, it is thought that AMC particles are not destroyed under the condition used. It was observed that AMC particles in every tablet were to some degree destroyed by tableting. As for the rate of destruction, although the effects of the particle size of AMC were not clear, the optimum amount of AMC was 60%, where the dissolution rates of AMC-L, AMC-M and AMC-S showed the minimum.

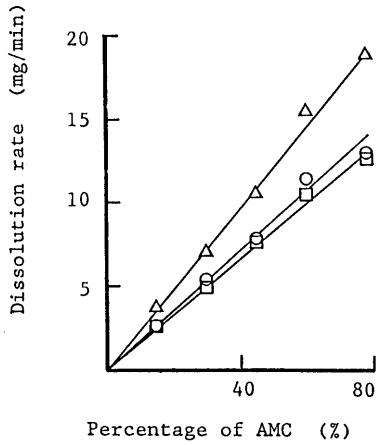

Fig. 7. Effect of Particle Size of AMC on Dissolution Rate
□, AMC-L; ○, AMC-M; △, AMC-S.

Figure 9 shows the effects of the size of MCC on the destruction of AMC using AMC-M at 60%. The increased percentage of dissolution rate was less with smaller MCC particle size. This is probably because the destruction rate of the AMC particles is lower since a smaller MCC particle size allows a higher flowability at compression.

Internal Structure of Tablets and the Destruction of AMC Particles The porosities of the tablets prepared under different compression pressures and different amounts and

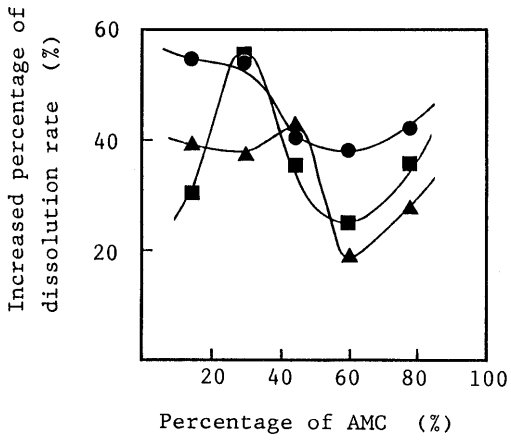

Fig. 8. Relation between Amount of AMC and Rate of Destruction of AMC Particles

■, AMC-L; ●, AMC-M; ▲, AMC-S.

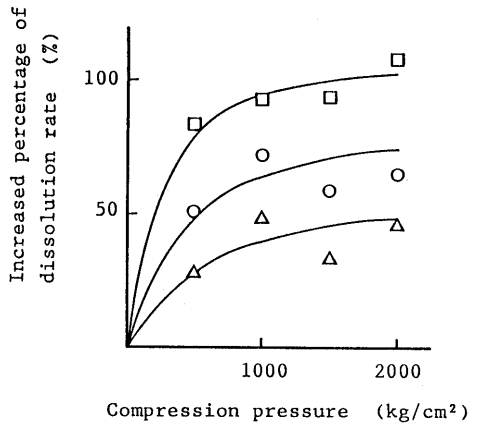

Fig. 9. Relation between Particle Size of MCC and Rate of Desruction of AMC Particles

□, MCC-L; ○, MCC-M; △, MCC-S.

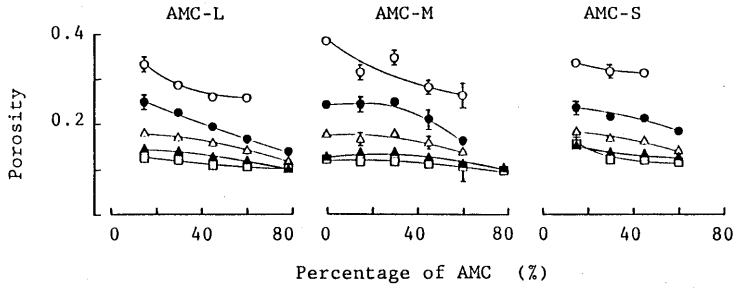

Fig. 10. Effect of Amount of AMC on Porosity of Tablets Containing Different Particle Sizes of AMC Compressed under Different Pressures

Compression pressure (kg/cm²): ○, 200; ●, 400; △, 600; ▲, 800; □, 1000. Each point represents the mean ± S.D. for 10 tablets.

sizes of AMC are shown in Fig. 10. The porosity decreased with higher compression pressure, larger amount and particle size of AMC. The decrease in porosity with increased compression pressure is due to compaction, and has been reported for larger particle size by many earlier investigators.[14,15] Two explanations are possible for the decrease in porosity with increased amount of AMC: that every size of AMC particles is the largest particle size of all the particles used, and that the density of MCC is the largest of all the powder densities, so that when the amount of AMC increases, the amount of MCC decreases.

Figure 11 shows the mean pore diameters of the tablets tableted under 1000 kg/cm² of compression pressure with different amounts and particle sizes of AMC. The mean pore diameter increased with the smaller particle size and larger amount of AMC, and all mean pore diameters were larger than that of tablets composed of only AMC-M particles tableted under 1000 kg/cm² of compression pressure. If the AMC particle neither breaks nor becomes deformed under the compression, the mean pore diameter should increase with larger particle size and amount of AMC. However, our results were the opposite, and it was thought that AMC particles deformed and broke under the compression and that the rate of deformation and breaking was less with the smaller particle size of AMC. Further, AMC-L and S showed the minimum mean pore diameter (shown in Fig. 11). This result coincided with that in Fig. 8 in which the dissolution rate for every particle size of AMC showed the minimum at 60% of AMC percentage. It can be surmised from these results that particles of MCC,

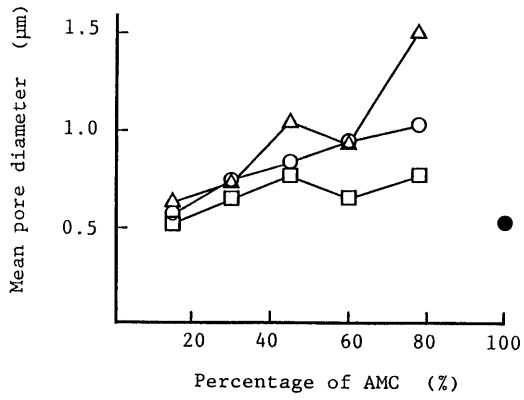

Fig. 11. Relation between Mean Pore Diameter of Tablets Containing Different Particle Sizes and Amounts of AMC.

□, AMC-L; ○, AMC-M; △, AMC-S; ●, composed of only AMC-M.

HPS and Aerosil are most suitably packed in a space between AMC particles at an AMC presence of 60% where a comparatively close packing state is formed. Here, the number of contact points and the contact area among particles in the tablet reaches maximum, the stresses caused in AMC particles are most apt to be dispersed, and thus the rate of deformation or breakage of these particles is lowered.

The mean pore diameters of the tablets prepared with 60% of AMC-M, 18% of MCC (PH 101), 20% of HPS and 2% of Aerosil under varying compression pressures are shown in Fig. 12.

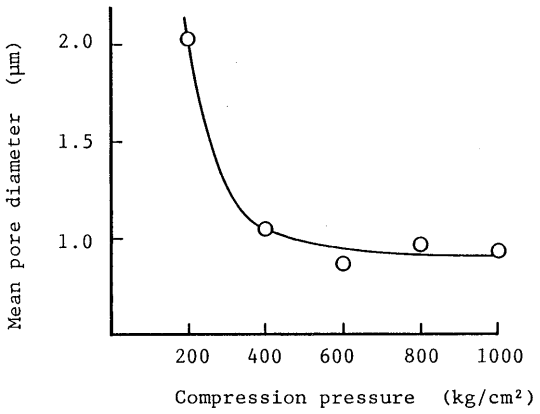

Fig. 12. Effect of Compression Pressure on Mean Pore Diameter of Tablet Composed of Mixed Powders

Although the mean pore diameter of the tablet composed of AMC particles markedly decreased up to 1000 kg/cm^2 of compression pressure (shown in Fig. 2), that of the tablet composed of the mixed powder notably decreased up to 400 kg/cm^2. These results suggest that a close packed state is formed under the compression of the mixed powder with a lower pressure than with AMC particles only, as the smaller particles of other additives can move into the space formed by AMC particles, the stresses caused in AMC particles are dispersed to other particles coming into contact with AMC particles, and, thus, AMC particles are difficult to deform and break.

Conclusion

The best conditions for manufacturing tablets were determined as follows: Aerosil 200 is added at 2%, MCC at 18%, HPS at 20% and AMC at 60%, and the mixture is tableted at about 800—1000 kg/cm^2 of compression pressure. The destruction of AMC particles could not be completely prevented under this condition. However, it was found that there was an optimum amount of AMC particles which had the largest particle size in the formulated powder, and it was possible to decrease the destruction of these particles using smaller AMC and MCC. Further, it was speculated that the results above mentioned were based on a close packing state caused by a high flowability of powder at the time of compression, which could disperse the stresses caused on AMC particles to other particles.

References and Notes

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