Tableting of Coated Particles. II. Influence of Particle Size of Pharmaceutical Additives on Protection of Coating Membrane from Mechanical Damage during Compression Process

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To compress coated particles into tablets without mechanical damage to the coating membrane during compression, the effect of the particle size of various pharmaceutical additives was investigated by comparing the dissolution rate and the membrane integrity of ethylcellulose coated theophylline powder. Results showed that smaller additive particle size was superior in protecting the membrane from damage, and thus additive particle size might be one of the most important factors affecting the dissolution characteristics of compressed tablets containing coated particles. Twenty μm seemed to be the critical particle size for each kind of additive to obtain good protective effect. Up to this size, all additives played the role of cushioning and the coating membrane was almost perfectly protected from potential damage by the compression force.

Key words tableting; coated particle; dissolution rate; critical particle size

In recent years, there has been increased interest in the development of sustained and controlled release dosage forms, to minimize side-effects, gain better patient compliance, and the effective treatment achieved by keeping an adequate concentration of the drug in the body.

Various technologies and methodologies have been developed and employed in pharmaceutical preparations to gain the desired release control of a drug substance after oral administration.[2)]

Controlled-release microparticulate systems, such as microcapsules or micromatrices, are thought to be a more desirable dosage form than single unit dosage form.

Capsules are often employed as a dosage form to facilitate oral administration of a controlled-release microparticulate system, because encapsulation may not affect the original drug release characteristics of microparticles, and the microparticles will be redispersed in the stomach by rapid disintegration. On the other hand, tablets are more preferable to both manufacturers and patients because of their high producibility and ease of swallowing. From this view point, tablets which contain many particles and disintegrate instantly in the GI tract after administration are very useful. In fact, such tablets have been developed and some products are already on the market.

Concerning tableting of the coated particles, it has often been pointed out that the coating membrane is to some extent ruptured during compression, resulting in reducing the membrane effectiveness of release rate control or masking an unpleasant taste.[3,4)] It was also pointed out that a matrix tablet was formed, resulting in nondisintegration of the tablet and decrease of the dissolution rate.[5,6)]

There are many factors that affect the rupturing of the coating membrane at the time of tableting of the coated particles. The above-mentioned problems have been addressed in studies conducted to develop technologies for minimizing changes in the characteristics of coated particles after compression, and many pharmaceutical additives were tested for their "cushion effect". Of those, the compaction behavior of beads containing microcrystalline cellulose was analyzed by the modified Athy–Heckel and Leuenberger equations.[7)] The effect of some additives, such as microcrystalline cellulose and calcium citrate, on the rupture of microcapsules was investigated by comparing their dissolution rate and compaction behavior of cellulose acetate phthalate microcapsules containing phenacetin.[8)] Nevertheless, reasonable explanation for the protective effect of additives or other factors involved in this phenomenon have yet been identified however.

The final goal of our study is to establish a practical technology for tablets so that they can be redispersed in multiparticulate systems, while retaining their original functions. In this paper, ethylcellulose-coated microcapsules containing theophylline, a model drug, are prepared as a model microparticulate system and are compressed with various additives into tablets under different tableting conditions to identify factors affecting the drug release characteristics of the microcapsules regenerated. All the data obtained are discussed, focusing on the contribution of particle size of additives.

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). Lactose (DMV, Netherlands), D-mannitol (Towa Kasei Co., Tokyo), carmellose calcium (Nichirin Chemical Industries, Hyogo, Japan), microcrystalline cellulose (Avicel PH102, PH-M25, M15, M06, Asahi Chemical Industry Co., Tokyo), croscarmellose sodium (Ac-Di-Sol, Asahi Chemical Industry Co., Tokyo), cornstarch (Nihon Shokuhin Kako Co., Tokyo), low substituted hydroxypropylcellulose (L-HPC, Shin-Etsu Chemical Co., Niigata, Japan) and ethylcellulose (EC, Ethocel standard premium, 10 cP, Dow Chemical Co., U.S.A.) were all of JP grade. Chitosan (Marine Chito 80MD-F10, Fuji Bouseki, Tokyo) was used as received. All other solvents and chemicals were of reagent grade.

Milling of Additives Lactose, D-mannitol, Ac-Di-Sol, carmellose calcium, and L-HPC were pulverized using a Jet mill (LJ, Japan New Matic Kogyo Co., Tokyo).

Coating of Theophylline Fine particles of theophylline (105—53 μm) were coated by spraying with an aqueous ethanolic solution of EC (concentration, 5% EC and 80% ethanol) using a fluidized-bed system (GPCG-1, Glatt, Germany). The coating level was 40% based on the percent weight increase. Details of the coating conditions have been described elsewhere.[9)]

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Tableting Before tableting, the EC-coated theophylline particles and pharmaceutical additives were blended in a polyethylene bag (coated particles/additives weight ratio: 5/5). 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.

Measurement of Particle Size The mean particle sizes (mass median diameter) of additives were determined by a particle size analyzer (MICROTRAC II 7997-10, LEEDS & NORTHRUP Co., North Wales, U.S.A.).

Dissolution Test A dissolution test was performed according to JP XIII paddle method in 900 ml of water at 37 °C with constant stirring at 100 rpm. Details of the procedure have been described elsewhere.[9]

Scanning Electron Micrograph After the dissolution test, the empty particles were collected and dried. Microphotographs of the particle surface were taken using a scanning electron microscope (S2250N, Hitachi, Tokyo).

Results and Discussion

Protective Effect of Various Kinds of Pharmaceutical Additives on Mechanical Damage of Coating Membrane during Compression Avicel is known as the most effective excipient to protect the membrane from damage caused by compression force[10] and such protective effect is believed due to the superior plastic deformability of this compound.[8] But, as shown in a previous report[9] in which the dissolution rate of the EC-coated theophylline particles (coated particles) and its tablets compressed with Avicel PH102 were compared, the addition of Avicel did not prevent the rupture of the coating membrane. On the other hand, however, Marine Chito, *i.e.*, small particle size chitosan, was found to have good protecting ability.[9] Though the protection mechanism was not clear, the difference in particle size between Marine Chito and Avicel PH102 seemed very meaningful.

Various commercial grades of Avicel of different particle size were examined for their protective effect. Figure 1 shows a comparison of drug release profiles of the coated particles and the tablets containing these coated particles and Avicel. Although identical compression force was applied, the protective effect observed varied depending on the commercial grade of Avicel. The effect became greater in the order of PH-M06, M15, M25, and PH102; it was notable that this order is compatible with the order of the mean particle size of Avicel. This suggested that particle size of the additive might be an important factor.

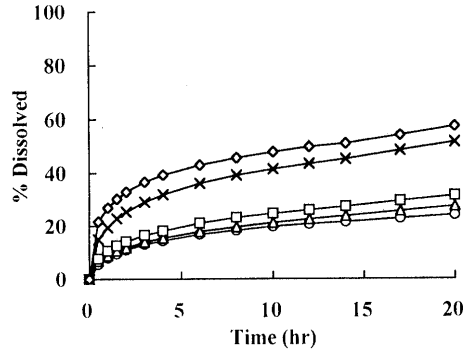

Fig. 1. Dissolution Profiles of Coated Particles and Tablets Compressed with Various Kinds of Avicels

Coated particles/Avicel ratio, 5/5; compression pressure, 62.5 MPa. ○, coated particles; △, Avicel PH-M06 (9 μm); □, Avicel PH-M15 (14 μm); ×, Avicel PH-M25 (24 μm); ◇, Avicel PH102 (101 μm).

Next, various pharmaceutical additives were tested for their ability to protect the coating membrane from damage, and some additives were found to provide superior protective effect compared to Avicel. Actually, when the coated particles were compressed with cornstarch, the drug release profile of the tablet was coincident with that of the coated particles, and was independent of compression force (Fig. 2). It was also observed that both of the above-mentioned tablets disintegrated quickly after start of the dissolution test and regenerated the coated particles into fluid. This must be related to the observed excellent coincidence of the dissolution behavior of tablets.

Effect of Particle Size of Additives Many factors can be enumerated that affect the protecting abilities of the materials from rupture of the coating membrane during the compression process. These are : membrane toughness, the particle size of the coated particles, the compaction characteristics of the additives, the ratio of additives to coated particles, and the additive particle size.

Taking account the dissolution behavior of tablets and the mean particle size of additives, our experimental results suggested that the particle size might be one of the most influential factors in determining the drug release characteristics of tableted particles. Further investigation was focused on the effect of this particle size of additives.

Figure 3 shows the theophylline release from tablets compressed with the coated particles and various commercial grades of L-HPCs of different particle size,

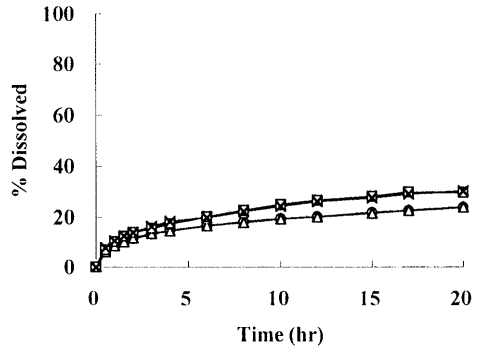

Fig. 2. Influence of Compression Pressure on Dissolution Rate of Theophylline from Tablets Compressed with Cornstarch

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

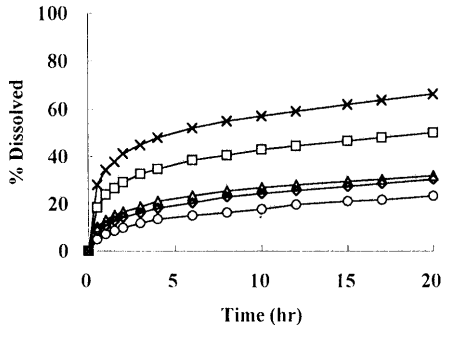

Fig. 3. Effect of Particle Size of L-HPC on Dissolution Rate of Theophylline from Tablets

Coated particles/L-HPCs ratio, 5/5; compression pressure, 62.5 MPa. ○, coated particles; △, LH-31; □, LH-21; ×, LH-11; ◇, micronized LH-11.

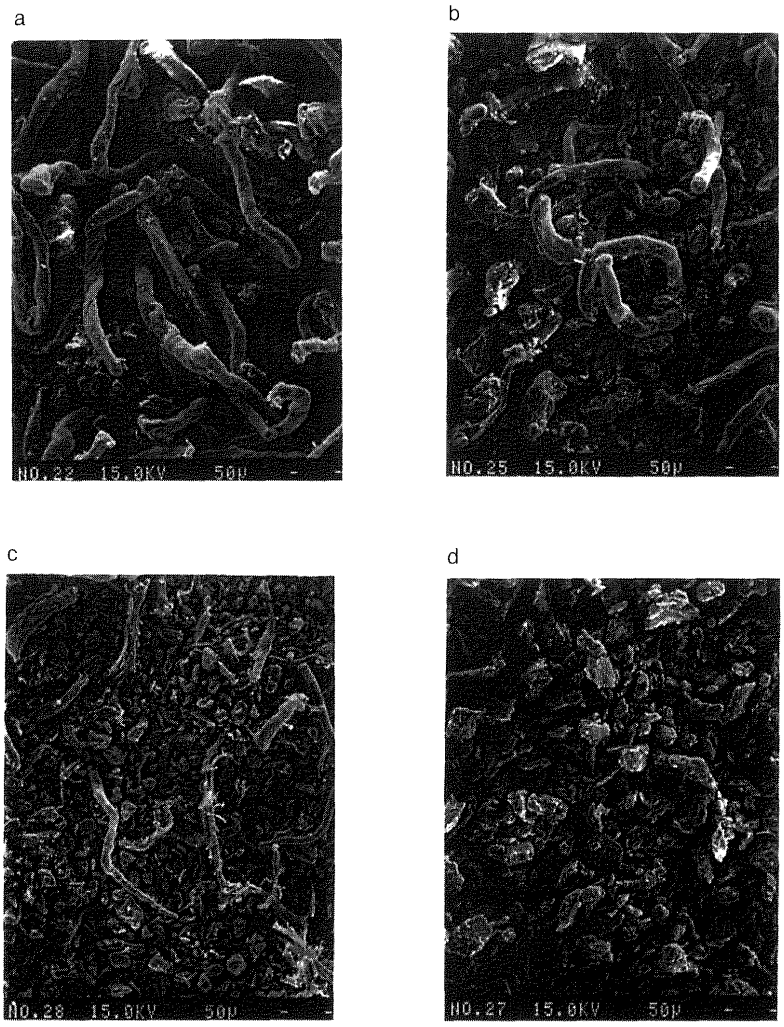

Fig. 4. Scanning Electron Micrographs of L-HPCs

a, LH-11 (59 μm); b, LH-21 (44 μm); c, LH-31 (16 μm); d, micronized LH-11 (15 μm).

and Fig. 4 shows scanning electron micrographs of the L-HPCs. No differences except for particle size were observed from the micrographs. As shown in Fig. 3, however, when the larger particle size grade (LH-11 and LH-21) was used, the drug release behavior of the tablet was drastically changed by compression. Less change was observed when the smaller particle size grade (LH-31) was used. Furthermore, when LH-11 was ground to 15 μm size, almost the same effect as that of LH-31 (16 μm) was obtained. A similar effect was also recognized when lactose and ground lactose were used as the additives (Fig. 5). These findings strongly supported the hypothesis that the particle size of additives plays an important role in preventing the rupture of the coating membrane by tableting.

Figure 6 shows scanning electron micrographs of the coated particles tableted with lactose or micronized lactose, each of which was taken after the dissolution test. When the coated particles were compressed with lactose (200 M, mean particle size, 32 μm), the coating film was found to be ruptured (Fig. 6a), while, when the coated particles were compressed with micronized lactose (5 μm), no damage or rupture was found on the coating film (Fig. 6b).

Quantitative Evaluation of Damage of Coating Membrane As mentioned above, when the coating membrane received mechanical damage during compression, the bursting of theophylline was observed more distinctly at the early phase of the dissolution test, so that the degree of damage was evaluated by comparing the initial drug release rate of the coated particles and the tablet. Thus the release rate for the first two hours after starting the dissolution test was adopted as the initial release rate. Defining the initial release rate of tablet and the coated

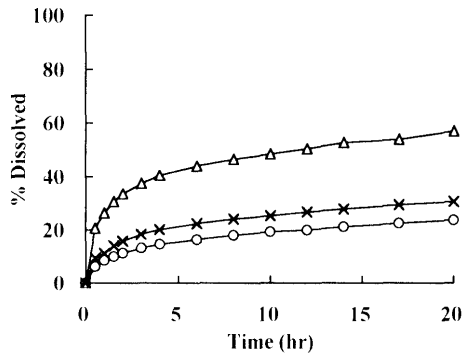

Fig. 5. Dissolution Profiles of Theophylline from Tablets Containing Coated Particles and Lactose

Coated particles/lactose ratio, 5/5; compression pressure, 62.5 MPa. ○, coated particles; △, lactose 200 mesh; ×, micronized lactose.

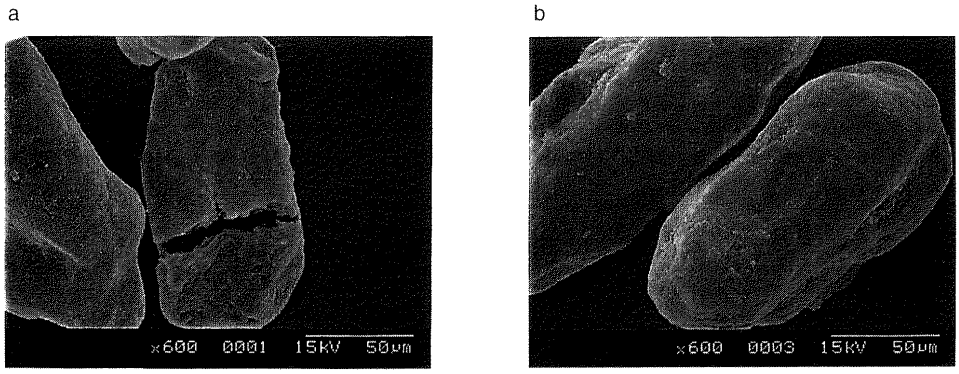

Fig. 6. Scanning Electron Micrographs of Coated Particles Compressed with Lactose after Dissolution Test

a, compressed with lactose 200 M (32 μm); b, compressed with micronized lactose (5 μm).

Table 1. Relationship between Particle Diameter of Protecting Agents and Dissolution Rate of Compressed Tablets

Symbol	Protecting agent	Diameter (μm)	Disintegration time (min)	Initial release rate ratio (D_t/D_g)
a	D-Mannitol	33	5	4.1
b	Micronized mannitol	4	10	1.4
c	Lactose	32	10	3.4
d	Micronized lactose	5	10	1.6
e	Chitosan (marine chito)	6	5	1.1
f	Cornstarch	13	5	1.3
g	Carmellose calcium	50	5	6.3
h	Micronized carmellose calcium	13	10	1.4
i	L-HPC (LH-11)	59	5	4.2
j	L-HPC (LH-21)	44	5	3.0
k	L-HPC (LH-31)	16	5	1.7
l	Micronized L-HPC (LH-11)	15	5	1.5
m	Ac-Di-Sol	37	5	3.6
n	Micronized Ac-Di-Sol	28	10	2.3
o	Avicel (PH-102)	101	5	3.3
p	Avicel (PH-M25)	24	5	2.0
q	Avicel (PH-M15)	14	5	1.2
r	Avicel (PH-M06)	9	5	1.1

particles as D_t and D_g, respectively, the D_t/D_g was regarded as a parameter representing the degree of damage of the coating film caused by tableting.

To determine the effect of additive particle size on the dissolution rate of compressed coated-particles, the relationship between particle size and the initial release rate ratio was investigated. Each of the various additives was either intact or micronized by pulverizing. After blending the coated particles with an additive, the mixture was compressed into tablets and the dissolution test was performed. Table 1 lists the particle size and the D_t/D_g value for all additives used in this study. As shown, some of them provided a very good effect in terms of small D_t/D_g value.

Figure 7 shows the change of D_t/D_g as a function of particle size, in which all the data in Table 1 are plotted together. The curved line in the figure was drawn by connecting each plotted point. A good correlation was found between both parameters: the D_t/D_g value rose with increase in particle size. By extrapolating the plotted line

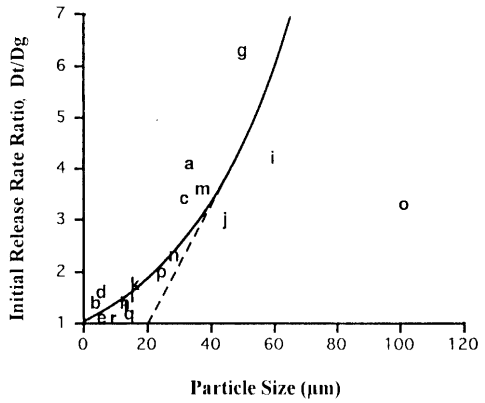

Fig. 7. Effect of Particle Size of Various Kinds of Additives on Dissolution Rate (D_t/D_g) of Theophylline from Tablets

Coated particles/additives ratio, 5/5; compression pressure, 62.5 MPa. Symbols are listed in Table 1.

to an x-axis as shown in Fig. 7, it was also found that compression with additives with a particle size of less than 20 μm caused the D_t/D_g value to approach unity. This means that the drug release rate of the coated particles was hardly affected by compression. Thus we defined 20 μm as the critical particle size for every additive. The fact that the D_t/D_g value of Avicel PH102 was plotted far from the expected line means that this compound has some ability to prevent the rupture of the coating membrane in spite of its large particle size; this is probably due to the plastic deformability of Avicel.

Although the reason for the observed protective effect of additives with small particle size is still obscure, some possible mechanism can be thought from the present study. At an early stage of compression, the particles would be rearranged and the fragmentation and deformation would take place. Additives with small particle size (below 20 μm), however, would deform plastically without fragmentation. So, i) when the coated particles are blended with the micronized additives, each coated particle could be covered by small additives to form a sort of ordered mixture, and thus a direct contact between coated particles would be effectively prevented during the compression process; ii) by mixing the coated particles with small additive particles, the mixture would tend to deform plastically, which might result in reducing the rupture of the coated particles during compression; iii) below a critical

particle size, the stress relaxation of additives against the compression force would increase the level enough to prevent the coated particles from fragmentation; and iv) additives could act as a cushion, and the cushioning effect might increase with a decrease in additive particle size.

Conclusion

The dissolution characteristics of tablets containing EC-coated theophylline particles were compared to those of the original particles, to investigate the influence of particle size of various pharmaceutical additives on mechanical damage to the coating membrane during compression.

The results demonstrated that smaller additive particle size resulted in superior protection of the membrane from compression damage. Also, it was found that 20 μm seemed to be a critical particle size for every additive to obtain good protective effect. From all the experimental results, it can be concluded that the coated particles could be compressed into tablets without mechanical damage to the coating membrane when additives of average particle size below 20 μm were used.

Further studies are necessary to find an explanation for the mechanism of micronized additives which protects the coating membrane from damage.

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