Tabletting of Solid Dispersion Particles Consisting of Indomethacin and Porous Silica Particles

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Received November 16, 2004; accepted February 5, 2005

We attempted to make the rapidly dissolving tablet (Tab) containing solid dispersion particles (SD) with indomethacin (IMC) and porous silica (Sylysia350) as carrier prepared by using spray-drying technique. Rapidly dissolving tablet was formulated with mannitol as a diluent and low substituted hydroxypropylcellulose (L-HPC) or partly pre-gelatinized starch (PCS) as a disintegrant. The percent dissolved from Tab (SD) was higher than that of tablet containing physical mixture (PM) at 20 min. Nearly 100% of drug in Tab (SD) was dissolved within 60 min, while the drug dissolution of Tab (PM) was not completed at the same time period. In addition, the tensile strength of Tab (SD) was much higher than that of Tab (PM). Adding L-HPC in Tab (SD) (Tab (SD-L-HPC)), the percent dissolved from Tab (SD-L-HPC) at 5 min became much higher than that from Tab (SD). The dissolution profile of IMC from Tab (SD-L-HPC) was almost the same irrespective of the compression pressure, while the tensile strength of tablet increased with increasing the compression pressure. In comparing the compaction property of these tablets by observing the ratio of residual die wall pressure (RDP) to maximum die wall pressure (MDP) (RDP/MDP), it was found that addition of L-HPC in the tablet formulation improved compactibility. In case that PCS was formulated as disintegrant, Tab (SD-PCS), similar improvement in the dissolution profile and tensile strength was observed, though the dissolution rate of IMC from Tab (SD-PCS) was slightly lower than that from Tab (SD-L-HPC) irrespective of the compression pressure.

Key words rapidly dissolving tablet; solid dispersion; spray-drying; porous silica; residual die wall pressure

Solid dispersion is a useful technique to improve the dissolution property of poorly water soluble drugs.[1—3] In general, solid dispersion is prepared with water soluble polymer, such as polyethylene glycol (PEG)[4] or polyvinylpyrrolidone (PVP)[5] as carrier, to disperse the drug molecules in the polymer matrix. Recently, the porous materials were also used as a carrier to disperse the drug molecules in the pores.[6,7] We have already reported that the solid dispersion particles prepared with fine porous silica (Sylysia350) as carrier by spray-drying method can improve the dissolution property of indomethacin[8] and tolbutamide.[9]

Considering the final dosage form of the solid dispersion particles, it is desirable to select the tablet among the various types of dosage form, because of its convenience in production and usage.[10] Tablet has various advantages, such as portability, patient compliance and lower cost in production compared with other solid dosage forms.

For the rapid drug dissolution from the tablet, its disintegrating property is important to ensure it. As the solid dispersion particle itself has a very rapid dissolution property, the tablet of solid dispersion has to be easily disintegrated. Based on this concept, easily dissolving sugar and sugar alcohol might be a candidate for their diluents of tablet. In the formulation of rapidly disintegrating tablets, which have recently been developed for elderly people and children who have swallowing or chewing difficulties, sugar or sugar alcohol are used as diluent. However, the sugar or sugar alcohol often has a tabletting troubles,[11] such as capping and sticking.

We have already evaluated the compaction property of sugars including mannitol by measuring the die wall pressure during tabletting process such as residual die wall pressure (RDP) and maximum die wall pressure (MDP).[12] These powders showed the high RDP/MDP and capping tendency. Adding a little amount of magnesium stearate in the powders decreased RDP/MDP and improved capping tendency. It has been also demonstrated that a good compaction property of some disintegrants such as low substituted hydroxypropylcellulose (L-HPC) and pre-gelatinized starch (PCS) has lower RDP/MDP in the same evaluation method.

In the present study, we attempted to prepare the rapidly dissolving tablet having the same dissolution rate as that of solid dispersion particles and a high tensile strength of tablet (more than 1.0 MPa). We also evaluated the compaction properties of the tablet formulations to optimize the formulation.

Experimental

Materials Indomethacin (Sumitomo Pharmaceuticals Co. Ltd., Japan) was used as a model drug having poorly water soluble property. Porous silica (Sylysia350, Fuji Silysia Chemical Ltd., Japan) was used as carrier in solid dispersion particles. Mannitol (Kishida Chemical Co., Japan) was used as diluent which is generally used as a conventional diluent for rapidly disintegrating tablet. Low-substituted hydroxypropylcellulose (LH-21, Shinetsu Chemical Co., Japan) and partly pre-gelatinized starch (PCS, Asahikasei Chemical Co., Japan) were used as disintegrant. Magnesium stearate

Table 1. Particle Size of Materials

Sample	Particle size (μm)		
	D_{16}	D_{50}	D_{84}
Indomethacin	8.8±0.3	32.7±3.9	147.3±28.5
Solid dispersion	1.9±0.0	3.4±0.1	5.4±0.1
Sylysia350	2.0±0.0	3.5±0.1	5.5±0.4
L-HPC	20.9±0.4	44.6±0.4	86.1±1.2
PCS	18.6±0.7	40.0±3.0	79.0±10.2
Mannitol	14.4±0.3	40.7±0.8	85.8±1.8
Magnesium stearate	4.7±0.2	10.7±0.6	19.2±1.2

The data are the average values of four runs.

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Table 2. Formulation of Tablet

Sample	Tab (SD)	Tab (PM)	Tab (SD-L-HPC)	Tab (PM-L-HPC)	Tab (SD-PCS)	Tab (PM-PCS)
Mannitol (1.0% Mg-st)	181.8	181.8	163.6	163.6	163.6	163.6
SD or PM	18.2 (SD)	18.2 (PM)	18.2 (SD)	18.2 (PM)	18.2 (SD)	18.2 (PM)
L-HPC or PCS	—	—	18.2 (L-HPC)	18.2 (L-HPC)	18.2 (PCS)	18.2 (PCS)

SD: solid dispersion particles, PM: physical mixture. (mg)

(Kishida Chemical Co., Japan) was used as lubricant. The particle sizes of these materials and solid dispersion particles are shown in Table 1.

Tabletting Tabletting process analyzer (TabAll: Okadaseiko Co., Japan) was used for dynamic compaction. Two hundreds milligram of sample was compressed in tabletting machine with flat faced punches with diameter of 8 mm. The applied compression pressure was 100—200 MPa. The compression speed was set up at 10 tablets per minute (10 spm). The formulation of tablet is shown in Table 2.

Calculation of Compaction Parameters The force profiles and punch displacements were outputed to computer with compression pressure recording software (DAATSU II: Okadaseiko Co., Japan). Maximum die wall pressure (MDP), residual die wall pressure (RDP), pressure transmission ratio from upper punch to lower punch (PTR) and ejection pressure of tablet (EP) were calculated, respectively. We have already reported that RDP/MDP is a useful parameter to describe the difference of compaction property of materials well. The calculation method of residual die wall pressure (RDP) was shown in the previous report.[12)]

Evaluation of Physicochemical Properties of Tablet Dissolution test was followed by JPXIV (Paddle method). Tablet in the sinker was put into 900 ml of No. 2 medium of JPXIV (pH 6.8) with stirring at 100 rpm at 37 °C. The drug concentration in the medium was measured spectrophotometrically at 320 nm (UV-160A, Shimadzu, Japan). Tensile strength of tablet was determined by diametrical-compression test by a particle hardness tester (GRANO, Okadaseiko Co., Japan).

Results and Discussions

To prepare the tablet of the solid dispersion particles having a good dissolution property of drug, mannitol was selected as a diluent of tablet, because it possesses an excellent dissolution property. Figure 1 shows the dissolution profile of indomethacin (IMC) from tablets, which contain solid dispersion particles (SD) of IMC and silica particles or physical mixture (PM) of IMC crystals and silica particles. The formulations of tablet are shown in Table 2. The percent dissolved of IMC from tabletted solid dispersion particles (Tab (SD)) without formulating a disintegrant was 19.1% at 5 min, which was smaller than that from solid dispersion particles (90.4%) and Tab (PM) (34.1%). However, the dissolution rate of Tab (SD) was accelerated up to 20 min because of disintegration occurred, while that of Tab (PM) was decreased. Resultantly, the percent dissolved of Tab (SD), 70.9%, exceeded that of Tab (PM), 66.0%, at 20 min and it reached nearly 100% and completely disintegrated at 60 min. These results suggested that disintegration of tablet was the rate determining step in the drug dissolution process of Tab (SD).

When the suitable amount of disintegrant was formulated to the Tab (SD) and Tab (PM), the dissolution property was much improved. It was confirmed that the percent dissolved of IMC from Tab (SD-L-HPC) was almost the same as that of solid dispersion particles. On the other hand, the dissolution profile of Tab (PM) was little improved by adding a disintegrant, L-HPC, to confirm that the disintegrating process was not important for dissolution profile in the tablet of the physical mixture. These results suggested that disintegration property was the key for rapid drug dissolution of tabletted solid dispersion particles by adding suitable disintegrant particles.

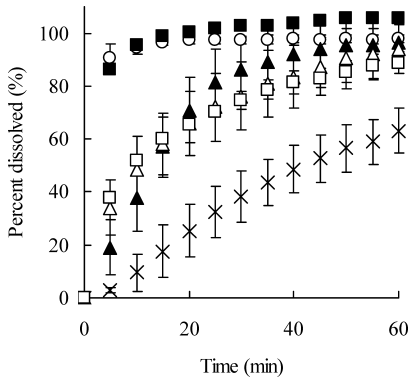

Fig. 1. Dissolution Profile of IMC from Tablet

Compression pressure is 100 MPa. ▲: Tab (SD), ■: Tab (SD-L-HPC), △: Tab (PM), □: Tab (PM-L-HPC), ○: solid dispersion particles, ×: IMC crystals. The data are the average values of three runs.

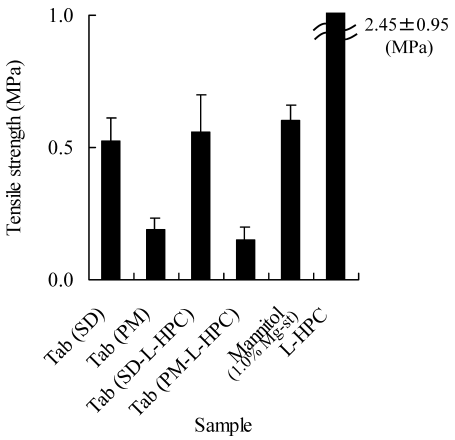

Fig. 2. Tensile Strength of Tablet

Compression pressure is 100 MPa. The data are the average values of four runs.

To design an optimum tablet of solid dispersion particles, hardness of tablets is an important factor as well as dissolution property. The tensile strength of tablet is shown in Fig. 2. The tensile strength of Tab (SD) and Tab (SD-L-HPC) was as high as that of mannitol containing 1.0% of magnesium stearate (Mg-st), while that of Tab (PM) and Tab (PM-L-HPC) was much lower than others. It was suggested that indomethacin crystals in Tab (PM) and Tab (PM-L-HPC) disturbed compaction property of the tablet.

The profile of die wall force during tabletting process is shown in Fig. 3. We have already reported that mannitol has a large residual die wall pressure (RDP) in compressing process and shows capping property. The addition of Mg-st

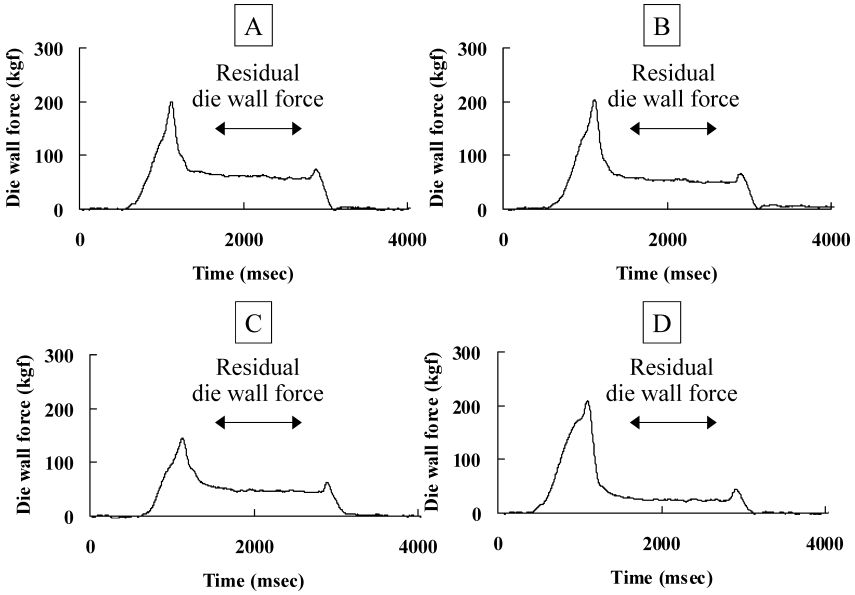

Fig. 3. Profile of Die Wall Force during the Tabletting Process

Compression pressure is 100 MPa. A: Tab (SD), B: Tab (SD-L-HPC), C: Mannitol (1.0% Mg-st), D: L-HPC.

Table 3. Compaction Parameters of Formulated Powder with L-HPC as Disintegrant

Sample	RDP (MPa)	MDP (MPa)	RDP/MDP (%)	PTR (%)	EP (MPa)
Tab (SD)	7.8±1.0	28.7±1.0	27.0±2.6	81.2±0.3	7.8±0.7
Tab (SD-L-HPC)	6.4±0.4	28.3±1.2	22.5±1.1	81.3±1.0	3.7±0.6
Mannitol (1.0% Mg-st)	5.9±0.6	22.9±0.8	26.0±3.1	72.8±0.7	3.6±0.3
L-HPC	3.8±1.0	25.4±4.0	15.6±5.5	79.7±6.5	1.9±0.7

RDP: residual die wall pressure, MDP: maximum die wall pressure, PTR: pressure transmission ratio, EP: ejection pressure of tablet. Compression pressure is 100 MPa. The data are the average values of four runs.

in mannitol decreased the large RDP value and capping tendency with depending on the amount of Mg-st added. Tab (SD) showed larger maximum die wall force and larger residual die wall force than those of mannitol containing 1.0% of Mg-st. The larger maximum die wall force might be interpreted by the improvement of transmission of pressure from upper punch to die wall. The larger residual die wall force also might be attributed to the high friction force between the compact of solid dispersion particles and die wall, probably because the solid dispersion particles containing the amorphous drug had sticky property to the die wall. The addition of L-HPC into SD tablet formulation (Tab (SD-L-HPC)) led to decreasing the residual die wall force as shown in Fig. 3.

The compaction parameters for these tablets are summarized in Table 3. The RDP and MDP of the both tablets (Tab (SD) and Tab (SD-L-HPC)) increased compared to those of mannitol containing 1.0% of Mg-st as shown in Fig. 3. We have previously proposed that the RDP/MDP is a useful parameter to evaluate the compaction property of pharmaceutical materials because the balance of RDP and MDP is important.[12,13] The RDP/MDP of Tab (SD-L-HPC) was lower than that of mannitol containing 1.0% of Mg-st, while that of Tab (SD) showed almost the same value as in the case of mannitol containing 1.0% of Mg-st. The PTR and MDP of Tab (SD) and Tab (SD-L-HPC) were much higher than that of mannitol containing 1.0% of Mg-st. It was indicated that the solid dispersion particles improved to transfer the pressure from upper punch to die wall and lower punch. The increased pressure from upper punch to die wall led to the increase in ejection pressure (EP) of Tab (SD) and Tab (SD-L-HPC). EP of Tab (SD-L-HPC) was lower than that of Tab (SD), being approximately same as that of mannitol containing 1.0% of Mg-st. This is the same tendency in the RDP value of these tablets.

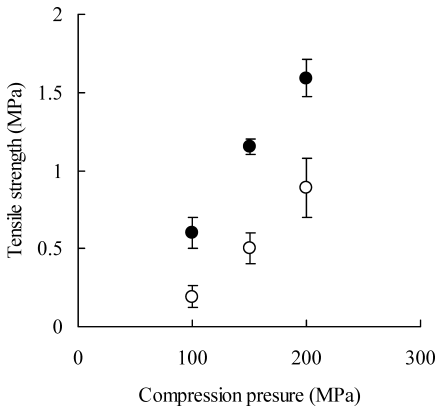

Fig. 4. Effect of Compression Pressure on the Tensile Strength of Tablet with L-HPC as Disintegrant

●: Tab (SD-L-HPC), ○: (PM-L-HPC). The data are the average values of four runs.

The effect of compression pressure on the tensile strength of Tab (SD-L-HPC) is shown in Fig. 4. The tensile strength

Table 4. Compaction Parameters of Formulated Powder with PCS as Disintegrant

Sample	RDP (MPa)	MDP (MPa)	RDP/MDP (%)	PTR (%)	EP (MPa)
Tab (SD)	7.8±1.0	28.7±1.0	27.0±2.6	81.2±0.3	7.8±0.7
Tab (SD-PCS)	8.1±0.8	29.6±0.3	27.5±2.4	68.3±0.7	6.4±0.5
Mannitol (1.0% Mg-st)	5.9±0.6	22.9±0.8	26.0±3.1	72.8±0.7	3.6±0.3
PCS	3.0±0.2	20.8±0.6	14.5±1.0	62.1±1.3	0.3±0.1

RDP: residual die wall pressure, MDP: maximum die wall pressure, PTR: pressure transmission ratio, EP: ejection pressure of tablet. Compression pressure is 100 MPa. The data are the average values of four runs.

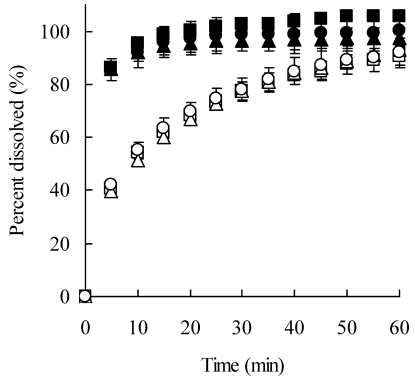

Fig. 5. Effect of Compression Pressure on the Dissolution Profile of IMC from Tablet with L-HPC as Disintegrant

Compression pressure: 100 MPa (●, ○), 150 MPa (▲, △), 200 MPa (■, □). Closed symbols represent Tab (SD-L-HPC) and opened symbols represent Tab (PM-L-HPC). The data are the average values of three runs.

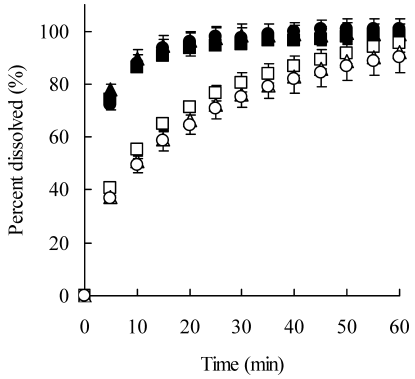

Fig. 6. Effect of Compression Pressure on the Dissolution Profile of IMC from Tablet with PCS as Disintegrant

Compression pressure: 100 MPa (●, ○), 150 MPa (▲, △), 200 MPa (■, □). Closed symbols represent Tab (SD-PCS) and opened symbols represent Tab (PM-PCS). The data are the average values of three runs.

of Tab (SD-L-HPC) and Tab (PM-L-HPC) increased with depending on the compression pressure as expected. The tensile strength of Tab (SD-L-HPC) was much higher than that of Tab (PM-L-HPC) at any compression pressure. The tensile strength of Tab (SD-L-HPC) prepared with compression pressure of 200 MPa was as high as that of a usually used tablet.

The effect of compression pressure on the dissolution profile of IMC from Tab (SD-L-HPC) and Tab (PM-L-HPC) is shown in Fig. 5. The percent dissolved of IMC from Tab (SD-L-HPC) was hardly affected by compression pressure. It was suggested that the disintegration property of L-HPC was strong enough. The percent dissolved of IMC from Tab (SD-L-HPC) was higher than that of Tab (PM-L-HPC) at any compression pressure.

PCS is also a useful disintegrant having good fluidity and compression property like L-HPC. We also reported that the dissolution rate of tolbutamide from tablet prepared with spray-dried particles consisting of PCS and tolbutamide was higher than that consisting of L-HPC and tolbutamide.[14] We characterized the property of solid dispersion tablets containing PCS instead of L-HPC in a same manner. A similar tendency was observed for the tablets as in the case of L-HPC in the point of the tensile strength of tablet, while tensile strength of tablet with PCS (0.78±0.10 MPa) was much lower than that with L-HPC (2.45±0.95 MPa). The compaction parameters for these tablets are shown in Table 4. In comparing the compaction parameter RDP/MDP, Tab (SD-PCS) showed a little bit higher value than that of Tab (SD), although that of Tab (SD-L-HPC) was rather lower than that of Tab (SD). This difference might be owing to the difference of the particle shape of the disintegrants. The particle shape of PCS is spherical, though that of L-HPC is fibrous. The addition of PCS in the tablet formulation also decreased the PTR of Tab (SD) probably, because the PTR of PCS was lower. The EP of Tab (SD-PCS) was as low as that of Tab (SD-L-HPC).

The effect of compression pressure on the dissolution profile of IMC from Tab (SD-PCS) was shown in Fig. 6. It showed the same tendency as observed for Tab (SD-L-HPC). However, the percent dissolved of Tab (SD-PCS) slightly lower than that of Tab (SD-L-HPC). It was suggested that the force for disintegration of PCS is weaker than that of L-HPC. The tensile strength of Tab (SD-PCS) increased with increasing the compression pressure and was higher than that of Tab (PM-PCS) at any compression pressure, same as that of Tab (SD-L-HPC).

Conclusion

The rapidly dissolving tablet containing solid dispersion particles consisting of IMC and Sylysia350 was prepared with mannitol and disintegrant (L-HPC or PCS). The addition of L-HPC in Tab (SD) remarkably improved the dissolution rate of IMC from the tablet and its compaction property. The dissolution rate of IMC from tablet was almost the same as observed for the solid dispersion particles. Compression pressure did not affect the dissolution rate of IMC from tablet. The tensile strength of the tablet was strong enough for practical use, more than 1.5 MPa at compression pressure of 200 MPa. PCS also could improve the dissolution and tabletting properties, but the dissolution rate of IMC slightly decreased and the compaction property was slightly lower

than that in the case of L-HPC.

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