Improvement of Dissolution Property of Poorly Water-Soluble Drug by Novel Dry Coating Method Using Planetary Ball Mill

Ryoichi SONODA,*[,a] Masashi HORIBE,[a] Takao OSHIMA,[a] Tomohiro IWASAKI,[b] and Satoru WATANO[b]

[a] *Drug Formulation Department, Central Research Laboratories, Kaken Pharmaceutical Co., Ltd.; 301 Gensuke, Fujieda, Shizuoka 426–8646, Japan: and* [b] *Department of Chemical Engineering, Graduate School of Engineering, Osaka Prefecture University; 1–1 Gakuen-cho, Naka-ku, Sakai, Osaka 599–8531, Japan.*
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The dissolution property of a poorly water-soluble drug, flurbiprofen (FP), was improved by a novel dry coating method using a planetary ball mill. Several mixtures composed of water-soluble additives (D-mannitol, lactose, and erythritol), light anhydrous silicic acid, and flurbiprofen were prepared. These mixtures and several starches were co-ground in a planetary ball mill, and the surface of the starches was dry coated with the mixtures. The size, appearance, yield, and drug dissolution property of the dry coated preparations were evaluated, and the optimal formulation which improved the dissolution property of poorly water-soluble flurbiprofen was determined. The dissolution rate of FP was increased by dry coating of the surface of starches with microparticulated FP. It was further increased by co-grinding of FP, starch, and a water-soluble additive, or dry coating of the starch surface with microparticulated FP and light anhydrous silicic acid, as a glidant. These co-ground and dry coated preparations could be recovered from the pot of the planetary ball mill readily without adhesion to the inside wall of the pot. These are considered to be novel, industrially applicable methods for improving the dissolution rate of poorly water-soluble drugs.

Key words poorly water-soluble drug; planetary ball mill; co-grinding; dry coating; dissolution rate

With the development of genomic and molecule-targeted drug technologies, the generated compounds have become larger in molecular weight and more complex in chemical structure. As a result, compounds poorly soluble in either water or oil have increased, and improvement of the dissolution rate of such poorly water-soluble drugs has become a very important subject for pharmaceutical researchers.

Methods such as microparticulation and amorphization as solid dispersions have been reported as techniques to improve the dissolution property of poorly soluble drugs in water.[1)]

Microparticulation of poorly water-soluble drugs by a dry grinding increases their surface area and is useful for improving their dissolution rate. However, microparticulation enhances their adhesive-agglomerative property, and the resultant microparticles often fail to retain their particle size immediately after grinding. As a method to overcome this problem, co-grinding of drugs with a sugar or water-soluble polymer has been reported.[2,3)]

Devices including the vibration ball mill and planetary ball mill are used widely for co-grinding. Since pharmaceutics deals with organic materials, there have been problems such as a decrease in the yield due to the clinging and adhesion of pulverized particles to the device, their physicochemical changes as a result of heat accumulation during prolonged operation, and their contamination by foreign matter during grinding (wearing, erosion, *etc.*), and these devices have been applied primarily to inorganic materials.

Recently, composite particle technology involving coating larger particles with microparticles in a dry state has attracted attention as a possible method to improve the handling properties and dissolution rates of poorly water-soluble drugs.[4)]

In this study, a novel method for improving dissolution rate of poorly water-soluble drugs by dry coating has been proposed.

Flurbiprofen (FP), a poorly water-soluble, non-steroidal, anti-inflammatory drug, was used as a model compound. Starches, which are used as binders, diluents, and disintegrants for solid oral preparations, were used as core materials to be coated with microparticles of flurbiprofen.

Mechanical composite particles by dry coating were conducted using a planetary ball mill, which is generally utilized for the grinding of inorganic materials. Since dry coating of starches with flurbiprofen by this method was suggested to improve its dissolution property, the method is reported by comparing it with co-grinding.

Experimental

Materials Flurbiprofen (FP) was used as a model drug of poorly water-soluble drug, which was obtained from BASF AG (Ludwigshafen, Germany). The mean particle diameter was 9.2 μm, the melting point was 114—117 °C and water solubility was 38 μg/ml at 37 °C. In the case of co-grinding, D-mannitol (MAN, Towa Chemical Industry Co., Ltd., Japan), lactose (LAC, Pharmatose 200M®, DMV International, Verghel, Netherlands), erythritol (ERY, Nikken fine Chemical Co., Ltd., Japan) were used as water-soluble additives. Rice starch (RS, Matsutani Chemical Industry Co., Ltd., Japan), corn starch (CS, Kato Kagaku Co., Ltd., Japan), potato starch (PS, Nippon Starch Chemical Co., Ltd., Japan) and pregelatinaized starch (PPS-A, PCS®, Asahi Kasei Chemicals, Japan, and PPS-C, starch 1500®, Nippon Calorcon, Japan) were used as core materials (Fig. 1, Table 1). Light anhydrous silicic acid (LASA, Aerosil 200FAD®, Nippon Aerosil Co., Ltd., Japan) was used as a glidant. All other chemicals were of analytical or HPLC grade.

Method of Preparations Figure 2 shows an experimental flow chart.

The water-soluble additives were ground to have particle size smaller than 2 μm by a jet mill pulverizing (Single Track Jet mill, Model FS-4, Seichin Enterprise Co., Ltd., Japan). The pulverizing condition was as follows; the pressure of pushing nozzle was 0.60 MPa and the pressure of grinding nozzle was 0.57 MPa. The dry coating was performed by using a planetary ball mill (PM-1200, Seishin Enterprise Co., Ltd., Japan). The mill pot had a volume of 350 ml and was loaded with 300 g (85 ml) of zirconia balls with a diameter of 3.0 mm. Flurbiprofen, jet mill pulverized water-soluble additives and various starches were mixed together by hand in a polyethylene bag for 10 min with a various weight ratio to obtain physical mixture, and 36 g of the physical mixture were ground in a planetary ball mill at 200 rpm (the ratio of revolution to rotation: 1.25) for 30 min at ambient temperature (21 °C). The

* To whom correspondence should be addressed. e-mail: sonoda_ryoichi@kaken.co.jp

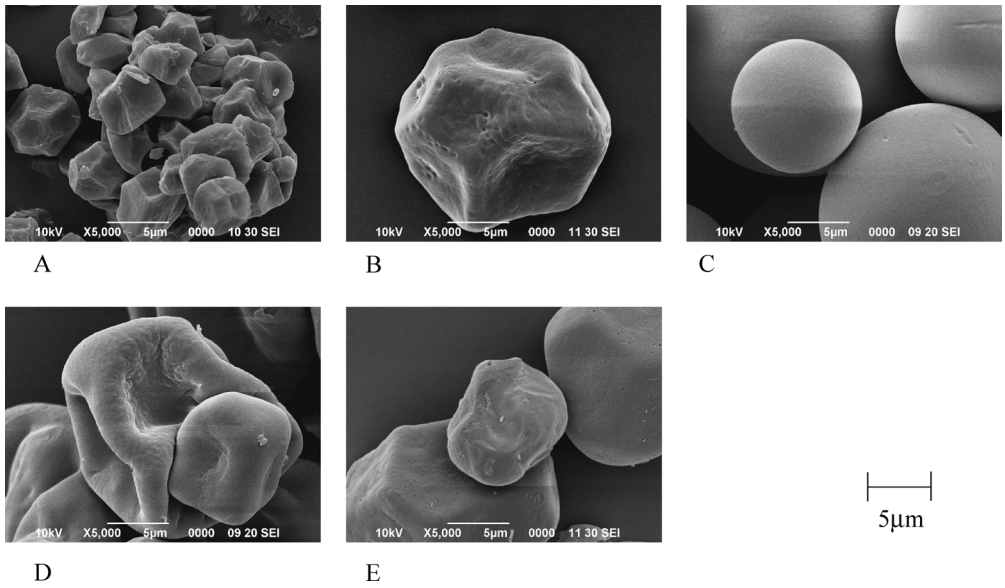

Fig. 1. SEM Photographs of Starches
(A) RS, (B) CS, (C) PS, (D) PPS-A, (E) PPS-C.

Table 1. Particle Size and Water Content of Starches

Starches	Particle size (μm)			Water content (%)[a]
	D_{10}	D_{50}	D_{90}	
Rice starch (RS)	4.4	11.5	26.8	8.68
Corn starch (CS)	9.9	15.3	21.3	10.34
Potato starch (PS)	14.8	25.0	37.8	4.67
PPS-A	15.0	25.4	38.2	7.39
PPS-C	8.8	19.4	52.0	8.55

a) Original, water content was measured by loss on drying test according to Japanese Pharmacopoeia or Japanese Pharmaceutical Excipients.

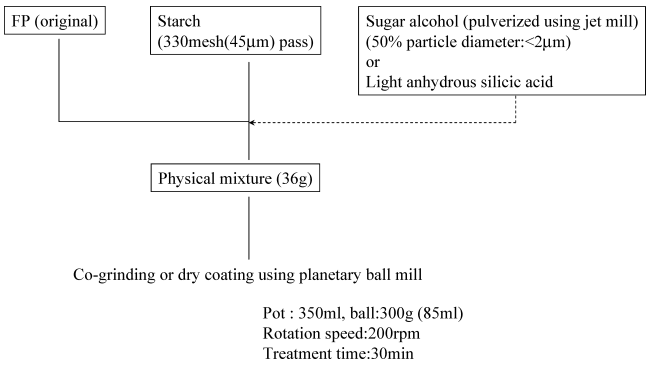

Fig. 2. Co-grinding or Dry Coating Procedures and Conditions
Solid line: bi-component dry coating procedure, dotted line: tri-component co-grinding or dry coating procedure.

surface temperature of co-ground and dry coated preparations was measured by using a non-contact thermometer (model 505S, Konica Minolta, Japan) before and immediately after the treatment in a planetary ball mill. The preparations were collected after milling and the weight was measured, the recovery rate (%) was calculated as follows.

$$\text{recovery (\%)} = \text{the weight of sample after milling/the weight of sample before milling (36 g)} \times 100$$

Evaluation of Physicochemical Properties of Particles Particle size was determined by a laser diffraction particle size analyzer (Model LSDA-1400A, Tohnichi Computer Applications Co., Ltd., Japan) with a dry powder dispersion system at the dispersion pressure of 0.4 MPa (Model PD-10S, Tohnichi Computer Applications Co., Ltd., Japan). The volume-weighted size distribution was determined together with the D_{10}, D_{50} and D_{90}, within D_{10}, D_{50} and D_{90} represent a cumulative 10%, 50% and 90% particle size, respectively. The surface appearance of the co-ground and dry coated preparations was observed with a scanning electron microscope (SEM, Model JSM-6390LA, JEOL, Japan).

Dissolution Studies[5] The amount of FP released from the preparations was determined using a dissolution test apparatus (Model NTR-6100A, Toyama Sangyo Co., Ltd., Japan) according to dissolution test method 2 (paddle method) described in the Japanese Pharmacopoeia XV. The paddles were rotated at 75 rpm. The preparations (equivalent to 40 mg of FP) were added to the dissolution medium (900 ml of water adjusted to 37±0.1 °C). Test fluids (about 10 ml) were withdrawn at predetermined time intervals from each vessel through a glass filter, and then filtered through a 0.45 μm membrane filter (Chromatdisk 25A, Kurabo Industries Ltd., Japan). After adding 0.5 ml of methanol to 0.5 ml of filtrate, the concentration of FP was measured using the LC-2010 HPLC system (Shimadzu Corporation, Japan). The same volume of flesh medium was replaced and a correction for the cumulative dilution was calculated. The amount of FP dissolved for each sample (n=3) was plotted *versus* time. The HPLC conditions were: reverse-phase column, STR-ODS (4.6×150 mm, 5 μm, Shimadzu GLC Ltd., Japan) at 40 °C; mobile phase, a mixture of water/acetonitrile/acetic acid (12 : 7 : 1); flow rate, 1.5 ml/min; and detection wavelength, 254 nm.

Results and Discussion

Recovery of the Preparations after Co-grinding and Dry Coating from the Planetary Ball Mill Pot Table 2 lists the recovery rates of the preparations after co-grinding and dry coating and surface temperatures of the preparations before and immediately after treatment in a planetary ball mill. The bi-component co-ground preparation of FP and MAN adhered tightly to the inside wall of the pot and could not be collected readily. However, the tri-component co-ground preparation containing a water-soluble additive, MAN, and CS adhered to the ball, but that of a water-soluble additive, LAC or ERY, and CS showed no adhesion to the inside wall of the pot or the ball. MAN has been reported to be microparticulated by dry grinding with a poorly water-soluble drug without changes in physicochemical properties such as the crystalline form of the drug, and to show very satisfactory redispersibility after grinding.[2,6] However, as treatment of bi-component mixtures containing MAN in the planetary

ball mill caused tight adhesion of the powder to the inside wall of the pot and a marked increase in the surface temperature of the preparations, bi-component mixtures containing MAN were considered to be inappropriate for this study. Further evaluation is necessary to determine the cause of adhesion with mixtures containing MAN. In bi-component mixtures containing starch, no adhesion to the inside wall of the pot was noted, and the powder could be recovered readily from it. When the recovery rate was compared according to the starch used, it decreased with increasing water content of the starch (Table 2), however the surface temperature of the dry coated preparations increased immediately after treatment in the mixtures with a low recovery rate (Table 2). The difference between RS and PPS-C, which are comparable in water content, is considered to have been caused by a difference in the mean particle size of individual core materials.

Shapes of Co-ground and Dry Coated Preparations Figures 3 and 4 indicate scanning electron micrographs (SEM) of co-ground and dry coated products prepared with FP bulk powder in a planetary ball mill.

As shown in Fig. 3A, the particle shape of FP before grinding was irregular, and linear depressions and elevations were noted on the particle surface. After the co-grinding, the bi-component mixture of FP/MAN showed the agglomeration of microparticles (Fig. 3B). However, in the bi-component mixture of FP/RS, the surface of RS was almost completely covered by microparticulated FP (Fig. 3C). In the bi-component mixtures of FP and other starches, the surface of starch particles was not sufficiently covered by microparticles of FP, and the surface of starch particles were exposed (Figs. 3D—G). In the tri-component mixture of FP/water-soluble additive/CS or FP/CS/LASA, the exposed surface of starch particles observed in the bi-component mixtures was covered by FP and the water-soluble additive or LASA (Figs. 4B—D, F). Similarly, in the tri-component mixtures of FP/water-soluble additive/RS or FP/RS/LASA, the surface of RS particles was covered by microparticles of FP and water-soluble additive or LASA (Figs. 4A, E).

Table 3 summarizes the particle size of various dry coated preparations measured with a laser diffraction particle size analyzer. Since the distributions of particle size were similar to those of the starches used, the dry coated preparations were composite particles in which microparticles of FP were fixed on the surface of starch particles, being in close agreement with the above SEM findings.

Drug Dissolution from Co-ground and Dry Coated Preparations Figures 5—7 show dissolution curves of FP from the co-ground and various dry coated preparations. The dissolution test showed increase in the dissolution rate of FP by dry coating in the bi-component mixtures of FP and starches (Fig. 5). The particle size of FP covered on each starch surface was reduced clearly as compared with the particles before dry-coating (Figs. 3C—G). This was probably because the particle size reduction of FP improved the dissolution rate. Also, in RS, the surface of which was completely covered by microparticles of FP, the improvement in the dissolution rate was smaller than in the other starches. This was probably because complete covering of the surface of RS by

Table 2. The Recovery and Powder Surface Temperature at the Start and the End of Milling of Samples

Formulation (mass ratio)	Recovery (%)[a)]	Powder surface temperature (°C)	
		Start	End
FP/MAN (1/5)	55.8		36
FP/RS (1/5)	90.0		26
FP/CS (1/5)	83.3		28
FP/PS (1/5)	95.6		32
FP/PPS-A (1/5)	92.8		32
FP-PPS-C (1/5)	86.2	21	31
FP/MAN/RS (1/0.5/5)	92.7		33
FP/MAN/CS (1/0.5/5)	78.3		34
FP/LAC/CS (1/0.5/5)	91.2		33
FP/ERY/CS (1/0.5/5)	88.5		33
FP/RS/LASA (1/5/0.02)	92.9		30
FP/CS/LASA (1/5/0.02)	89.9		33

a) recovery (%)=the weight of sample after milling/the weight of sample before milling (36 g)×100.

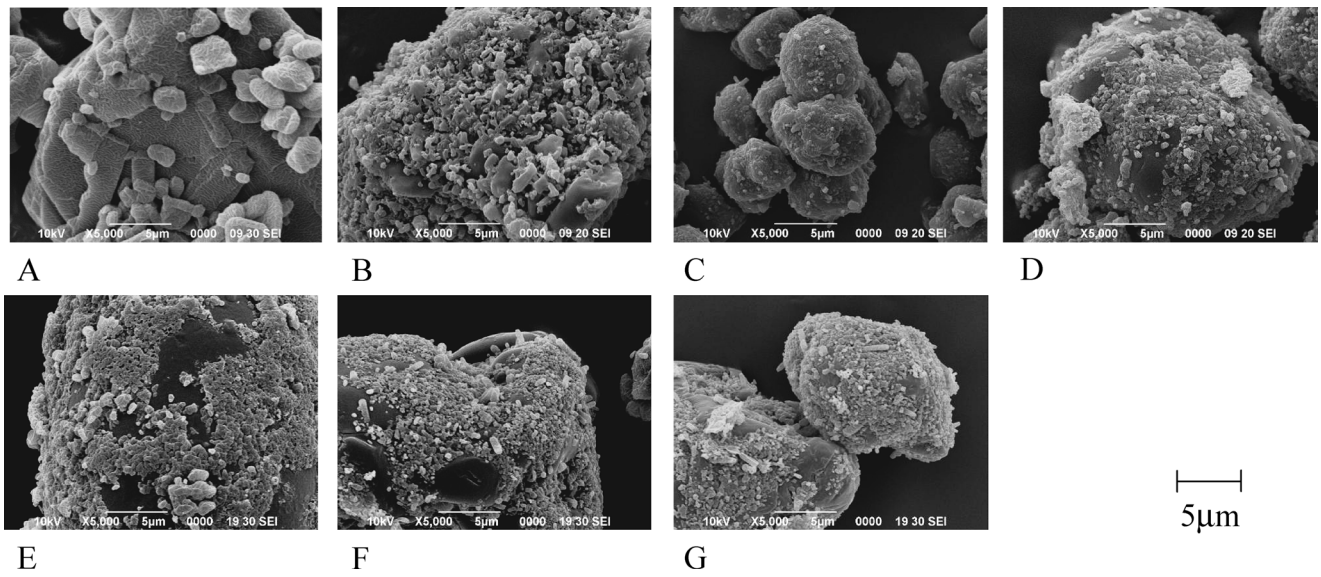

Fig. 3. SEM Photographs of the Bi-component Co-ground and Dry Coated Preparations

(A) FP original, (B) FP/MAN=1/5, (C) FP/RS=1/5, (D) FP/CS=1/5, (E) FP/PS=1/5, (F) FP/PPS-A=1/5, (G) FP/PPS-C=1/5.

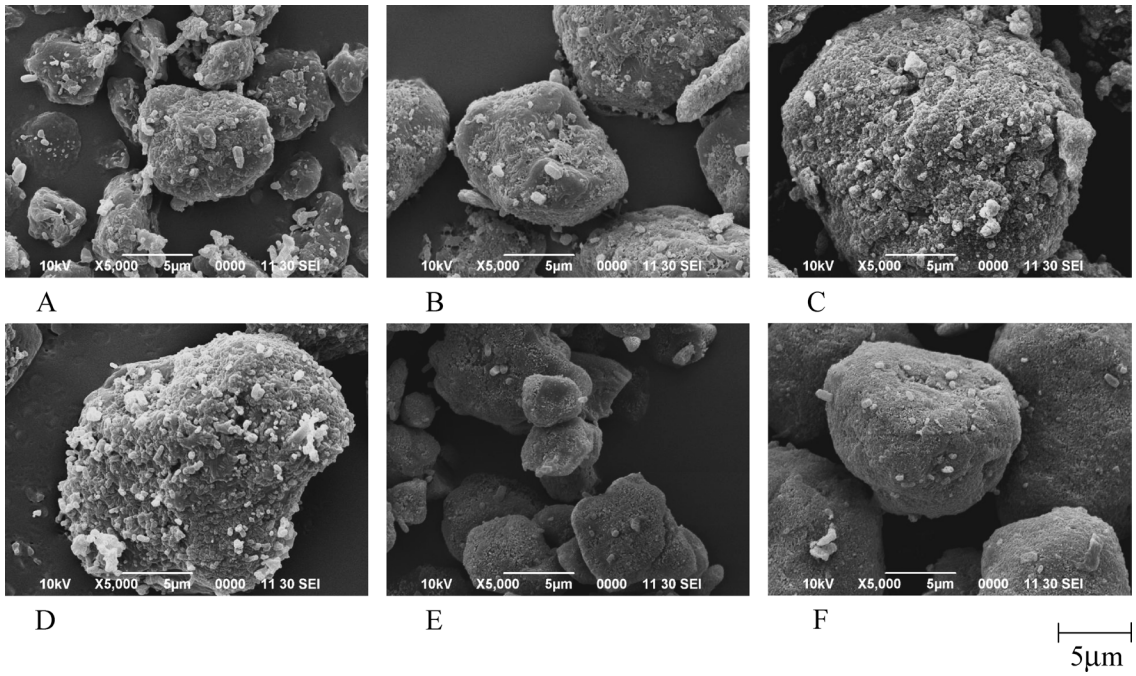

Fig. 4. SEM Photographs of the Tri-component Co-ground and Dry Coated Preparations

(A) FP/MAN/RS=1/0.5/5, (B) FP/MAN/CS=1/0.5/5, (C) FP/LAC/CS=1/0.5/5, (D) FP/ERY/CS=1/0.5/5, (E) FP/RS/LASA=1/5/0.02, (F) FP/CS/LASA = 1/5/0.02.

Table 3. Particle Size of Co-ground and Dry Coated Preparations of Flurbiprofen

Formulation (mass ratio)	Particle size (μm)		
	D_{10}	D_{50}	D_{90}
FP/MAN (1/5)	2.3	8.9	27.8
FP/RS (1/5)	3.4	5.9	9.1
FP/CS (1/5)	7.6	13.6	19.8
FP/PS (1/5)	12.8	21.4	36.6
FP/PPS-A (1/5)	26.8	35.2	44.1
FP-PPS-C (1/5)	11.7	16.6	21.8
FP/MAN/RS (1/0.5/5)	4.3	6.7	9.8
FP/MAN/CS (1/0.5/5)	9.0	14.5	20.4
FP/LAC/CS (1/0.5/5)	7.7	14.3	20.5
FP/ERY/CS (1/0.5/5)	10.0	15.6	20.9
FP/RS/LASA (1/5/0.02)	4.0	6.6	9.8
FP/CS/LASA (1/5/0.02)	9.5	14.3	20.2

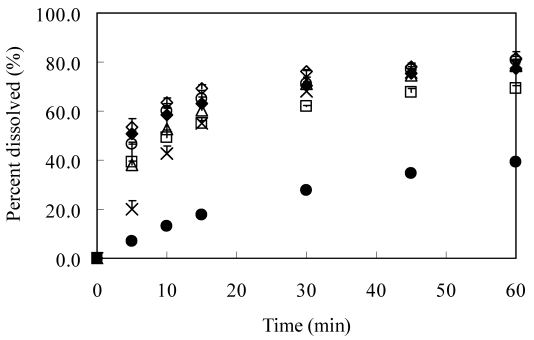

Fig. 5. Dissolution Profiles of the Bi-component Co-ground and Dry Coated Products of Flurbiprofen prepared by Using Planetary Ball Mill

●: FP original, ◆: FP/MAN=1/5, ◇: FP/PPS-A=1/5, ○: FP/PPS-C=1/5, △: FP/CS=1/5, □: FP/PS=1/5, ×: FP/RS=1/5. Each point represents the mean±S.D. (n=3).

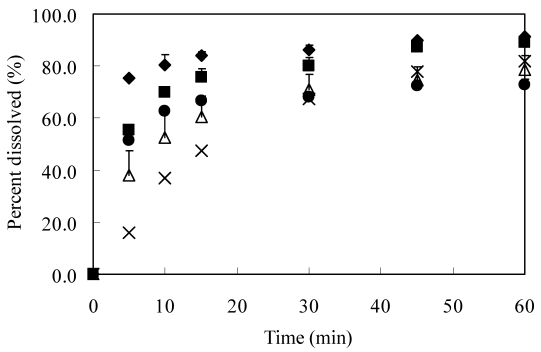

Fig. 6. Dissolution Profiles of the Tri-component Co-ground Products of Flurbiprofen Prepared by Using Planetary Ball Mill

△: FP/CS=1/5, ◆: FP/MAN/CS=1/0.5/5, ■: FP/LAC/CS=1/0.5/5, ●: FP/ERY/CS=1/0.5/5, ×: FP/MAN/RS=1/0.5/5. Each point represents the mean±S.D. (n=3).

FP reduced the wettability of RS to water.

Figure 6 indicates the dissolution curves of FP from tri-component, co-ground preparations of FP/water-soluble additive/starch. The dissolution rate of FP was found to be improved by the addition of a water-soluble additive, probably because the wettability of microparticulated FP to water was improved by the water-soluble additive that covered the starch surface. Also, the improvement in the dissolution rate was the best in MAN. However, as mentioned above, the tri-component, co-ground preparation containing MAN and CS markedly adhered to the ball and was considered to be inappropriate as a formula.

Figure 7 shows the dissolution curves of FP from the tri-component, dry coated preparations of FP/starch/LASA. The initial dissolution rate of FP was improved by the addition of LASA when the starch was CS. However, the initial dissolution rate was not improved by the addition of LASA when the starch was RS. This was probably because RS particles

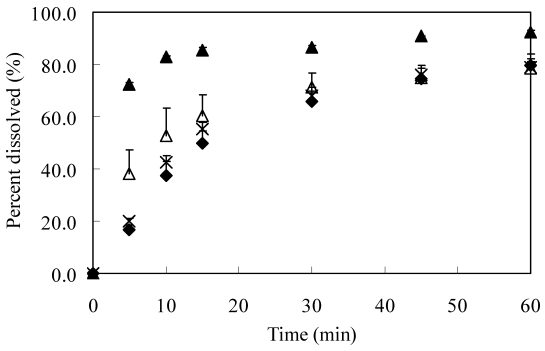

Fig. 7. Dissolution Profiles of the Tri-component Dry Coated Products of Flurbiprofen Prepared by Using Planetary Ball Mill

△: FP/CS=1/5, ▲: FP/CS/LASA=1/5/0.02, ×: FP/RS=1/5, ◆: FP/RS/LASA=1/5/0.02. Each point represents the mean±S.D. (n=3).

Table 4. Formulation of Co-ground and Dry Coated Preparations of Flurbiprofen and Percent Dissolution at 10 min

Formulation (mass ratio)	Percent dissolved at 10 min	Ratio of improvement
FP original	12.9	1.0
FP/MAN (1/5) (physical mixture)	44.7	3.5
FP/MAN/CS (1/0.5/5) (physical mixture)	58.4	4.5
FP/MAN (1/5)	58.5	4.5
FP/RS (1/5)	40.5	3.1
FP/CS (1/5)	52.6	4.1
FP/PS (1/5)	47.7	3.7
FP/PPS-A (1/5)	63.3	4.9
FP-PPS-C (1/5)	59.5	4.6
FP/MAN/RS (1/0.5/5)	37.3	2.9
FP/MAN/CS (1/0.5/5)	80.5	6.2
FP/LAC/CS (1/0.5/5)	70.1	5.4
FP/ERY/CS (1/0.5/5)	68.1	5.3
FP/RS/LASA (1/5/0.02)	37.3	2.9
FP/CS/LASA (1/5/0.02)	82.9	6.4

coated with microparticulated FP and LASA agglomerated, as shown in Fig. 4E, and showed less improvement of the wettability due to LASA.

Table 4 investigates the dissolution rate of FP from the co-ground and dry coated preparations during a 10-min period and dissolution ratios relative to the dissolution of the bulk powder of FP during a 10-min period (=1.0). The dissolution of FP from the physical mixture of FP/MAN, and of FP/MAN/CS was higher than that of FP original (dissolution ratio: 3.5 and 4.5, respectively). The dissolution rate from bi-component, dry coated preparations of FP and a starch were improved regardless of the starch used (dissolution ratios: 3.1—4.9). The dissolution of FP from the tri-component, co-ground preparation of FP/water-soluble additive/CS was even higher than that of the bi-component, dry coated preparation of FP/CS with dissolution ratios of 5.3—6.2. The dissolution rate of FP from the tri-component, dry coated preparations consisting of FP/CS/LASA was similar to that of the tri-component, co-ground preparation containing MAN, and its dissolution ratio was 6.3. The dissolution rate of FP from the physical mixture was found to be improved, probably because the wettability of FP to water was improved by the water-soluble additive. In contrast, co-ground FP/MAN, FP/CS/MAN showed a higher rate of dissolution than that of the physical mixture. When comparing co-ground preparations with physical mixture in the same formula, this was probably because the particle size reduction of FP improved the dissolution rate rather than the wettability of microparticulated FP to water. From the above results, in order to improve the dissolution property of FP, it was considered that the important factors were both the increase in specific surface area by particle size reduction of FP and improvement in the wettability of FP to water.

Generally, the improvement effect of co-grinding and mechanical composite particles is based on the particle size reduction of an active pharmaceutical ingredient, the increase in specific surface area, the decrease in crystallinity, and improvement in dispersibility. Further studies are needed to investigate the decrease in crystallinity at the treatment in a planetary ball mill.

Conclusion

In this study, to improve the dissolution property of a poorly water-soluble flurbiprofen (FP), dry coating of the surface of various starch particles with FP was conducted using a planetary ball mill and investigated the dissolution rate of these preparations. The dissolution rate of FP was increased by dry coating of the surface of starches with microparticulated FP. It was further increased by co-grinding of FP, starch, and sugar alcohol, a water-soluble additive, or dry coating of the starch surface with microparticulated FP and light anhydrous silicic acid (LASA), as a glidant.

These co-ground and dry coated preparations could be recovered from the pot of the planetary ball mill readily without adhesion to the inside wall of the pot. It was thus found that are useful for the industrial manufacturing.

In addition, the dissolution rate of FP could be increased by co-grinding of FP with starch and sugar alcohol, a water-soluble additive, or uniform dry coating of the surface of starch particles with a microparticulated poorly water-soluble drug and LASA, as a glidant. Therefore, in order to improve the dissolution property of FP, it was considered that the important factors were both the increase in specific surface area by particle size reduction of FP and improvement in the wettability of FP to water.

These are considered to be novel, industrially applicable methods for improving the dissolution rate of drugs.

Further studies are needed to clarify the mechanism of the suitability of starches as core particles in dry coating using a planetary ball mill, and to determine the optimal conditions for the preparation of composite particles. We will also aim to evaluate the stability of tri-component, dry coated preparations and establish a manufacturing method on an industrial scale including continuous tabletting.

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