Evaluation of the Compaction Properties of a Solid Dispersion of Indomethacin with Crospovidone by Tableting Process Analyzer

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A powder solid dispersion system (SD) of indomethacin (IM) with crospovidone (CrosPVP) possesses good fluidity and can be used for tablet formulation. Tablets of SD can be prepared by direct compression and have adequate hardness and a small variation in weight. Forces during the tableting process were measured with a tableting process analyzer (TabAll) equipped with a single-punch. The pressure transmission ratio (PTR) from the upper to the lower punch and the die wall force (DWF) were examined during the tableting process. Ejection force (EF) and scraper pressure (SP) were measured for determining the capping and sticking properties during the tableting process. Adding 1% magnesium stearate (MS) to the SD resulted in high PTR and DWF values and a low EF value. PTR and DWF values increased and EF value decreased when MS and microcrystalline cellulose (MCC) were added to the SD. A thousand tablets could be manufactured without problems such as sticking or capping when 1% MS and 50% MCC were added to the SD containing 25% IM.

Key words solid dispersion; crospovidone; tablet; compaction property; direct compression; indomethacin

Solid dispersion systems (SD) improve the solubility and/or dissolution rate of poorly water-soluble drugs by dispersing a drug in a carrier to render it amorphous.[1,2] However, the method possesses several disadvantages, including manufacturing difficulties due to materials that are soft, tacky, or have poor fluidity for SD,[3] and preparation of tablets using SD, which allow only slow dissolution of drugs.[4] SD methods also require a variety of excipients and a complicated procedure for preparing tablets or capsules.[5] Thus, only a few marketed products utilize this system. Therefore, an SD method involving simple manufacturing and formulation processes for preparation of tablets or capsules that enhance drug dissolution would be a great advance.

In this study, SD was applied to the preparation of tablets, because tablets can be manufactured inexpensively and in high quantity. Crospovidone (CrosPVP) was chosen as a carrier because it has two useful characteristics. First, it is a powder with good fluidity and it is used as a disintegration agent in tablet. Second, CrosPVP has the same chemical structure as povidon, which is commonly used as carrier of SD. We developed an SD of indomethacin (IM) with CrosPVP by mechanically mixing and heating and forming tablets by direct compression with only 1% magnesium stearate (MS) as a lubricant.[6] However, to prevent capping and sticking during the tableting process, the compaction properties of the powders and the quality of the tablets need to be evaluated and optimized. We evaluated compaction properties of the SD of IM with CrosPVP using a single-punch machine equipped with several force analysis elements.

Experimental

Materials CrosPVP (Polyplasdone XL®, USP grade, mean particle size, 75 μm (<75 μm; 22%, 75—150 μm; 42%, 150 μm<; 35%)) was a gift from ISP Japan (Tokyo). IM (JP grade, particle size, 1—2 μm) was obtained from Nippon Bulk Yakuhin (Osaka). MCC (Avicel® PH-102, mean particle size, 90 μm (<75 μm; 26%, 75—150 μm; 32%, 150 μm<; 41%)) and MS were obtained from Asahi Kasei Chemicals (Tokyo) and Wako Pure Chemical Industries (Osaka), respectively. All other reagents were of analytical grade.

Preparation of SD The SD was prepared according to a procedure published previously.[6] Briefly, a weight ratio of IM : CrosPVP = 1 : 3 or 2 : 3 was used. A physical mixture (Pmix) was obtained by blending IM and CrosPVP using a spatula. The Pmix then was mixed with a high-speed elliptical-rotor type mixer (Theta-Composer Lab® type THC, Tokujyu Kousakusyo, Kanagawa) for 30 min, followed by heating in air at 125 °C (IM : CrosPVP = 1 : 3) or 145 °C (IM : CrosPVP = 2 : 3) for 30 min.

Powder Fluidity of SD and Related Materials The angles of repose of the SD and related materials were measured with a turntable apparatus (Tsutsui Rikagaku Kikai, Tokyo).

Compressibility index (CI) was calculated using the following equation:

$$CI = (V_0 - V_f)/V_0 \times 100$$

where V_0 is powder volume before tapping and V_f is powder volume after tapping infinitely. V_f was calculated by Kawakita's equation[7] using data from 200 tapping times with a tapping density analyzer (Tapdenser KYT-1000® Seishin Enterprise, Tokyo) containing a 20-ml cylinder.

Preparation of Tablets The SD or mixture of SD and MCC (SD content, 50—100%) with or without 1% MS as lubricant (Table 1) was directly compressed to tablets (200 mg) by a tableting process analyzer (Model N-30EX, TabAll, Okada Seiko, Tokyo) equipped with flat-faced punches (8 mm diameter), using a compression force of 5 kN and press speed of 10 tablets/min. For comparison, Pmix also was directly compressed to tablets.

Characterization of Tablets The weight variation among tablets was determined using 20 tablets. The crushing strength of the tablets (hardness) was measured with a digital crushing tolerance-measuring machine (TS-

Table 1. Formulation of Tablets

	SD (No excipient)	SD (+MS)	SD (+MS+10%MCC)	SD (+MS+30%MCC)	SD (+MS+50%MCC)
SD	200	200	180	140	100
MCC			20	60	100
MS		2	2	2	2
Total (mg)	200	202	202	202	202

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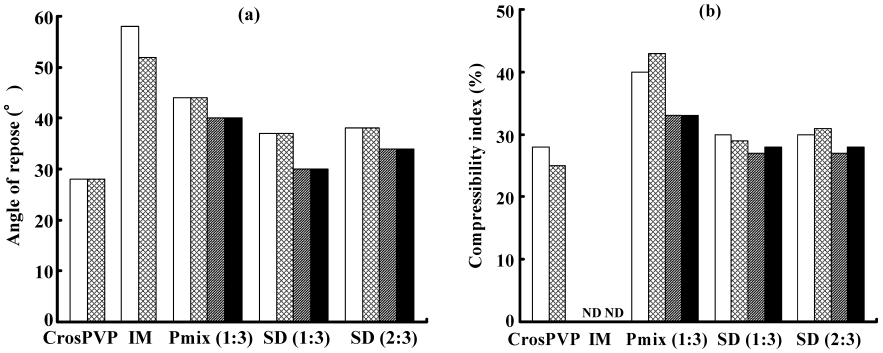

Fig. 1. Powder Fluidity Characteristics of SDs and Related Materials

(a) Angle of repose (°); (b) compressibility index (%). □, no excipient; ▨, +MS; ▨, +50%MCC; ■, +MS+50%MCC; ND: not determined.

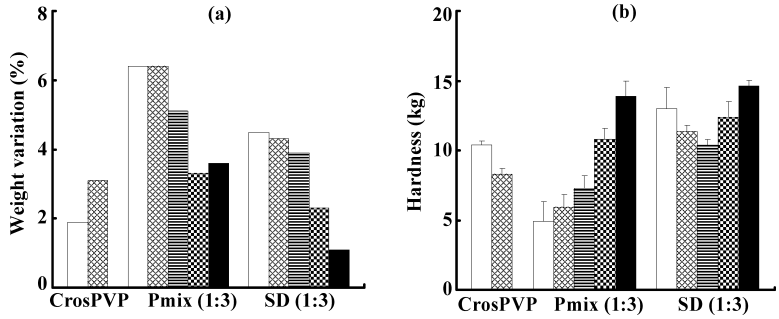

Fig. 2. Weight Variation (a) or Hardness (b) of Tablets from SD and Related Materials

□, no excipient; ▨, +MS; ▤, +MS+10%MCC; ▨, +MS+30%MCC; ■, +MS+50%MCC.

50N®, Okada Seiko, Tokyo).

Measurement of Compaction Parameters The compaction properties of the materials were determined using a TabAll[8—10] instrument, which measures 7 parameters during compaction: upper punch displacement, under punch displacement, upper punch force, under punch force, die wall force (DWF), ejection force (EF), and scraper pressure (SP). Data were recorded using DAATSU II software (Okada Seiko, Tokyo). During force parameter measurement, the maximum value of each tablet was observed directly on the control unit of the TabAll. Pressure transmission ratio (PTR) was calculated by dividing lower punch force by upper punch force. The data presented are averages of 100 tablets.

Dissolution Studies Dissolution of IM from various forms containing 50 mg of IM was tested at 37 °C using a JP dissolution test apparatus with 900 ml purified water and a rotation of paddle at 100 rpm. IM concentration was determined by UV absorption at 320 nm.

Results and Discussion

Fluidity of SD Powder X-ray diffraction and differential scanning calorimetry results confirmed that the IM in the SD was in an amorphous state. The SDs prepared for IM : CrosPVP = 1 : 3 and 2 : 3 were defined as SD(1 : 3) and SD(2 : 3), respectively. Prepared SD exists as a powder that dose not require crushing. Thus, the resulting SD was sieved with a mesh sieve (sieve opening 180 μm). The particle sizes of SD was as follows; <75 μm; 15%, 75—150 μm; 21%, 150 μm<; 63%.

Figure 1 shows the powder fluidity characteristics of the SDs and related materials. CrosPVP, widely used as a superdisintegrant,[11] showed good fluidity, with an angle of repose of 28° and CI of 29%. IM showed poor fluidity due to the 1—2 μm size; CI could not be determined because of static electricity. The angle of repose and CI of the SD were lower than those of the Pmix, independent of the ratio of IM to CrosPVP. These findings demonstrated that fluidity and packability were improved by transforming the Pmix to an SD.

MS is an efficient lubricant in the fluidity of the powders during material flow, elimination of binding to the compact to the die, and minimization of sticking and picking to the punch surfaces.[12] In all cases, no changes in angle of repose and CI occurred when MS was added as a lubricant because Pmix and SD themselves possessed good fluidity. When MCC was added, both the angle of repose and CI decreased compared to that without MCC in the case of Pmix. In the case of SD, angle of repose decreased compared to that without MCC, however CI did not change. It was suggested that neither MS nor MCC had an effect on packability because SD itself possessed good fluidity. The angle of repose should be under approximately 45°[13,14] for tableting using the direct compression method. Therefore, these results indicate that the fluidity of the SD and Pmix makes them suitable for direct compression.

Characteristics of Pmix and SD Tablets The characteristics of Pmix and SD tablets were evaluated using various formulations in the direct compression method. This study involved the formulations shown in Table 1. Figure 2 shows the effect of excipients on weight variation and hardness of the tablets of SD(1 : 3) and related materials. Difficulties were encountered during the continuous compression of Pmix(1 : 3) because the powder did not consistently fill the die, resulting in a greater weight variation among Pmix(1 : 3) tablets compared to SD(1 : 3) for all formulations. Weight variation of tablets of CrosPVP was 1.9%; when MS was added to the powder, the weight variation of the tablets increased to 3.1%. For SD(1 : 3), the weight variation among SD(No excipient) tablets was 4.5%; weight variation among

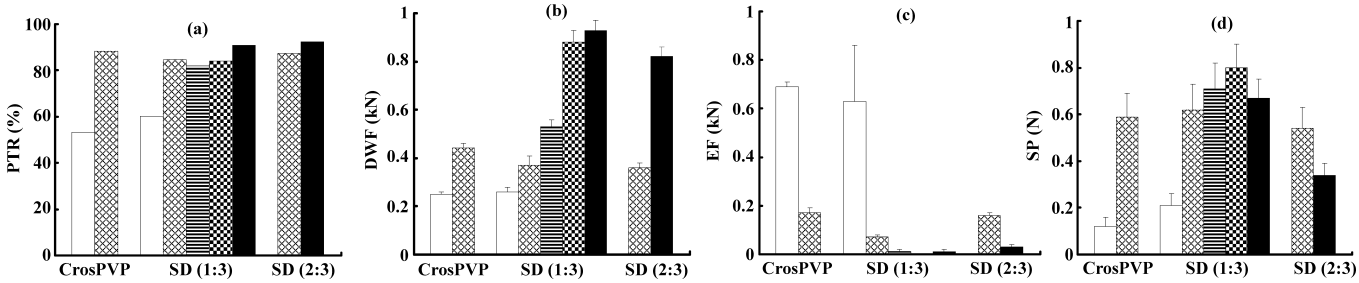

Fig. 3. Compaction Parameters of CrosPVP and SD

(a) PTR; (b) DWF; (c) EF; (d) SP. □, no excipient; ▨, +MS; ▤, +MS+10%MCC; ▩, +MS+30%MCC; ■, +MS+50%MCC.

SD(+MS) tablets was 4.3%. Thus, the MS had no significant effect on tablet weight variation. When MCC was added to the formulations, weight variation among SD(1 : 3) tablets decreased. Thus, MCC affected the weight variation of the tablets. SD(1 : 3) tablets containing various amounts of MCC showed a small weight variation because with MCC possessed greater fluidity than did SD(1 : 3) without MCC, allowing powder to fill consistently from feeder to die.

For SD(2 : 3), the weight variations among SD(+MS) and SD(+MS+50%MCC) tablets were 4.4% and 3.5%, respectively; similar weight variation values were obtained when the IM ratios in the SD were changed.

The hardness of the CrosPVP tablets was 10.4 kg; when MS was added to the powder, hardness of the tablets decreased to 8.3 kg. For SD(1 : 3), the hardness of SD(No excipient) tablets was 13.0 kg and decreased to 11.3 kg upon addition of MS [SD(+MS)], as indicated in previous reports.[15] For SD(1 : 3) formulations containing MCC, tablet hardness was similar to those of SD(No excipient) and SD(+MS). SD(1 : 3) tablets were thought to possess adequate hardness because the characteristics of SD are similar to those of CrosPVP. MCC increased the hardness of Pmix(1 : 3) tablets and SD(1 : 3) tablets, SD(1 : 3) possessed adequate hardness without MCC.

For SD(2 : 3), tablet hardness for SD(+MS) and SD(+MS+50%MCC) was 13.7±0.6 kg and 14.8±1.6 kg, respectively; tablet hardness was similar when the ratio of IM in SD was changed.

Thus, Pmix tablets required MS and MCC, while SD could be compressed directly in all formulations, resulting in tablets with positive features including small weight variation and excellent hardness.

Compaction Property of SD To prevent problems, such as capping and sticking, during the tableting process, the compaction properties of the SD powder must be optimized. We evaluated the compaction properties of SD powder using the parameters: PTR, DWF, EF, and SP.

Compaction parameter results were expressed as the average of 100 tablets, as shown in Fig. 3. The PTR of CrosPVP was 53%, which increased to 88% when MS was added. For SD(No excipient), PTR was 60%. When SD(+MS) was formulated, PTR increased to 85%. Adding MCC did not change its PTR. PTR was improved by MS, but MCC had no effect on PTR.

DWF was determined by measuring the area of tablet contact with the die wall after the upper and lower punch showed maximum values. DWF of CrosPVP was 0.25 kN. Upon addition of MS, it increased to 0.44 kN. For SD(No excipient) and SD(+MS), DWF values were 0.26 kN and 0.37 kN, respectively. When MCC was added, the DWF was higher than that of SD(+MS), and it increased with MCC amount. Both MS and MCC had an effect on DWF.

PTR and DWF are useful parameters to evaluate compaction during tableting.[16—18] High PTR and DWF values indicate favorable compaction properties that prevent problems such as capping during mass manufacturing of tablets.[16,19] The low PTR and DWF values for SD(No excipient) (lowest of the formulations tested) indicated that it may not be suitable for the mass manufacture of tablets. The PTR of SD(+MS) was similar to formulations containing MCC. In contrast, the DWF of SD(+MS) was low in comparison with formulations involving MCC. Thus, SD(+MS+50%MCC), which produced the highest PTR and DWF values, was the optimal formulations in relation to compaction in this study.

EF was measured as the lower punch pressure upon discharge of the tablet from the die wall. The EF value of CrosPVP was 0.69 kN, which decreased to 0.17 kN when MS was added. For SD(No excipient), EF was 0.63 kN, which decreased to 0.07 kN for SD(+MS). When MCC was added, EF became lower than that of SD(+MS), and decreased with increasing MCC. The lowest EF value was obtained for SD with MCC; this formulation also possessed low adhesive force and frictional force during ejection of the tablets from the die cavity. These results agree with those of previous studies reporting that tablet sticking and capping was decreased by the use of MCC.[20]

The SP value was determined using a unit mounted on the head of the TabAll feeder, which measured shear stress between tablet and lower punch surface. The SP of CrosPVP was 0.12 N, which increased to 0.59 N when MS was added. For SD(No excipient), the SP was 0.21 N and increased to 0.62 N upon addition of MS [SD(+MS)]. No tableting problems were encountered with SD(No excipient) or SD(+MS) during compression of 100 tablets. MS is an efficient lubricant in the prevention of the problems such as sticking and picking,[12] and it is thought that adding MS decrease the SP. In the cases of other excipients such as MCC, the SP has a tendency to increase with adding MS (data not shown). It is presumed that it related with PTR increase with adding MS. In the case of SD, MS was no effect on the adhesion to the punch face surfaces with the compressed SD tablet because SD itself has small adhesion character. Adding MCC did not change the SP value for the SD.

Adhesion of the tablet to the scraper head was observed for CrosPVP alone, SD(No excipient), and SD(+MS). The tendency of the tablet to adhere to the scraper head was im-

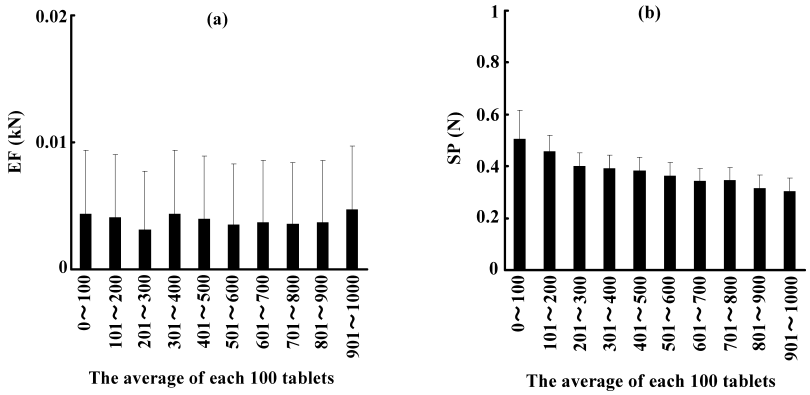

Fig. 4. Comparison of 100-Tablet Averages for SD and EF (a) or SP (b) Values during the Tableting Process

The weight ratio of IM : CrosPVP was 1 : 3 containing +MS+50%MCC.

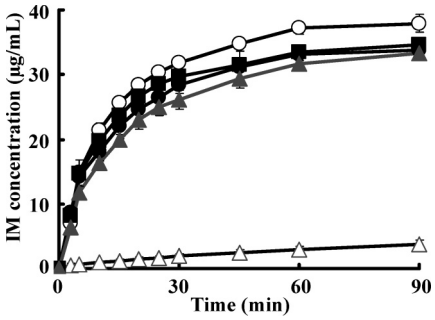

Fig. 5. Dissolution Profiles of IM from Tablets Prepared by SD

▲, SD(No excipient); ●, SD(+MS); ■, SD(+MS+50%MCC); △, IM powder; ○, SD powder. Each data represents the mean±S.D. of 3 experiments.

proved by adding MCC and by removing the scraper head sensor. Problems involving adhesion to the scraper head could be reduced by improving the material composing the scraper head.

EF and SP are useful parameters for predicting tableting problems such as sticking and capping; low EF and SP values are preferable.[18,21] CrosPVP, SD(No excipient), and SD(+MS) had a tendency to stick to the scraper head. By adding MCC, the EF of formulations was decreased, reducing the adhesive tendency of the tablets.

Thus, the formulation containing MS and MCC was optimal from the point of manufacturing.

For SD(2 : 3), compaction properties of SD(+MS) and SD(+MS+50%MCC) were as good as those for SD(1 : 3).

Manufacturing of SD Tablets Tableting complications, such as sticking and capping, occur during tablet manufacturing, by particles generated within tablets adhering to the punch.[21—24] Analysis of the compaction process (PTR, DWF, EF and SP) indicated that SD formulations containing MS and MCC are suitable for tablet manufacture by direct compression. In addition, a formulation containing 50% MCC would allow a dosage of 25 mg indomethacin. Thus, SD(+MS+50%MCC) was chosen for the manufacture of 1000 tablets by direct compression.

The PTR and DWF values of this formulation were 88% and 0.85 kN, respectively, which were maintained during the manufacture of 100 tablets. Figure 4 shows the average values obtained during tablet processing for each batch of 100 tablets. The EF and SP of the last 100 tablets (901—1000) were not significantly different from the values obtained for the first 100 tablets (1—100). Tableting difficulties such as sticking and capping did not occur. The weight variation and hardness of the tablets were 2.4% and 11.5±0.5 kg, respectively. Therefore, SD with MS and MCC using CrosPVP was suitable for manufacture by direct compression.

Influence of Excipient on Dissolution of IM The dissolution of drug from SD is sometimes reduced by preparation of dosage form because the characteristics of SD were changed by excipients added and/or the process.[4] The dissolutions of IM from SD(No excipient), SD(+MS) and SD(+MS+50%MCC) were determined (Fig. 5). The solubility of IM in purified water is 8.5 μg/ml. The improved solubility of IM with forming SD was maintained in all formulations. Since CrosPVP was the original disintegrating agent, the tablet broke up very quickly. Simple procedure and formulation prevented the change of dissolution of IM from SD tablet.

Conclusion

A powder SD prepared by mechanical mixing and heating possessed good fluidity. Although tablets of the SD exhibited small weight variation and adequate hardness and could be produced easily by direct compression, analysis using TabAll indicated that adding magnesium stearate (MS) and microcrystalline cellulose (MCC) to the SD improved the compaction properties. The formulation SD(+MS+50%MCC) containing 25 mg indomethacin was used to manufacture 1000 tablets by direct compression without tableting problems. The improved solubility of IM maintained in SD tablet in all of formulations in this study. Thus, the SD containing MS and MCC and using CrosPVP as a carrier possessed excellent compaction properties and produced tablets by direct compression.

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