Drug Development and Industrial Pharmacy, 32:449–456, 2006
Copyright © Taylor & Francis Group, LLC
ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500529127

Taylor & Francis

Fluidity and Tableting Characteristics of a Powder Solid Dispersion of the Low Melting Drugs Ketoprofen and Ibuprofen with Crospovidone

Yusuke Shibata, Makiko Fujii, Shinobu Noda, Makiko Kokudai, Hideko Okada, Masuo Kondoh, and Yoshiteru Watanabe
Showa Pharmaceutical University, 3-3165 Higashi-Tamagawagakuen, Machida, Tokyo 194-8543, Japan

ABSTRACT A powder solid dispersion system (SD) of ketoprofen (KP) or ibuprofen (IP), which possess low melting points, plus crospovidone (CrosPVP), have good fluidity characteristics and can be used to formulate tablets. Tablets of KP or IP in the SD of adequate hardness within a narrow weight range can be prepared by direct compression. Addition of microcrystalline cellulose (MCC) resulted in greater hardness characteristics and less variation in tablet weight. Forces during the tableting process were measured with a tableting process analyzer (TabAll) equipped with a single-punch for determining capping and sticking properties during the tableting process. Pressure transmission ratio from the upper to the lower punch and die wall force were increased by adding 1% magnesium stearate (MS) to the SD. Ejection force decreased when MS was added to the SD. When tablets of the IP SD were prepared without excipient, scraper pressure (SP) was large, resulting in sticking. However, addition of 1% MS, lowered the SP value and eliminated sticking. Thus, an SD of compounds with a low melting point such as KP or IP is suitable for tablet manufacture by direct compression with the addition of 1% MS.

KEYWORDS Solid dispersion, Crospovidone, Low melting point, Fluidity, Tablet, Direct compression

INTRODUCTION

Solid dispersion systems (SDs) improve the solubility and/or dissolution rate of poorly water-soluble drugs by dispersing a drug in a carrier that renders it amorphous (Sekiguchi & Obi, 1961; Chiou & Riegelman, 1971). However, the method possesses several disadvantages, including manufacturing difficulties due to materials that are soft, tacky, or have poor fluidity in the SD (Ford et al., 1979), and challenges in tablet preparation using the SD which allows unexpected sustained drug release (Serajuddin, 1999). Solid dispersion system (SD) methods also require excipients and a complicated procedure for preparing tablets and capsules (Leuner & Dressman, 2000). Thus, only few products on the market utilize this system.

Address correspondence to Makiko Fujii, Showa Pharmaceutical University, 3-3165 Higashi-Tamagawagakuen, Machida, Tokyo 194-8543, Japan; Tel: +81-42-7211511; Fax: +81-42-7233585; E-mail: fujii@ac.shoyaku.ac.jp

We have developed an SD for indomethacin (IM) with crospovidone (CrosPVP) by mechanical mixing and heating; 1000 tablets of the SD containing 1% magnesium stearate (MS) and 50% microcrystalline cellulose (MCC) can be manufactured by a direct compression method (Fujii et al., 2005; Shibata et al., 2005). Studies have reported that tableting difficulties, such as sticking and picking, occur for materials with low melting points (Danjo et al., 1993). Thus, we evaluated the compaction properties of the SD of ketoprofen (KP, mp, 97°C) and ibuprofen (IP, mp, 74°C) with CrosPVP using a single-punch machine equipped with several force analysis elements.

MATERIALS AND METHODS

Materials

Crospovidone (CrosPVP) (Polyplasdone XL®, USP grade) was a gift from ISP Japan (Tokyo). Ketoprofen (KP) (JP grade) and IP (JP grade) were obtained from Nippon Bulk Yakuhin (Osaka). Microcrystalline cellulose (MCC) (Avicel® PH-102) 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 the Solid Dispersion System

The solid dispersion system (SD) was prepared according to a procedure published previously (Fujii et al., 2005). Briefly, a weight ratio of drug:CrosPVP of 1:3 was used. A physical mixture (Pmix) was obtained by blending a drug and CrosPVP with 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 the melting point of drug, 95°C (KP) or 75°C (IP), for 30 min. Obtained SD was stored in a bottle with a cap at room temperature.

Powder x-ray diffraction pattern (XRD) and thermal analysis data were obtained to examine drug crystallinity in the SD. Powder x-ray diffraction pattern (XRD) data were obtained using an XRD diffractometer (M03X-HF, Mac Science, Yokohama), with Ni-filtered CuKα radiation (40 kV and 30 mA; scanning at width of steps 0.1° per 2.0 s over the range of $2\theta = 5 \sim 30$ degrees). Thermal analysis was conducted using differential scanning calorimetry (DSC, Thermoflex TAS200, Rigaku, Tokyo). Samples containing 1 mg of test compound were sealed in an aluminum crimp cell and heated at a rate of 20°C/min under a nitrogen atmosphere.

Powder Fluidity of the Solid Dispersion System 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, and was calculated from Kawakita's equation (Kawakita, 1956) using data from 200 tapping points obtained with a tapping density analyzer (Tapdenser KYT-1000® Seishin Enterprise, Tokyo) equipped with a 20-mL cylinder.

Results of these measurements were shown as the mean of three determinations.

Tablet Preparation

The solid dispersion system (SD) or mixture of SD and MCC with or without 1% MS as lubricant (Table 1) was directly compressed into 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 was also directly compressed into tablets.

TABLE 1 Formulation of Tablets

	No excipient	+MS	+MS + MCC
SD or Pmix	200	200	100
MCC			100
MS		2	2
Total (mg)	200	202	202

Tablet Characterization

Weight variation among tablets was determined on 20 tablets. Tablet crushing strength (hardness) was measured with a digital crushing tolerance-measuring machine (TS-50N®, Okada Seiko, Tokyo) and expressed as the mean ± S.D. of 20 tablets.

Measurement of Compaction Parameters

Compaction properties of the materials were determined using a TabAll instrument which measures seven parameters during compaction: upper punch displacement, lower punch displacement, upper punch force, lower punch force, die wall force (DWF), ejection force (EF), and scraper pressure (SP). Data were recorded using DAATSU II software (Okada Seiko Co., Tokyo). During force parameter measurements, 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. Data presented are averages of 100 tablets.

Dissolution Studies

Dissolution of KP from various forms containing 450 mg of KP was tested at 37°C using a JP dissolution test apparatus with 900 mL purified water and a rotation of paddle at 100 rpm. Ketoprofen (KP) concentration was determined by UV absorption at 260 nm.

RESULTS AND DISCUSSION

Preparation of Solid Dispersion System

Figure 1 shows XRD patterns and DSC curves. For both IP and KP, the Pmix contains drug crystals according to XRD patterns and endothermic peaks of melting points in the DSC curves. The solid dispersion system (SD) shows no drug peaks, confirming that the KP and IP in the SD existed in an amorphous state. This phenomenon may be due to interactions between carboxyl groups of KP or IP and amide carbonyl groups of CrosPVP (Shibata et al., submitted). The Ketoprofen (KP) and IP SDs were designated as KP (SD) and IP (SD), respectively. As prepared, the SD exists as powder that does not require crushing. Thus, the resulting SD was sieved at a mesh size of 180 μm.

SD Fluidity with KP or IP

Previously, we reported the fluidity and direct tableting ability of the SD of IM with CrosPVP (Fujii et al., 2005; Shibata et al., 2005). Here, we examined the suitability of the KP and IP SDs for direct tableting. Table 2 compares the fluidity characteristics of SD and related materials. CrosPVP, which has been used as a super-disintegrant (Visavarungroj & Remon, 1990), showed good fluidity with an angle of repose and CI of 28° and 28%, respectively. Ketoprofen (KP) or IP alone had poor fluidity and packability characteristics. For KP, the angle of repose and CI of the SD

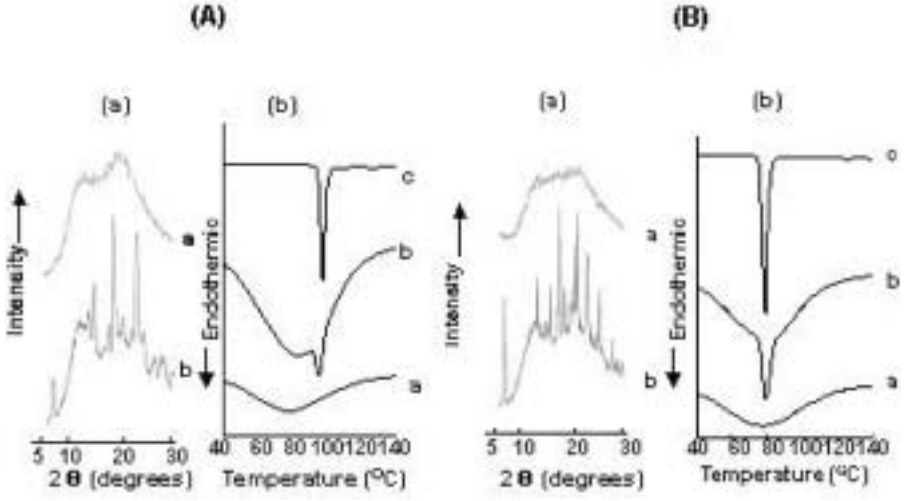

FIGURE 1 X-ray Diffraction Patterns (a) and DSC Curves (b) of SD and Related Materials (A) KP, (B) IP; a, SD; b, Pmix; c, drug.

TABLE 2 Characteristics of Fluidity of SD and Related Materials

		Angle of repose (°)	CI (%)
CrosPVP		28	28
KP	crystals	50	ND
	Pmix	48	45
	SD	38	28
IP	crystals	58	41
	Pmix	ND	ND
	SD	ND	ND
	SD*	40	30

ND: Could not be determined because of low fluidity.
SD*: SD prepared at 100°C.

were lower than those of the Pmix, suggesting that fluidity and packability improved when the Pmix was formulated as the SD. In contrast, the angle of repose and CI of the Pmix and SD of IP could not be determined because of the high cohesivity and adhesivity of IP (Rasenack & Muller, 2002). When the preparation temperature of IP(SD) was increased from 75°C to 100°C [IP(SD*)], the angle of repose and CI were 40° and 30%, respectively. The fluidity of IP(SD) prepared at 75°C differed from that of the IP(SD*) prepared at 100°C. The powder x-ray diffraction (XRD) pattern and DSC curve were not influenced by heating temperature. When the amount of IP in the SD was decreased to 1:9, angle of repose and CI were 36° and 28%, respectively, raising the possibility that the distribution of IP in CrosPVP was affected by heating temperature and that IP is localized deeper into the CrosPVP popcorn cavity (Carli & Garbassi, 1985) rather than on the surface of CrosPVP when heated at 100°C.

The angle of repose should be less than 45° (Oya et al., 1989; Wadke et al., 1990) for tablets prepared by direct compression. Therefore, these results indicate that the fluidity of the SDs of KP and IP allows direct compression.

Effect of MS and MCC on Fluidity

Figure 2 shows the effect of MS and MCC on powder fluidity characteristics of the SDs. Ibuprofen physical mixture [IP(Pmix)] exhibited high cohesivity and adhesivity, even upon addition of MS and MCC, although the angle of repose and CI could not be determined.

Magnesium stearate (MS) is an efficient lubricant that promotes powder fluidity during material flow, eliminates binding of the compact to the die, and minimizes sticking and picking to the punch surfaces (Shah & Mlodozeniec, 1977). In all cases, no changes in angle of repose and CI were observed when MS was added as an excipient. Microcrystalline cellulose (MCC) improved the fluidity and packability of KP(Pmix). In contrast, MCC had little effect on SD fluidity and packability because the SD already possessed good fluidity. Thus, MS and MCC exerted little effect on SD fluidity, although MCC improve fluidity of the KP(Pmix).

Characteristics of Physical Mixture and Solid Dispersion Tablets

Various formulations of Pmix and SD tablets (shown in Table 1) were characterized using the direct compression method. Figure 3 shows the effect of excipients on weight variation and tablet hardness of

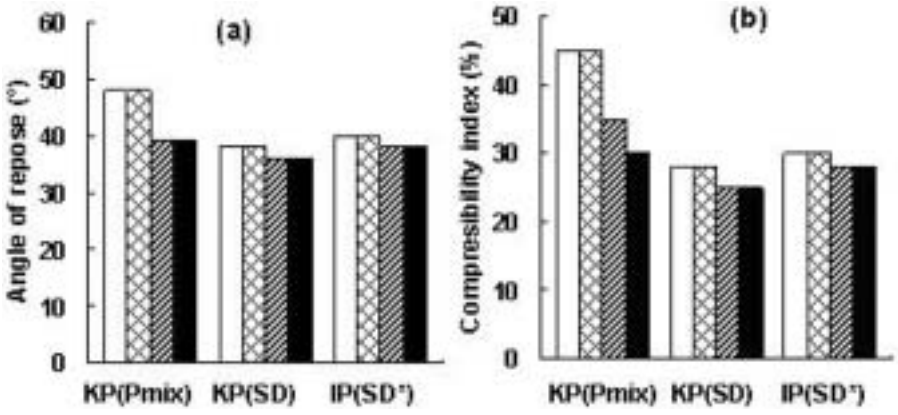

FIGURE 2 Characteristics of SD and Related Materials from the Point of Powder Fluidity: (a) Angle of Repose (°); (b) Compressibility Index (%). □, No Excipient; ▨, +MS; ▩, +MCC; ■, +MS + MCC. Both Parameter of IP(Pmix) and Related Materials Could Not Be Determined Because of Poor Fluidity.

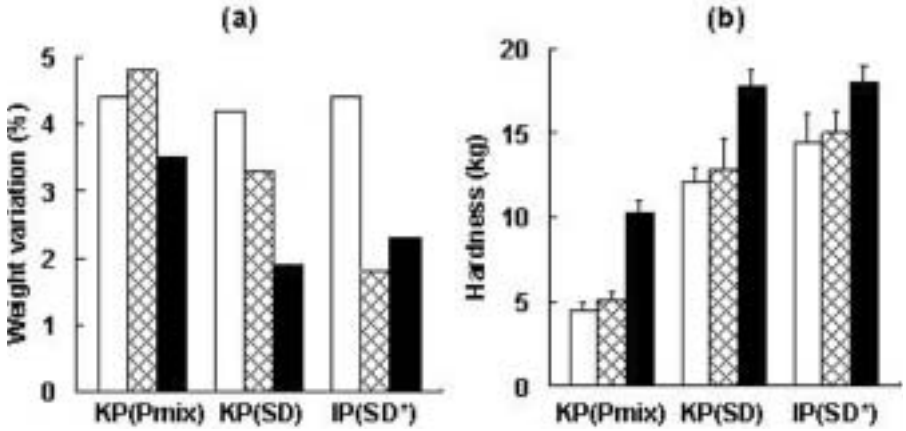

FIGURE 3 Weight Variation (a) or Hardness (b) of the Tablets of SD and Related Materials. □, No Excipient; ▨, +MS; ■, +MS + MCC. IP(Pmix) and Related Materials Could Not Be Tableting Because of Poor Fluidity.

SD and related materials. Ibuprofen physical mixture [IP(Pmix)] tablets could not be prepared by direct compression because of low fluidity. Difficulties were encountered during continuous compression without an excipient because the powder did not consistently fill the die resulting in a weight variation greater than 4%. For KP(Pmix), formulation with MS and MCC showed the wide variation in tablet weight, 3.5%, supposedly because fluidity was not improved enough. For KP(SD), the weight variation among tablets of the SD with no excipient was 4.2% which decreased to 3.3% by adding MS and to 1.9% by further addition of MCC. When MS or MS and MCC was added to the formulations, weight variation among IP(SD*) tablets decreased to 1.8% and 2.3%, respectively. Thus, MS and MCC were effective in reducing weight variation among tablets.

Figure 3(b) shows the hardness of various formulations. When CrosPVP was compressed under identical conditions, resulting tablet hardness was 10.4 kg. Tablets of KP(Pmix) with no excipient had a hardness of 4.5 kg which increased to 10.2 kg upon addition of MCC. The hardness of KP(SD) tablets was 12.1 kg with no excipient and 12.8 kg with MS. The hardness of IP(SD*) tablets was 14.4 kg with no excipient and 15.0 kg with addition of MS. Previous reports indicated that MS might negatively affect tablet hardness (Regnarsson et al., 1979), but the hardness of tablets was not changed by MS addition to KP(SD) and IP(SD*). Addition of MCC did increase the hardness of KP(Pmix), KP(SD), and IP(SD) tablets. SD tablets possessed adequate hardness with characteristics similar to those of CrosPVP.

Thus, formulations were developed that provided tablets with no wide variation in weight or hardness problems. For tablets with small weight variation and excellent hardness, both MS and MCC were required for Pmix, while only 1% MS was needed for SD.

Compaction Properties of Solid Dispersion

Tableting difficulties such as sticking and picking occur readily in materials with low melting points (Danjo et al., 1993). To prevent such problems during the tableting process, the compaction properties of the SD powder must be optimized. We evaluated the compaction properties of SD powder using PTR, DWF, EF, and SP.

Compaction parameter results were expressed as the average and standard deviation of 100 tablets (Table 3), except in the case of IP(SD*) with no excipient, which experienced sticking during tableting and was difficult to manufacture more than 70 tablets continuously.

Pressure transmission ratios (PTRs) of SD with no excipient were 51% and 55% for KP and IP, respectively. When MS was added to the formulation, PTR increased to 89% (KP) and 75% (IP). Adding MCC did not change the PTR of KP(SD), but increased PTR slightly of IP(SD*). Thus, MS improved PTR significantly, but MCC had little or no effect on PTR.

Die wall force (DWF) value of KP(SD) with no excipient was 0.22 kN. Addition of MS increased DWF, but decreased it with MCC. Die wall force (DWF) of MCC with MS was 0.72 kN, thus, the

TABLE 3 Compaction Parameters of SD Tablets With or Without Excipient

		PTR (%)	DWF (kN)	EF (kN)	SP (N)
KP (SD)	no excipient	50.9 ± 0.5	0.22 ± 0.01	0.38 ± 0.01	0.35 ± 0.04
	+MS	88.9 ± 0.8	1.62 ± 0.22	0.00 ± 0.00	1.07 ± 0.22
	+MS + MCC	85.4 ± 0.6	0.97 ± 0.02	0.00 ± 0.00	0.6 ± 0.08
IP (SD)	no excipient*	55.6 ± 0.5	0.23 ± 0.05	0.05 ± 0.02	5.02 ± 4.63
	+MS	75.3 ± 0.6	0.50 ± 0.04	0.00 ± 0.01	1.13 ± 0.17
	+MS + MCC	82.0 ± 0.5	0.40 ± 0.04	0.00 ± 0.00	1.03 ± 0.12

*Average of 70 tablets.

characteristics of MCC might have some influence. For IP(SD*) without excipient, DWF was 0.23 kN, similar to that for KP(SD). However, when MS was added, DWF increased to 0.50 kN, significantly lower than the value found for KP(SD), indicating that MS increases DWF with different extent.

Pressure transmission ratio (PTR) and DWF are useful parameters to evaluate compaction during tableting (Bessho et al., 1969; Doelker & Massuelle, 2004; Takeuchi et al., 2004). High PTR and DWF values indicate favorable compaction properties that prevent problems such as capping during mass manufacturing of tablets (Bessho et al., 1969; Shotton & Obiorah, 1975). The low PTR and DWF values for SD with no excipient indicated that this formulation may not be suitable for the mass manufacture of tablets. When MS or MS and MCC were added to SD, PTR and DWF increased, as in the case of indomethacin solid dispersion with CrosPVP (Shibata et al., 2005). Thus, SD with added MS or MS and MCC produce optimal formulations for compaction.

Ejection force (EF) was measured as the lower punch pressure upon discharge of the tablet from the die wall. Ejection force (EF) values for KP(SD) and IP(SD*) with no excipient were 0.38 kN and 0.03 kN, respectively. Magnesium stearate (MS) or MS and MCC addition to KP (SD) and IP (SD*) reduced EF to 0.01 or 0.00 kN. These formulations possess low adhesive force and frictional force during ejection of the tablets from the die cavity and agree with data from previous studies that show tablet sticking and capping decreases upon addition of MS or MCC (Shibata et al., 2005; Ichibagase et al., 1990).

The scraper pressure (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. Scraper pressure (SP) of KP(SD) with no excipient was 0.35 N, and increased to 1.07 N or 0.60 N upon addition of MS or MS and MCC, respectively. No tableting problems were encountered with the formulations during compression of 100 tablets. Magnesium stearate (MS) is an efficient lubricant that prevents sticking and picking (Shah & Mlodozeniec, 1977), and thus it should decrease SP. The same phenomenon was observed with MCC: SP increased with MS addition (data not shown). Increasing SP value might be related with PTR increase with adding MS. Magnesium stearate (MS) had no effect on adhesion of KP(SD) tablets to the punch face surfaces because the SD itself causes little adhesion. Adding MCC did not change the SP value for SD.

For IP(SD*) with no excipient, sticking was observed during tableting, increasing SP value significantly to 6 N (Fig. 4). The melting point of IP is lower than that of KP (Danjo et al., 1993) resulting in strong adhesion, therefore, sticking was observed. Scraper pressure (SP) decreased to 1.13 N and 1.03 N upon addition of MS or MS and MCC, respectively. Magnesium stearate (MS) was a useful excipient to prevent sticking for IP(SD*).

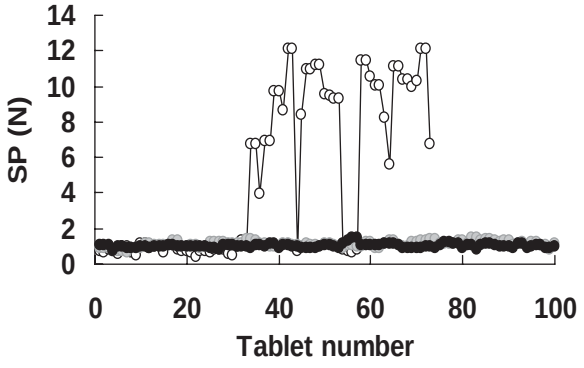

FIGURE 4 Change of SP Value During Tableting of IP (SD*) With or Without Excipient. ○, No Excipient; ▒, +MS; ●, +MS + MCC.

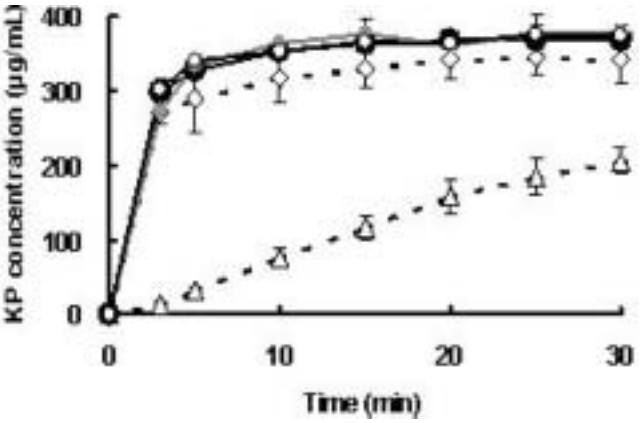

FIGURE 5 **Dissolution of KP from Various Form. Tablet of SD With No Excipients, ○; +MS, ◍; +MS + MCC, ●. KP Powder, △ SD Powder, ◇.**

Ejection force (EF) and SP are useful parameters for predicting tableting problems such as sticking and capping; low EF and SP values are preferable (Takeuchi et al., 2004; Naito et al., 1977; Watanabe et al., 1998). By adding MS, EF was decreased, reducing adhesive tendency of the tablets. Thus, the formulation containing MS was optimal from a manufacturing view.

Analysis of the compaction process (PTR, DWF, EF, and SP) indicated that SD with MS formulations of KP and IP, which have low melting points, are suitable for tablet manufacture by direct compression.

Influence of Excipient on Dissolution of Ketoprofen

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. The dissolutions of KP from the tablets of SD(No excipient), SD(+MS), and SD(+MS + 50%MCC) were determined (Fig. 5). The improved solubility of KP with forming SD was maintained in all formulations.

CONCLUSIONS

Solid dispersions with the low melting point drugs, ketoprofen and ibuprofen, prepared by mechanical mixing and heating possessed good fluidity. Tablets of the solid dispersions exhibited small weight variation and adequate hardness and could be produced easily by direct compression. Analyses using TabAll indicated that adding magnesium stearate is needed for manufacturing. Further addition of microcrystalline cellulose improved the weight variation and hardness of tablets. Thus, a solid dispersion formulation of ketoprofen or ibuprofen with magnesium stearate and microcrystalline cellulose is suitable for tablet manufacture by direct compression.

ACKNOWLEDGMENTS

We are grateful to ISP Japan for providing CrosPVP.

REFERENCES

Bessho, S., Tomioka, S., & Ito, S. (1969). Studies on the compression of powderlike materials. III. Proposition of some experimental equations for the pressure transmission in compression direction and a presumption equation for the pressure transmission ratio in mixture and multi-layer compression. *Yakugaku Zasshi*, *89*, 599–606.

Carli, F., & Garbassi, F. (1985). Characterization of drug loading in crospovidone by X-ray photoelectron spectroscopy. *J. Pharm. Sci.*, *74*, 963–967.

Chiou, W. L., & Riegelman, S. (1971). Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, *60*, 1281–1302.

Danjo, K., Kamiya, K., & Otsuka, A. (1993). Effect of temperature on the sticking of low melting point materials. *Chem. Pharm. Bull.*, *41*, 1423–1427.

Doelker, E., & Massuelle, D. (2004). Benefits of die-wall instrumentation for research and development in tabletting. *Eur. J. Pharm. Biopharm.*, *58*, 427–444.

Ford, J. L., Stewart, A. F., & Rubinstein, M. H. (1979). The assay and stability of chlorpropamide in solid dispersion with urea. *J. Pharm. Pharmacol.*, *31*, 726–729.

Fujii, M., Okada, H., Shibata, Y., Teramachi, H., Kondoh, M., & Watanabe, Y. (2005). Preparation, characterization, and tableting of solid dispersion of indomethacin with crospovidone. *Int. J. Pharmaceut.*, *293*, 145–153.

Ichibagase, H., Uekama, K., & Odagiri, M., Eds. (1990). *Pharmaceutical Research and Development.* Hirokawa, Tokyo, vol. 12, 156–177.

Kawakita, K. (1956). Compression of powder. *Kagaku*, *26*, 149–150.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.*, *50*, 47–60.

Naito, S., Masui, K., & Shiraki, T. (1977). Prediction of tableting problems such as capping and sticking: Theoretical calculations. *J. Pharm. Sci.*, *66*, 254–259.

Oya, A., Nakai, Y., Nagai, E., & Takei, Y. (1989). Comprehensive course for pharmaceutical technology: compression and consolidation (1). *Pharm. Tech. Japan.*, *5*, 1199–1201.

Rasenack, N., & Muller, B. W. (2002). Ibuprofen crystals with optimized properties. *Int. J. Pharmaceut.*, *245*, 9–24.

Ragnarsson, G., Holzer, A. W., & Sjogren, J. (1979). The influence of mixing time and colloidal silica on the lubricating properties of magnesium stearate. *Int. J. Pharmaceut.*, *3*, 127–131.

Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic mixtute. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem. Pharm. Bull.*, *9*, 886–872.

Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.*, *88*, 1058–1066.

Shah, A. C., & Mlodozeniec, A. R. (1977). Mechanism of surface lubrication: Influence of duration of lubricant-excipient mixing on processing characteristics of powders and properties of compressed tablets. *J. Pharm. Sci.*, *66*, 1377–1382.

Shibata Y., Fujii M., Kokudai M., Noda S., Okada H., Kondoh M., & Watanabe Y. (submitted). Effect of characteristics of compounds on keeping amorphous state in solid dispersion with crospovidone.

Shibata, Y., Fujii, M., Okada, H., Noda, S., Kondoh, M., & Watanabe, Y. (2005). Evaluation of the compaction properties of a solid dispersion of indomethacin with crospovidone by tableting process analyzer. *Chem. Pharm. Bull.*, *53*, 759–763.

Shotton, E., & Obiorah, B. A. (1975). Effect of physical properties on compression characteristics. *J. Pharm. Sci.*, *64*, 1213–1216.

Takeuchi, H., Nagira, S., Yamamoto, H., & Kawashima, Y. (2004). Die wall pressure measurement for evaluation of compaction property of pharmaceutical materials. *Int. J. Pharmaceut.*, *274*, 131–138.

Visavarungroj, N., & Remon, J. P. (1990). Crosslinked starch as a disintegrating agent. *Int. J. Pharmaceut.*, *62*, 125–131.

Wadke, D., Serajuddin, A. T. M., & Jacobson, H. (1990). Preformulation testing. In *Pharmaceutical Dosage Forms: Tablets*, Lieberman, H. A., Lachman, L., & Schwartz, J. B., Eds.; New York: Marcel Dekker, vol. 1, 1–74.

Watanabe, Y., Endo, K., Koizumi, K., & Matsumoto, M. (1998). A new compression tableting method using a punch coated with amorphous alloy. *J. Pharm. Sci. Technol, Jpn.*, *58*, 147–154.

Copyright of Drug Development & Industrial Pharmacy is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.