ELSEVIER

International Journal of Pharmaceutics 249 (2002) 71–79

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Preparation and dissolution characteristics of griseofulvin solid dispersions with saccharides

Masataka Saito, Takashi Ugajin, Yasuo Nozawa *, Yasuyuki Sadzuka, Atsuo Miyagishima, Takashi Sonobe

School of Pharmaceutical Science, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan

Received 25 February 2002; received in revised form 13 July 2002; accepted 8 August 2002

Abstract

To improve the solubility of poorly water-soluble drugs, we studied physical characteristics of griseofulvin (GF) solid dispersions with saccharides as the dispersion carrier using a roll mixing method. In all carriers tested, roll mixtures of GF and saccharides gradually became amorphous, and the solubility of GF increased. The solubility of GF was higher in the mixtures with higher molecular weight carriers such as corn starch and processed starch. The dissolution of GF was markedly improved by the GF–Britishgum roll mixture. The initial dissolution rate of these mixtures was 170-fold higher than GF alone. The surface tension of carrier aqueous solutions was low in the processed starch with branched sugar chains. The initial dissolution rate of GF in physical mixtures was correlated with the surface tension of carrier aqueous solutions. The stability of the amorphous state of GF at a high humidity was maintained in the mixtures with carriers with a high molecular weight. These results indicated that the solubility of GF was markedly improved in the roll mixtures. It was suggested that the saccharides with a high molecular weight are useful carriers for solid dispersions.

Keywords: Solid dispersion; Roll mixing; Saccharides; Corn starch; Processed starch; Griseofulvin

1. Introduction

To improve the solubility of poorly water-soluble drugs, solid dispersion techniques using organic solvents in which both carrier and drug are dissolved are used. However, these techniques have problems such as negative effects of the solvents on the environment, and high cost of production due to extra facility for removal of solvents (Serajuddin, 1999). Preparation of solid dispersions without using solvents is mechanically performed by the co-ground mixing, for example ball mixing or roll mixing methods. The advantage of these methods is that they require no drying process.

It has been reported that the solubility of griseofulvin (GF) was improved by roll mixing with linear dextrin or starch as the carrier (Saito et al., 2001). In the present study, solid dispersions were prepared using highly soluble disaccharides and processed starch as carriers. Pregelatinized

* Corresponding author. Tel.: +81-54-264-5611; fax: +81-54-264-5615

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00455-6

corn starch, roast dextrin and British gum were used as the processed starch. Pregelatinized corn starch shows high water-swelling, while roast dextrin (yellow dextrin) has a multibranching structure (Brimhall, 1944) and a high solubility in cold water. British gum, of which the molecular weight and the degree of branching are higher than roast dextrin, has a very high solubility also in cold water.

Attempts to improve the solubility of drugs have been performed using saccharides with a low molecular weight such as mannitol (Takahata et al., 1992; Kubo et al., 1996; Kubo and Mizobe, 1997), using a co-ground mixture with crystalline cellulose (Yamamoto et al., 1974, 1976), and using starch particles covered with drug crystal powders by a hybridizer (Ishizaka et al., 1988, 1989, 1993). Other methods that have been reported include a solid dispersion method with the melting process using saccharides with a low molecular weight (Allen et al., 1977; Ghanem et al., 1980; Danjo et al., 1997; Hirasawa et al., 1999), the spray-dry method using saccharides as the core material (Takeuchi et al., 1987), and controlled release of drugs with saccharides as the carrier (Lenaerts et al., 1991; Wierik Te et al., 1993; Chebli and Cartilier, 2000; Henrist et al., 1999; Henrist and Remon 1999a,b). However, there have been only few studies on the improvement of the solubility of drugs using dextrin and processed starch. In the present study, we investigated feasibility of a roll mixing method for preparing solid dispersion of GF, which is a model of poorly water-soluble drug.

2. Materials and methods

2.1. Materials

Griseofulvin (JPXIV griseofulvin, GF), maltose (Mal), lactose (Lac) and corn starch (CornS) (Wako Pharmaceuticals Inc.) were purchased. Linear dextrin (Amycol®10 (Amy10): mean M.W. 1000), Amycol®6H (Amy6H): mean M.W. 3000), pregelatinized corn starch (AMCOL®C (AmyC): mean M.W. is near corn starch), roast dextrin (Dextrin JP® (DexJ)), British gum (Britishgum APA® (BriG)) were provided from Nippon Starch Chemical Co., Ltd. DexJ and BriG have mixture of ingredient starch and processed starch, so these mean M.W. are not definite. However, BriG is processed more mild condition, so its molecular has high branches and high M.W. than DexJ. Distilled water that had been treated by ion exchange was used.

2.2. Preparation of roll mixtures

A roller mill (Kodaira Engineering Inc.) with three horizontal ceramic rollers (14.5 × 6.35 cm ϕ) at a rotation ratio of 1:2.5:5.8 was used. The low rate roller at 20 per min and intermediate roller at a rate of 50 per min were used to mix samples. The clearance between the rollers was set as 60 μm. Powders were supplied to the rollers attached to the intermediate rotation roller, and were continuously compressed and mixed by high shearing stress in the gap between the rollers.

To determine an optimal mixing ratio of GF and carriers, we used CornS as a carrier and prepared roll mixtures at different mixing ratios of GF to CornS, i.e. GF: CornS = 1:2–1:10. It was found that at GF: CornS = 1:2, the solubility of GF did not sufficiently increase and at GF: CornS = 1:8 and 1:10, due to predominant amount of CornS, the mixtures were poorly dispersed in the dissolution medium, causing low dissolution of GF. Also, powder X-ray diffraction intensities of GF in these samples were too small, compared with ratios of GF to CornS 1:3–1:6, to detect the grinding effect of GF by roll mixing. Therefore, a ratio of GF to CornS of 1:4 was selected for further tests in this study.

To prepare roll mixtures, 1.0 g mixture of GF and carrier powders at a weight ratio of 1:4 was lightly mixed in a mortar for about 1 min (physical mixture), and mixed using the roller mill for 5, 20 and 40 min. Because disaccharide carriers firmly attached to the rollers while mixing, 40 min mixing was not performed. Mixtures for measurement were prepared at the range of particle sizes between 45 and 150 μm.

2.3. Powder X-ray diffraction studies

Powder X-ray diffraction study was performed with a powder X-ray diffraction apparatus (RAD-C, Rigaku Denki Co., Ltd.) using CuKα radiation at 30 kV and 50 mA at room temperature. The scanning rate was 5°/min, and diffraction angle (2θ) was 2–30° used.

2.4. Thermal analysis

Thermal analysis was performed using 10 mg of the samples (2 mg of GF contained) at a temperature heating rate of 5 °C/min within a temperature range of 30–300 °C. A differential scanning calorimeter (DSC100, Seiko Electronics Inc.) was used.

2.5. Dissolution tests

Dissolution tests were performed by the JPXIV paddle method using 900 ml of JPXIV 2nd fluid (pH6.8). A powder sample equivalent to 15 mg GF (GF alone: 15 mg, other mixtures: 75 mg) was subjected to the dissolution test for up to 8 h ($n = 3$). The apparatus used for the dissolution tests and the test conditions were as follows:

Flow cell automatic dissolution test apparatus (NTR-VS6P, Toyama Industry Inc.), spectrophotometer (UV-160A, Shimadzu Inc.), and cell heat insulator (CPS-240B, Shimadzu Inc.). Measurement wavelength, 295.3 and 330 nm; measurement temperature, 37±0.5 °C; paddle rotation rate, 100 rpm.

2.6. Stability tests

The stability of amorphous GF was evaluated by the rate of recrystallization as measured by powder X-ray diffraction after standing the samples at 40±2 °C and at 75%RH±5% for the indicated time. The humidity was adjusted in a desiccator with a saturated solution of NaCl. The samples prepared by roll mixing for 40 min were used.

2.7. Measurement of the surface tension

The surface tension in 5% solution (w/v) of a carrier material dissolved in 200 ml water at 21 °C was determined using a Du Nouy surface tension meter (TAIHEI RIKA Co., Ltd.). The surface tension was measured five times, and expressed as the means±S.D. The outer diameter of the platinum ring in the surface tension meter was 13.27 mm, the inner diameter was 12.45 mm, and the diameter of the wire was 0.41 mm. The diameter of the piano wire was 0.28–0.29 mm.

3. Results and discussion

3.1. Properties of GF in the roll mixtures

The intensional peaks of GF by powder X-ray diffraction were observed at 10.8, 13.3, 14.7, 16.6, 24.0, 26.0 and 28.6°. The disaccharide carriers showed high crystalline peaks (Fig. 1-B), while the polysaccharide carriers showed halo patterns (Fig. 2-B, Fig. 3-B). In the physical mixture of Mal and GF, diffraction peaks derived from both materials were present (Fig. 1-C). These peaks were markedly attenuated in the sample prepared by roll mixing for 5 min, and almost disappeared in the sample prepared by roll mixing for 20 min. In the

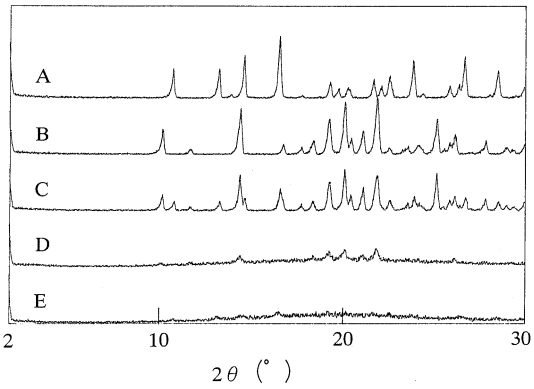

Fig. 1. Powder X-ray diffraction patterns of GF–Mal mixtures A, GF alone; B, CornS alone; C, physical mixture D, roll mixture (mixing duration 5 min); E, roll mixture (mixing duration 20 min).

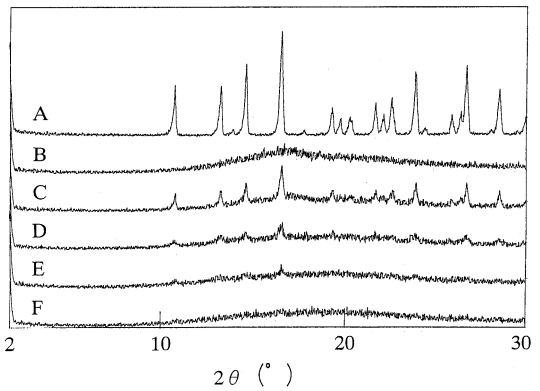

Fig. 2. Powder X-ray diffraction patterns of GF–Amy6H mixtures A, GF alone; B, CornS alone; C, physical mixture D, roll mixture (mixing duration 5 min); E, roll mixture (mixing duration 20 min); F, roll mixture (mixing duration 40 min).

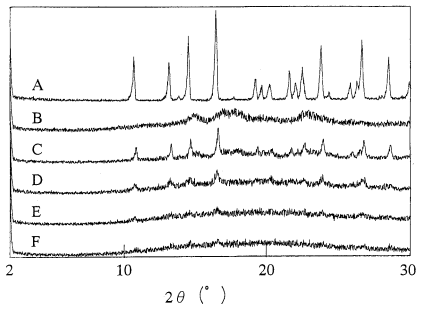

Fig. 3. Powder X-ray diffraction patterns of GF–CornS mixtures A, GF alone; B, CornS alone; C, physical mixture D, roll mixture (mixing duration 5 min); E, roll mixture (mixing duration 20 min); F, roll mixture (mixing duration 40 min).

mixture of Lac and GF, the amorphous pattern of GF was similar to that of GF–Mal mixture.

As shown in Fig. 2-F, Fig. 3-F, the diffraction peaks of GF almost disappeared in the samples of polysaccharides roll mixing for 40 min.

Fig. 4 shows the results of DSC measurement of the mixtures of CornS and GF. An endothermic peak by melting of GF was observed at 219 °C, while an endothermic peak of CornS by dehydration at about 100 °C and a peak by thermal decomposition at higher than 260 °C were observed. GF crystals were not detected in the samples prepared by 40 min roll mixing by powder X-ray diffraction analysis, but the DSC measurement revealed clear endothermic peaks and the

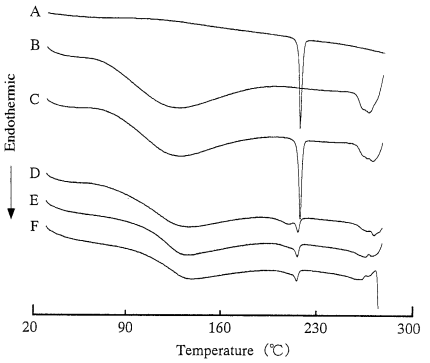

Fig. 4. The DSC thermograms of GF–CornS mixtures A, GF alone; B, CornS alone; C, physical mixture; D, roll mixture (mixing duration 5 min); E, roll mixture (mixing duration 20 min); F, roll mixture (mixing duration 40 min).

enthalpy changes of mixtures were about 26% of GF crystals, suggesting existence of small quantity of GF crystals in mixtures. Because the peak by melting of Mal and Lac crystals at about 227 °C and 207 °C, respectively, overlapped with that of GF in the GF–Mal mixture and GF–Lac mixture, it was difficult to confirm the generation of the amorphous body of GF. In the mixtures of GF and any of the carrier materials prepared by 5 min roll mixing, the enthalpy changes of mixtures were about 50% of GF crystals, suggesting existence of small quantity of GF crystals in mixtures. The amount of GF crystals in the samples prepared by 40 min roll mixing was similar to that in the samples by 20 min roll mixing.

3.2. Solubility of GF

Figs. 5–8 show the profile of the dissolution of GF in the GF–Mal, GF–Amy6H, GF–CornS and GF–BriG mixtures, respectively. Fig. 9 shows the initial dissolution rate of GF in these mixtures. The initial dissolution rate of GF was calculated assuming that dissolution of GF follows apparent zero (0) order kinetics, i.e. the quantity of dissolved drug at 5 min was divided by the dissolution time.

The dissolution of GF in the GF–Lac mixture was similar to that in the GF–Mal mixture shown in Fig. 5. In the mixtures of GF and the disaccharide carriers, a good dispersion of GF to

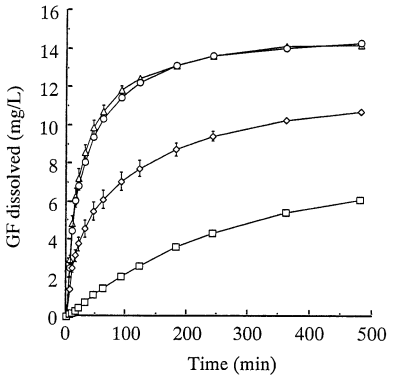

Fig. 5. Dissolution profiles of GF in various mixtures with and without Mal ($n = 3$) (□) GF alone, (◇) physical mixture, (○) roll mixture (mixing duration 5 min), (△) roll mixture (mixing duration 20 min).

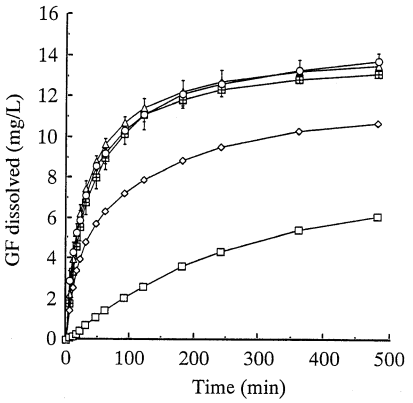

Fig. 6. Dissolution profiles of GF in various mixtures with and without Amy6H ($n = 3$) (□) GF alone, (◇) physical mixture, (○) roll mixture (mixing duration 5 min), (△) roll mixture (mixing duration 20 min), (⊞) roll mixture (mixing duration 40 min).

the solution was obtained. In both samples, the concentration of GF was almost the same 120 min after the start of dissolution. The GF–Lac roll mixture showed results similar to the GF–Mal roll mixture. As shown in Fig. 9, the initial dissolution rate of GF powders alone was very low, while the initial dissolution rates of GF in physical and roll mixtures of GF–disaccharide carriers improved to about 15-fold and 30–45-fold higher, respectively, than that in GF powders alone.

Fig. 6 shows the results with the GF–Amy6H mixture. The solubility of GF in the GF–Amy10

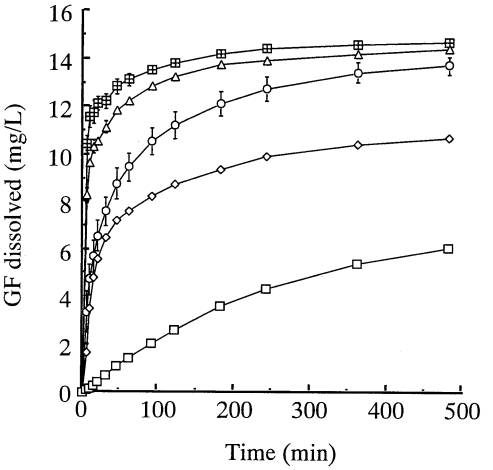

Fig. 7. Dissolution profiles of GF in various mixtures with and without CornS ($n = 3$) (□) GF alone, (◇) physical mixture, (○) roll mixture (mixing duration 5 min), (△) roll mixture (mixing duration 20 min), (⊞) roll mixture (mixing duration 40 min).

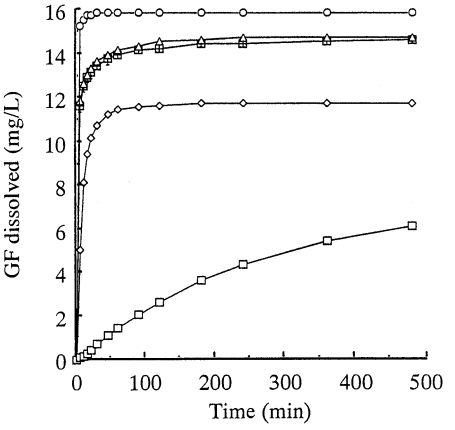

Fig. 8. Dissolution profiles of GF in various mixtures with and without BriG ($n = 3$) (□) GF alone, (◇) physical mixture, (○) roll mixture (mixing duration 5 min), (△) roll mixture (mixing duration 20 min), (⊞) roll mixture (mixing duration 40 min).

mixture was similar to that in the GF–Amy6H mixture. The initial dissolution rate of GF in the roll mixtures with linear dextrins was lower than that in the roll mixtures with disaccharides, which are highly water-soluble.

It has been reported that tablets containing amylodextrin as the main excipient decomposed slowly and the dissolution of drug components

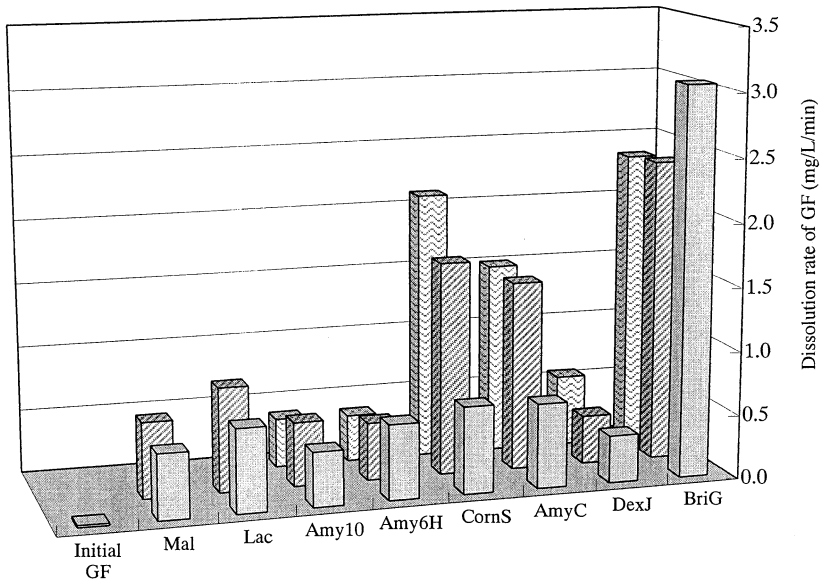

Fig. 9. Initial dissolution rate of GF in various roll mixtures (▨) mixing duration 5 min, (▨) mixing duration 20 min, (▨) mixing duration 40 min.

was slow (Wierik Te et al., 1993). Amy10 and Amy6H have a linear structure similar to amylodextrin; thus, it was considered that the GF–Amy10 and GF–Amy6H roll mixtures showed the slow decomposition and low initial dissolution rates of GF.

Fig. 7 shows the dissolution time-course of GF in the GF–CornS mixtures. The concentration of GF was continuously elevated up to 8 h in all samples. The concentration of GF 8 h after the start of dissolution was 10.8 mg/l in the physical mixture, 13.8 mg/l in the sample prepared by 5 min roll mixing, 14.5 mg/l in the sample prepared by 20 min roll mixing, and 14.8 mg/l in the sample prepared by 40 min roll mixing. These concentrations were similar to those in the mixtures of GF and the disaccharides, and about 1 mg/l higher than in the mixtures of GF and the linear dextrins. The initial dissolution rate of GF markedly increased with the roll mixing time (Fig. 9). In the physical GF–CornS mixture, the initial dissolution rate of GF was almost the same as that in the physical mixtures of GF and linear dextrins. But it was 93-fold higher in the 20 min roll mixture and 117-fold higher in the 40 min roll mixture than GF alone. As a result of DSC measurement, the amount of residual GF crystals was larger in the GF–CornS mixture than in the GF–linear dextrin mixtures. The difference of the solubility of GF between the GF–CornS mixture and the GF–linear dextrin mixtures was probably due to branching molecules and polymeric sugar chains contained in CornS. The ratio of linear molecules to branching molecules in CornS is about 3:7 (Whistler and Hilbert, 1945).

The initial dissolution rate of GF was very high in the GF–BriG mixture (Fig. 8), and it was the highest in the sample prepared by 5 min roll mixing, which was 170-fold higher than in GF alone. The concentration of GF was about 16 mg/l 30 min after the start of dissolution, and the same level was maintained 8 h after the start of dissolution. Even in the physical GF–BriG mixture, the initial dissolution rate and concentration of GF were much higher than in the mixtures of GF and the remaining carrier materials.

3.3. Stability of amorphous GF

Fig. 10 shows the stability of amorphous GF in the GF–AmyC mixture. Amorphous GF in the GF–AmyC mixture remained almost unchanged 1

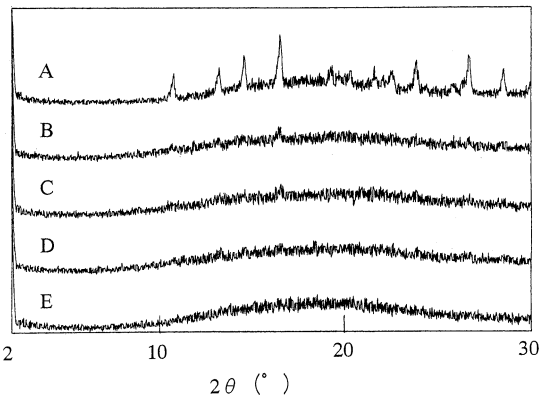

Fig. 10. Powder X-ray diffraction patterns of GF–AmyC mixtures roll mixed for 40 min stored at 40 °C and 75%RH. A, physical mixture (reference); B, stored for 1 month; C, stored for 3 weeks; D, stored for 2 weeks; E, initial.

month after mixing, indicating that amorphous GF was more stably maintained in the GF–AmyC mixture than in the mixtures of GF and the remaining carrier materials. Almost all powders of the disaccharide carriers and GF were amorphous after roll mixing, but they were completely recrystallized after stored at 40 °C and 75%RH for 24 h. The roll mixture of GF and Amy10, of which the molecular weight was low among the linear dextrin carriers, became wet in the form of paste after 24 h storage, and GF was recrystallized as in the physical mixture. The GF–Amy6H roll mixture was solidified after 24 h storage, and recrystallization of GF was observed. In the GF–Amy6H roll mixture that had been left standing still at 20 °C and 76%RH, amorphous GF was maintained for 4 weeks (Saito et al., 2001). The above results can be interpreted as a consequence of the elevated motility of amorphous GF molecules under the processing condition at 40 °C, which would result in enhancement of recrystallization. These recrystallized samples presumably give equivalent dissolution characteristics to the physical mixture shown in Figs. 5 and 6. In the roll mixtures of GF and CornS or BriG of a larger molecular weight, amorphous GF was stably maintained. This suggests an existence of significant interaction between GF and those carriers, which is a subject of further study.

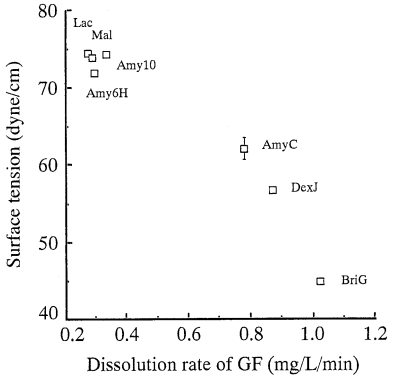

Fig. 11. Relationship between the surface tension in the carrier solutions and the initial dissolution rate of GF in the physical mixtures.

3.4. Surface tension

Fig. 11 shows the relationship between the surface tension in the carrier solutions and the initial dissolution rate of GF in the physical mixtures. The surface tension was markedly low in the solutions of DexJ and BriG, which have branch sugar chains. A high initial dissolution rate of GF in the physical mixtures of GF and these carrier materials may be due to a decrease of the interfacial tension on GF particle by the carriers.

The dissolution characteristics of GF tended to be further improved in the roll mixtures. This was probably due to an increase in the surface area of GF directly exposed to the carrier materials by roll mixing.

These results indicated that the solubility of GF was markedly improved by roll mixing with saccharides of a relatively high molecular weight such as CornS, AmyC and BriG, and will provide useful new means about the improvement of the solubility of poorly water-soluble drugs without using organic solvents.

4. Conclusions

The results obtained can be summarized as follows.

1) GF in the roll mixtures with saccharides became increasingly more amorphous with

mixing time. The amorphous state was stably maintained in the roll mixtures of GF and saccharides with a high molecular weight (CornS, AmyC, and BriG) at 40 °C and 75%RH. In the GF–AmyC mixture, amorphous GF was not recrystallized for 1 month.

2) The dissolution characteristics of GF differed depending on the carrier materials. The initial dissolution rate of GF in the CornS or AmyC roll mixtures increased with mixing time, reaching levels 117-fold higher than in the sample of GF alone. In the GF–BriG mixture, the initial dissolution rate of GF was markedly high in the sample prepared by 5 min roll mixing, which was 170-fold higher than in that of GF alone.
3) The surface tension of carrier solutions was markedly low in DexJ and BriG, which have branch sugar chain structures. The high initial dissolution rate of GF in the physical mixtures with these carriers was induced apparently by a decrease of the interfacial tension on GF particle.

Acknowledgements

We would like to thank Toru Nakajima of Nippon Starch Chemical Co., Ltd. for providing the carrier materials for this study.

References

Allen, L.V., Jr, Yanchick, V.A., Maness, D.D., 1977. Dissolution rate of corticosteroids utilizing sugar glass dispersions. J. Pharm. Sci. 66, 494–497.

Brimhall, B., 1944. Structure of pyrodextrins. Ind. Eng. Chem. 36, 72–75.

Chebli, C., Cartilier, L., 2000. Effect of some physical parameters on the sustained drug-release properties of substituted amylose matrices. Int. J. Pharm. 193, 167–173.

Danjo, K., Nakata, T., Otsuka, A., 1997. Preparation and dissolution behavior of ethenzamide solid dispersions using various sugars as dispersion carriers. Chem. Pharm. Bull. 45, 1840–1844.

Ghanem, A., Meshali, M., Ibraheem, Y., 1980. Dissolution rates of sulfamethoxazole utilizing sugar glass dispersions. J. Pharm. Pharmacol. 32, 675–677.

Henrist, D., Remon, J.P., 1999a. Influence of the formulation composition on the in vitro characteristics of hot stage extrudates. Int. J. Pharm. 188, 111–119.

Henrist, D., Remon, J.P., 1999b. Influence of the process parameters on the characteristics of starch based hot stage extrudates. Int. J. Pharm. 189, 7–17.

Henrist, D., Lefebvre, R.A., Remon, J.P., 1999. Bioavailability of starch based hot stage extrusion formulations. Int. J. Pharm. 187, 185–191.

Hirasawa, N., Okamoto, H., Danjo, K., 1999. Lactose as a low molecular weight carrier of solid dispersions for carbamazepine and ethenzamide. Chem. Pharm. Bull. 47, 417–420.

Ishizaka, T., Honda, H., Ikawa, K., Kizu, N., Yano, K., koishi, M., 1988. Complexation of aspirin with potato starch and improvement of dissolution rate by dry mixing. Chem. Pharm. Bull. 36, 2562–2569.

Ishizaka, T., Honda, H., Kikuchi, Y., Ono, K., Katano, T., Koishi, M., 1989. Preparation of drug–diluent hybrid powders by dry processing. J. Pharm. Pharmacol. 41, 361–368.

Ishizaka, T., Honda, H., Koishi, M., 1993. Drug dissolution from indomethacin–starch hybrid powders prepared by the dry impact blending method. J. Pharm. Pharmacol. 45, 770–774.

Kubo, H., Mizobe, M., 1997. Improvement of dissolution rate and oral bioavailability of a sparingly water-soluble drug, (±)-5-[[2-(2-naphthalenylmethyl)-5-benzoxazolyl]-methyl]-2,4-thiazolidinedione, in co-ground mixture with D-mannitol. Biol. Pharm. Bull. 20, 460–463.

Kubo, H., Osawa, T., Takashima, K., Mizobe, M., 1996. Enhancement of oral bioavailability and pharmacological effect of 1-(3,4-dimethoxyphenyl)-2,3-bis(methoxycarbonyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (TA-7552), a new hypocholesterolemic agent, by micronization in co-ground mixture with D-mannitol. Biol. Pharm. Bull. 19, 741–747.

Lenaerts, V., Dumoulin, Y., Mateescu, M.A., 1991. Controlled release of theophylline from cross-linked amylose tablets. J. Control. Rel. 15, 39–46.

Saito, M., Nozawa, Y., Sadzuka, Y., Miyagishima, A., Sonobe, T., Nakajima, T., 2001. Preparation and dissolution characteristics of griseofulvin solid dispersions with dextrin or starch. J. Pharm. Sci. Technol. Jpn. 61, 11–20.

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.

Takahata, H., Nishioka, Y., Osawa, T., 1992. Micronization of poorly soluble drugs to submicron size by mixing grinding with low-molecular water-soluble crystalline additives. Solids Handling Process. Ind. Jpn. 24, 53–59.

Takeuchi, H., Handa, T., Kawashima, Y., 1987. Enhancement of the dissolution rate of a poorly water-soluble drug (tolbutamide) by a spray-drying solvent deposition method and disintegrants. J. Pharm. Pharmacol. 39, 769–773.

Whistler, R.L., Hilbert, G.E., 1945. Separation of amylose and amylopectin by certain nitroparaffins. J. Am. Chem. Soc. 67, 1161–1165.

Wierik Te, G.H.P., Van der Veen, J., Eissens, A.C., Besemer, A.C., Lerk, C.F., 1993. Preparation, characterization and application of linear dextrins. VI. General applicability and mechanism of programmed release from amylodextrin tablets. J. Control. Rel. 27, 9–17.

Yamamoto, K., Nakano, M., Arita, T., Nakai, Y., 1974. Dissolution rate and bioavailability of griseofulvin from a ground mixture with microcrystalline cellulose. J. Pharmacokinet. Biopharm. 2, 487–493.

Yamamoto, K., Nakano, M., Arita, T., Takayama, Y., Nakai, Y., 1976. Dissolution behavior and bioavailability of phenytoin from a ground mixture with microcrystalline cellulose. J. Pharm. Sci. 65, 1484–1488.