ELSEVIER

International Journal of Pharmaceutics 241 (2002) 203–211

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

The role of the kneading paddle and the effects of screw revolution speed and water content on the preparation of solid dispersions using a twin-screw extruder

Kouichi Nakamichi [a,*], Tomio Nakano [a], Hiroyuki Yasuura [a], Shogo Izumi [a], Yoshiaki Kawashima [b]

[a] *Pharmaceutics Research Laboratory, Nippon Shinyaku Co., Ltd., 14, Nishinosyou-Monguti-cho, Kisshoin, Minami-ku, Kyoto 601-8550, Japan*

[b] *Department of Pharmaceutical Engineering, Gifu Pharmaceutical University, 5-6-1, Mitahora-higashi, Gifu 502-8585, Japan*

Received 26 January 2001; received in revised form 22 March 2002; accepted 5 April 2002

Abstract

The twin-screw hot-melt extrusion process is useful for preparing solid dispersions which can improve the dissolution and absorption of drugs. The kneading paddle elements of the screws play an important role in changing the crystallinity and dissolution properties of a solid dispersion of kneaded nifedipine–hydroxypropylmethylcellulose phthalate (NP–HPMCP). After operating the machine, a small amount of kneaded material adhereing to the screws was collected and its physicochemical properties examined. Samples from the kneading paddle with a twist angle of 60° were transparent and exhibited super-saturation on dissolution testing. When the kneading paddle elements were detached from the screws and only the feed screw elements were operated, the physicochemical properties of the extruded material were significantly influenced by the operating conditions of the machine e.g. revolution rate of screws, and the amount of water added to the feed materials. Slow revolution of the screws and the addition of a suitable amount of water to the mixture increased the rate of drug dissolution, although no super-saturation occurred. As the kneading paddle elements can retain the mixture in the machine for a longer period under intense shear, desired solid dispersions can be prepared routinely irrespective of the operating conditions. Moreover, a capillary rheometer can be useful to predetermine the amount of water added and the temperature for the preparation of solid dispersions using a twin-screw extruder.

Keywords: A twin-screw extruder; Kneading paddle elements; Nifedipine; Solid dispersions; Revolution speed; Water content

1. Introduction

Many techniques, including drug micronization and addition of solubility enhancers to the formulation, have been tried to improve the solubility of poorly water soluble drugs to increase their bioavailability.

* Corresponding author. Tel.: +81-75-321-9124; fax: +81-75-321-9038

E-mail address: k.nakamichi@po.nippon-shinyaku.co.jp (K. Nakamichi).

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00134-5

The solid dispersion technique is also useful for improving the solubility and bioavailability of insoluble drugs (Sekiguchi and Obi, 1961; Chiou and Riegelman, 1970; Hasegawa and Sugimoto, 1986; Sugimoto et al., 1980; Hasegawa et al., 1985; Takeuchi et al., 1987; Ozeki et al., 2000). Sekikawa et al. (1979) have reported that minute coacervation droplets are formed around solid dispersions when they are immersed in dissolution medium. This phenomenon is considered to be an important mechanism for improving the solubility and bioavailability. Chiou et al. have described three methods of preparing solid dispersions: co-fusion, co-evaporation with organic solvents, and a combination of these (Chiou and Riegelman, 1970). The co-fusion method involves a mixture of drug and additives which is melted by heating and then solidified by cooling. In this method, a high temperature is required which may result in drug decomposition and, so, it is necessary to mix the drug thoroughly with additives. In the co-evaporation method, the drug solution containing other additives is evaporated under vacuum to remove volatile solvents. In fact, this method has been applied to spray coating during the production of a commercial product, Sepamit®, and was developed by Hasegawa and Sugimoto (1986). However, in recent years there has been a move to restrict the use of organic solvents. In a previous study, we reported that solid dispersions of nifedipine (NP) in hydroxypropylmethylcellulose phthalate (HPMCP) could be prepared using a twin-screw extruder (Nakamichi et al., 1996). One of the advantages of this method is that no organic solvents are needed for the preparation of solid dispersions. Another important point is that solid dispersions can be produced at a lower temperature than the melting point of the drug and the softening temperature of the polymer used. Therefore, this new pharmaceutical process is useful from an ecological standpoint and can produce solid dispersions efficiently without degradation of drug. Also, more than two kinds of carrier can be used so that various combinations of formulation can be employed.

In the present study, we chose NP as a model drug and HPMCP as an enteric polymer in the same manner as a previous study (Nakamichi et al., 1996) and investigated the effects of the kneading paddle elements of screws in preparing a solid dispersion. Also, the process parameters, such as screw revolution and the amount of water added, were investigated. The crystallinity and dissolution properties of kneaded materials were evaluated in each experiment.

2. Experimental

2.1. Materials

NP (a calcium antagonist, melting point 173 °C.) was supplied as a model drug by Sumika Fine Chemicals, Gifu, Japan. HPMCP (HP-55F, Shinetsu, Japan) was employed as an enteric polymer. Physical mixtures were prepared by mixing NP with HPMCP in a weight ratio of 1: 5 (40:200 g) using a polyethylene bag.

2.2. Preparation of solid dispersions with a twin-screw extruder (KEX-30, Kurimoto Co. Ltd.)

2.2.1. Extrusion process

The twin-screw extruder is illustrated in Fig. 1. A physical mixture was fed into the hopper. Both screws were rotated in the same direction and kept at a constant temperature in the 'barrel'. The mixture was constantly moved and kneaded by the screws. Extruded material was obtained from the end-plate and die section. However, in this study, the end-plate was removed in order to clearly monitor the role of the kneading paddles. The feed screws were positioned at the second, third and fifth barrel. The pitch of the gap width of the screws was 8–16 mm and the closer to the fifth barrel the narrower the pitch of the screw elements. Kneading paddles, with twist angles of 30 and 60°, were positioned at the fourth barrel. Also, extra experiments were conducted in which the extruder consisted of only the feed screw elements without the kneading paddle elements. The barrel temperature was set at 100 °C in all experiments. Before extrusion, a predetermined amount of water was added to the physical mixture, followed by manual mixing in a vinyl bag.

Extruded material was crushed using a small milling machine (Konishi Co. Ltd., Japan) and passed through 180 and 250 μm sieves to evaluate its physicochemical properties.

2.2.2. Operating conditions were modified as follows

(a) For testing the usefulness of kneading paddle elements. Water content, 10%w/w; screw revolution speed, 20 rpm; powder feed, 15 g/min.

(b) Factors influencing preparation of solid dispersions.

(i) Screw revolution speed. Water content, 10% w/w; screw revolution speed, 20–100 rpm; powder feed, 15 g/min.

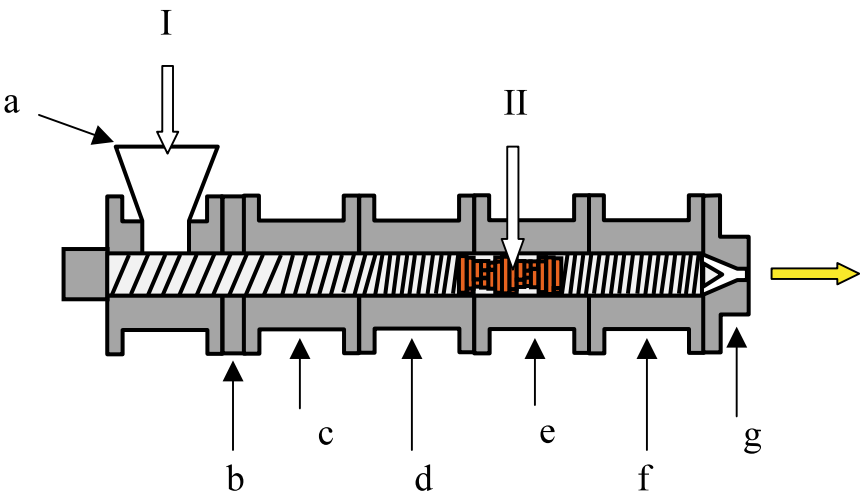

Fig. 1

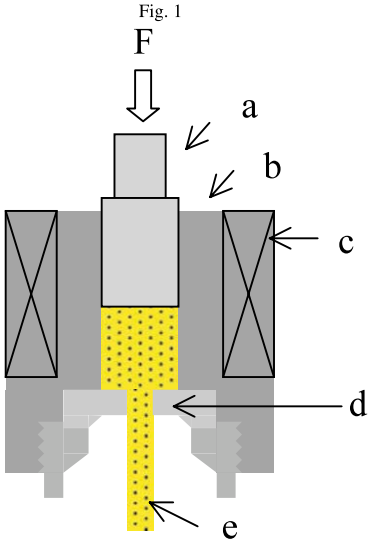

Fig. 2

Fig. 1. Scheme of twin-screw extruder. (I) Physical mixture. (II) Kneading paddle (twist-angle, 30; 60°), (a) hopper; (b) plate barrel; (c) 2nd barrel; (d) third barrel; (e) fourth barrel; (f) fifth barrel; (g) end plate and die.

Fig. 2. Scheme of Flowtester. (a) Piston; (b) cylinder; (c) heater; (d) die (1 mmϕ); (e) sample.

(ii) Water content. water content, 0–50% w/w; screw revolution speed, 20 rpm; powder feed, 15 g/min.

2.2.3. Evaluation of physicochemical properties of extruded material

2.2.3.1. Powder X-ray analysis. Powder X-ray diffraction patterns were obtained by a diffractometer (RAD-2B, Rigaku, Tokyo), using Cu-Kα radiation and a nickel filter. The operating conditions were as follows: voltage, 40 kV; current, 20 mA; and scanning speed, 4° per min.

2.2.3.2. Thermal analysis. Differential scanning calorimetry (DSC) curves were determined using DSC equipment (DSC-7, Perkin–Elmer, USA). The measuring conditions were as follows: sample weight, approximately 10 mg; sample cell, aluminum open cell with a cell cover; heating rate, 20 °C/min; nitrogen gas flow.

2.2.3.3. Dissolution test of the drug. Dissolution studies were conducted according to the paddle method specified in the Japanese Pharmacopoeia XIII under the following conditions; sample weight, corresponding to NP 90 mg; dissolution medium, 900 ml liquid, pH 6.8 (defined as the second fluid in the Japanese Pharmacopoeia XIII); temperature, 37 ± 0.5 °C; paddle rotation rate, 100 rpm. At predetermined intervals, 5 ml dissolution medium was withdrawn and immediately passed through a membrane filter (0.45 μm pore size, MILEX-HA, Millipore). After adding 1 ml methanolic solution of internal standard (0.1 mg/ml, p-hydroxy benzoic acid isobutyl ester) to 1 ml filtrate, the concentration of NP was measured by high-performance liquid chromatography (HPLC). HPLC analysis was performed using LC-10 AS and SPD-10A equipment (Shimadzu, Japan). The HPLC conditions were as follows: mobile phase, water/methanol 4:6 (v/v) mixture; flow rate, 1 ml/min; reverse-phase column (Cosmosil 5C18-AR, 4.6 mm I.D. × 150 mm; Nakalai) at 40 °C; detection wavelength, $\lambda = 237$, 325nm.

2.2.3.4. Observation of the kneaded samples adhering to the screws. The samples adhering to the screws were monitored by video microscope (PV10, Olympus). Photographs were obtained using a color video printer (VY-170, Hitachi, Japan).

2.2.4. Measurement of flow temperature using a capillary rheometer

Physical mixture (1.2 g) was compressed using a press (autograph AG-5000A, Shimadzu; compression speed, 10 mm/min; load weight, 500 kg/cm^2) and made into a cylindrical block 10 mm in diameter. The flow temperature (Tfb, the temperature when samples start to flow) was measured using a capillary rheometer (Flowtester, CFT-500C, Shimadzu) as shown in Figs. 2 and 3. The measuring conditions were as follows: pore size of die, 1 mmϕ; heating rate, 6 °C/min, load weight 100 kg/cm^2.

3. Results

3.1. Usefulness of kneading paddle elements for preparing solid dispersions

To examine the action of the kneading paddle elements, after carrying out the extrusion for approximately 5 min, the screw was detached from the barrels, and the material adhering to the screw at each barrel position was recovered. The powder X-ray diffraction patterns and the DSC curves of recovered samples and their physical mixture are shown in Fig. 4. In the powder X-ray diffraction patterns, crystalline peaks of NP were observed in the physical mixture and the sample recovered from the third barrel, while there were no crystalline peaks in the sample adhering to the kneading paddle elements and the fifth barrel. Crystalline peaks were observed in all samples treated without the kneading paddle elements. Also, following thermal analysis using DSC, no melting peak of NP corresponding to ca 173 °C was observed in the sample adhering to the kneading paddle elements and the fifth barrel.

The dissolution profiles of these samples are shown in Fig. 5. The maximum concentrations of these samples had increased in comparison with that of a physical mixture. Moreover, when the kneading paddle elements with a twist angle of 60° were installed, super-saturation in the dissolu-

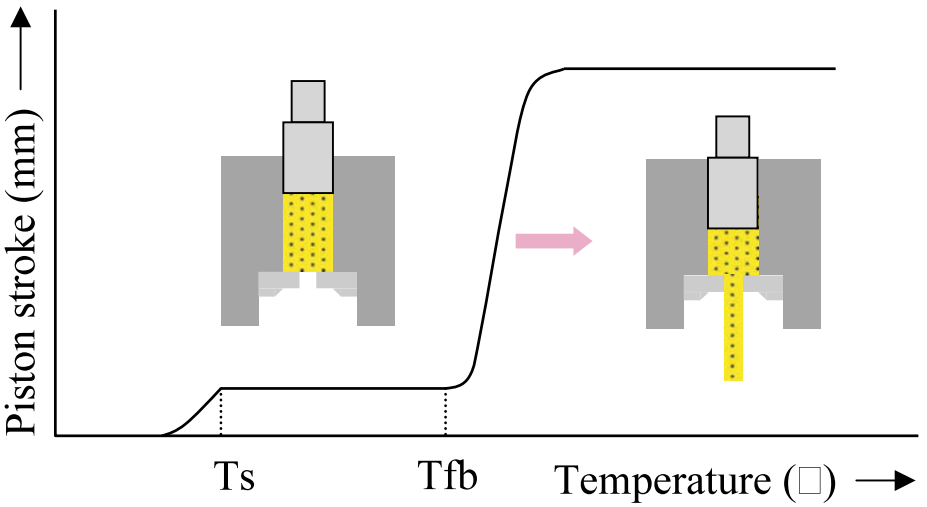

Fig. 3. Measurement of flow temperature (Tfb).

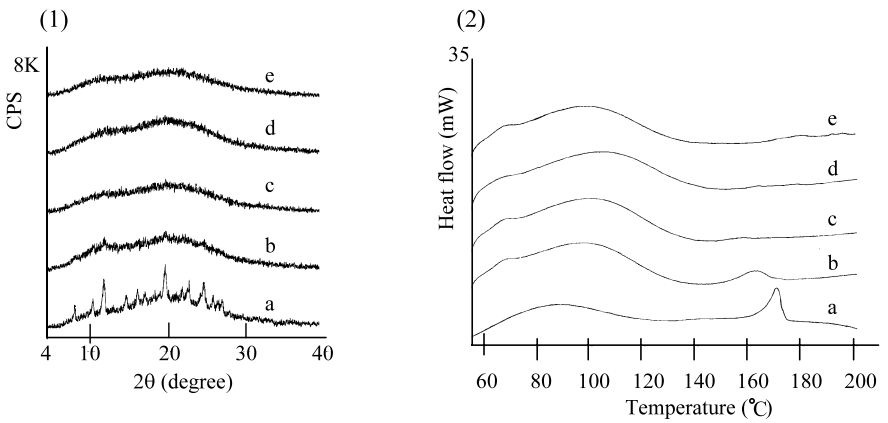

Fig. 4. Crystallinity of NP in the kneaded sample with screw positioned at each barrel. (1) Powder X-ray diffraction patterns. (2) DSC curves, (a) unprocessed physical mixture; (b) feed screw (third barrel); (c) kneading paddle position (twist angle, 30°); (d) kneading paddle position (twist angle, 60°); (e) feed screw (fifth barrel).

tion profile was observed for the resultant kneaded sample as well as the sample at the fifth barrel; without kneading paddle elements, no super-saturation was obtained. Photographs of the samples are shown in Fig. 6. NP appeared yellow was dissolved uniformly in the polymer and the resultant dispersions passing through the kneading paddle became transparent. These findings confirmed the need for kneading paddle elements in the screw when preparing solid dispersions.

3.2. Factors influencing the preparation of solid dispersions

There are some important factors associated with the use of a twin screw extruder, such as the rate of screw revolutions (corresponding to the material feeding speed) and the weight ratio of water added to the material to influence the physicochemical properties of the resultant preparations.

3.2.1. Effect of screw revolution speed

In case where kneading paddle elements were used, a transparent mass was produced irrespective of the screw revolution speed and an enhanced dissolution profile was obtained. However, in case where the screws consisted of feed screw elements alone, i.e. the kneading paddle elements were removed, the physicochemical state of the treated samples was different. The powder X-ray diffraction patterns and dissolution

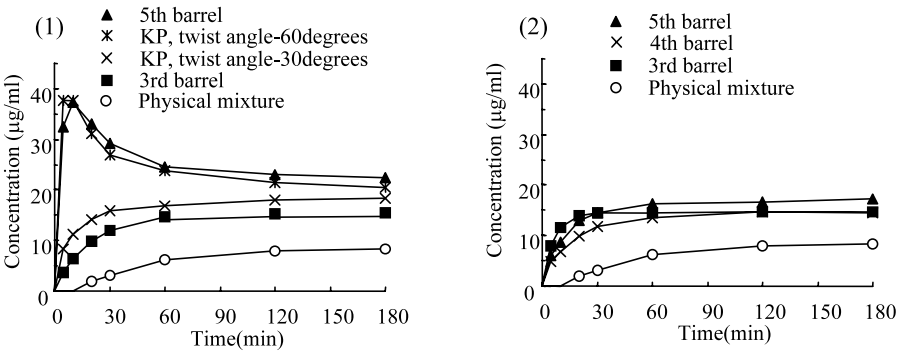

Fig. 5. Effect of kneading paddle on dissolution profiles of NP. (1) With kneading paddle elements. (2) Without kneading paddle elements.

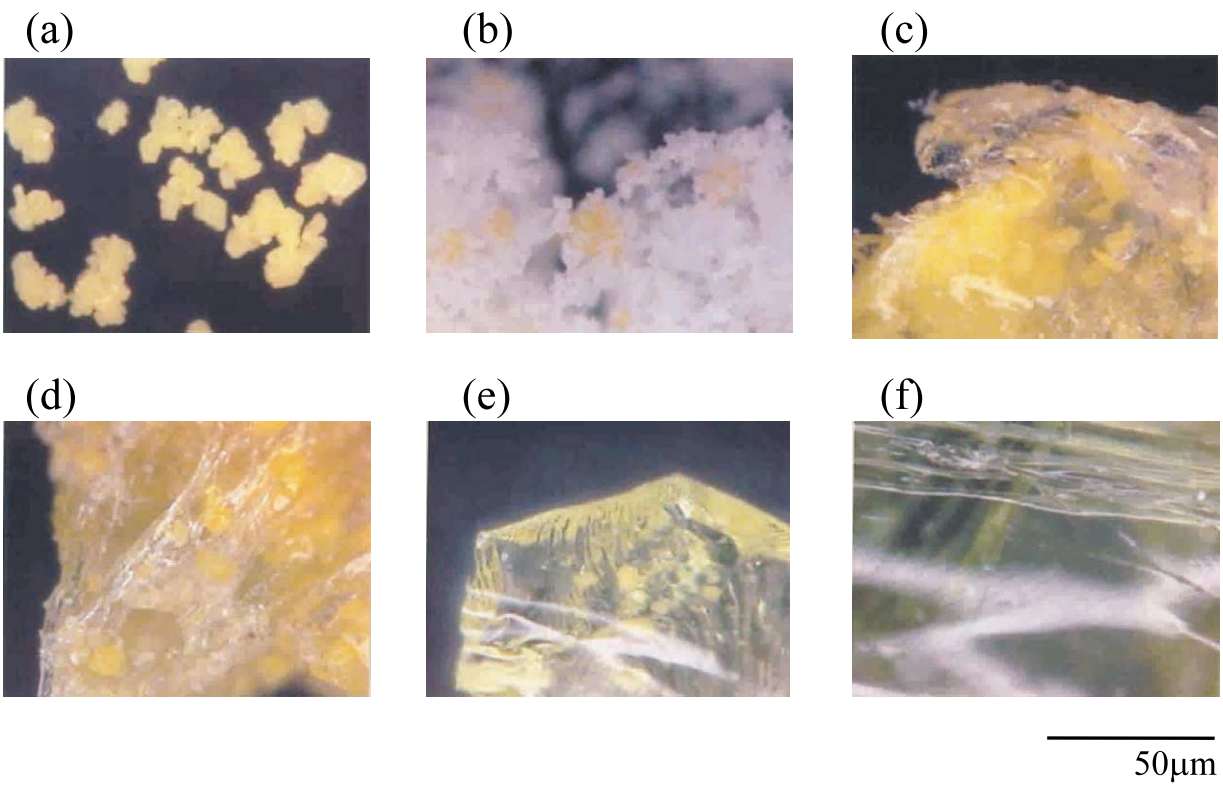

Fig. 6. Photographs of the kneaded sample with screw positioned at each barrel. (a) NP alone; (b) Physical mixture; (c) third barrel; (d) Kneading paddle (twist angle, 30°); (e) kneading paddle (twist angle, 60°); (f) fifth barrel.

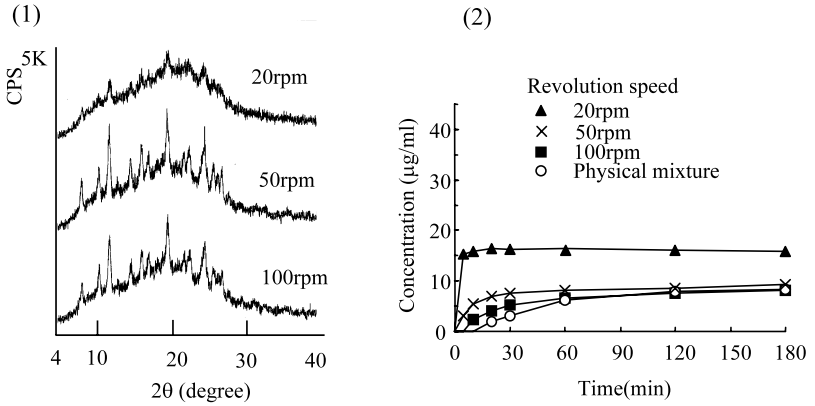

Fig. 7. Effect of the revolution speed of the screw on preparation of solid dispersions. (1) Powder X-ray diffraction patterns. (2) Dissolution profiles.

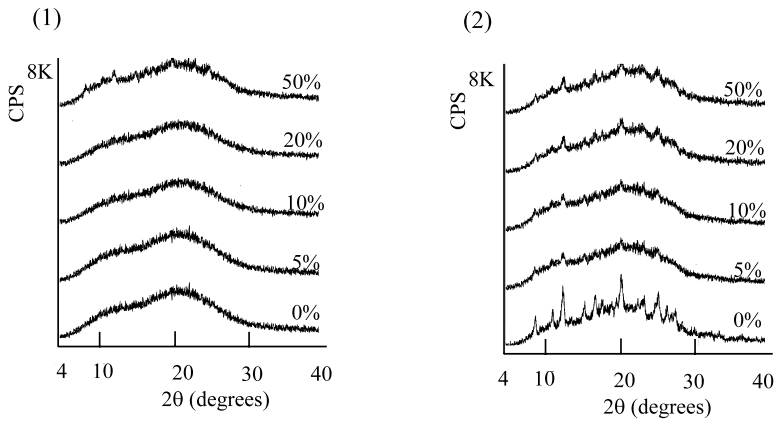

Fig. 8. Effect of water added to the powder on crystallinity of NP. (1) With kneading paddle elements. (2) Without kneading paddle elements.

properties of the resultant preparations are shown in Fig. 7. The feed screw serves only to transport the material in the extruder. Therefore, when the screw revolution speed was fast, e.g. 50 and 100 rpm, the resultant preparations were obtained in powdery states without any paste formation. However, when the screw revolution speed was slower, e.g. 20 rpm, there was an increase in the paste mass. Its crystallinity was reduced and the dissolution rate increased. However, no super-saturation in the dissolution pattern was observed. These findings confirm that the kneading paddle elements are useful for mixing and kneading the materials.

3.2.2. Effect of the amount of water added to the materials

The effects of the amount of water added to the materials on the powder X-ray diffraction patterns and the dissolution properties of the resultant preparations are shown in Figs. 8 and 9, respectively. In the case where the screws consisted of only the feed screw elements, i.e. where no kneading paddle elements were used, without any additional water, powdery preparations were obtained similar to the raw materials, so-called physical mixtures. In fact, a similar powder X-ray diffraction pattern to the physical mixture was obtained. By adding 5, 10, and 20% water, based

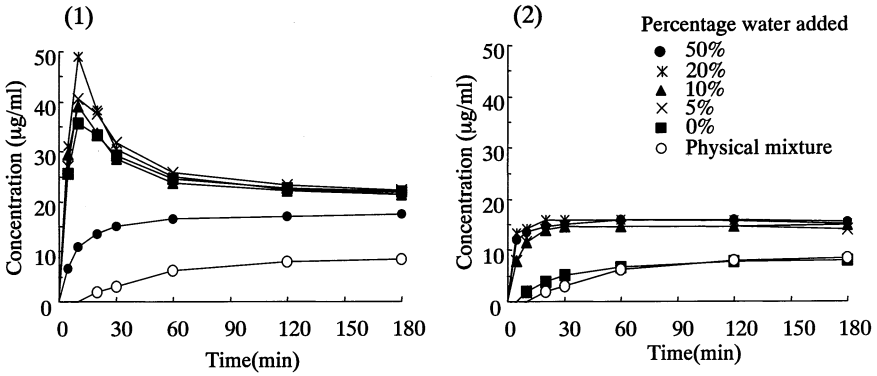

Fig. 9. Effect of water added to the powder on dissolution profiles of NP. (1) With kneading paddle elements. (2) Without kneading paddle elements.

on the weight of physical mixture, a paste mass was obtained with powder X-ray diffraction patterns that had faint peaks. When adding excess water (corresponding to 50%), the water was extruded from the kneaded samples, forming granules.

When kneading paddle elements were used, the kneaded samples became pastes except for the case where excess water was added. The powder X-ray diffraction pattern became hollow, which means that the NP was in an amorphous state. Provided that 20% water was added initially, the water was extruded from the samples, as was the case with 50% water. However, after extruding for a more than 5 min, the kneaded mixture suddenly became a paste and the solubility of the preparation increased.

In the case where no kneading paddle elements were used, the kneaded preparations without any additional water had the same solubility as the physical mixture. However, the preparations treated with additional water had twice the solubility of the physical mixture. In the case with the kneading paddle elements, except for the sample in which excess of water corresponding to 50% was used, all preparations exhibited super-saturation in dissolution. In particular, when 20% water was added to the physical mixture, the preparation had a 6-fold higher solubility than the physical mixture, as shown in the drug concentration profile (Fig. 9). The presence of water during the preparation of solid dispersions appears to change the heat-fusion properties of the materials in association with the change in glass transition temperature (Hancock and Zografi, 1994; Hamaura and Newton, 1999).

4. Discussion

We evaluated the fusion properties with a capillary rheometer (Fig. 10). When 0–20% water (w/w) was added to the physical mixture, the more water added, the lower the flow temperature (Tfb) of the material. This implies that materials can be extruded below the melting temperature. Fig. 10 demonstrates that it is easy to predict the amount of water added at a constant temperature, e.g. in the case where the temperature was set at 100 °C, a 10% w/w water content is desirable. In fact, it is clear that additional water influences the

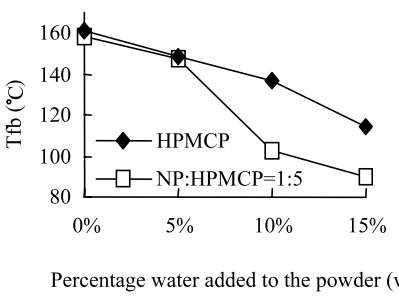

Fig. 10. Flow (fusion) temperature of materials measured by flowtester

preparation of solid dispersions using a twin-screw extruder. At a higher temperature, which caused the formation of solid dispersions regardless of the shear effect of extrusion, it is possible for drugs and other ingredients to decompose. The twin-screw extruder is useful for avoiding decomposition of ingredients during the preparation of solid dispersions. In these experiments, we have shown that kneading paddle elements affect the preparation of solid dispersions. It is thought that kneading paddle elements play a role in the mechanical shear and longer stay in the machine. Yoshinaga et al. (2000) also reported that screw geography with kneading paddle elements affected the residence time distribution, which was monitored by the marker tracking method. In the preparation of solid dispersions using a twin-screw extruder of limited length, highly efficient kneading is necessary and the kneading paddle elements have marked effects on the length of stay and high shear mixing and facilitate dispersing the drug into the polymer.

5. Conclusion

The kneading paddle elements of a twin-screw extruder play a key role in transforming the crystalline drug to an amorphous form i.e. the solid dispersed form, during the preparation of solid dispersions. Moreover, operating conditions such as screw revolution speed and the amount of water added are important parameters for the preparation of solid dispersions. It is important to set the screw revolution speed to maintain the residence time of the materials required in the extruder in order to obtain ideal dispersion of the drug in the polymer matrix. Addition of the proper amount of water lowers the softening temperature of the mixture, i.e. 100 °C, for the preparation of solid dispersions. A capillary rheometer is useful to predetermine the operating conditions, such as the amount of water added and temperature for the preparation of solid dispersions. Therefore, it is important to control the time the sample spends in the device (screw revolutions etc.) and how soft the sample is (additional water, temperature used etc.).

References

Chiou, W.L., Riegelman, S., 1970. Oral absorption of griseofulvin in dogs. Increased absorption via solid dispersion in polyethylene glycol 6000. J. Pharm. Sci. 59, 937–942.

Hamaura, T., Newton, J.M., 1999. Interaction between water and poly(vinylpyrrolidone) containing polyethylene glycol. J. Pharm. Sci. 88, 1228–1233.

Hancock, B.C., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11, 471–477.

Hasegawa, A., Sugimoto, H., 1986. Kotai-bunsan-iyakuhin-seizai. Kagaku-kougyo 37, 309–317.

Hasegawa, A., Nakagawa, H., Sugimoto, I., 1985. Application of solid dispersions of nifedipine with enteric coating agent to prepare a sustained-release dosage form. Chem. Pharm. Bull. 33, 1615–1619.

Nakamichi, K., Yasuura, H., Fukui, H., Oka, M., Izumi, S., Andou, T., Shimizu, N., Ushimaru, K., 1996. Preparation of Nifedipine-Hydroxypropylmethylcellulose phthalate solid dispersion by twin screw extruder and its evaluation. J. Pharm. Sci. Technol. Jpn. 56, 15–22.

Ozeki, T., Yuasa, H., Kanaya, Y., 2000. Controlled release from solid dispersion composed of poly (ethylene oxide)-carbopol interpolymer complex with various cross-linking degrees of carbopol. J. Control. Release 63, 287–295.

Sekiguchi, K., Obi, N., 1961. Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull. 9, 866–872.

Sekikawa, H., Nakano, M., Arita, T., 1979. Dissolution Mechanisms of Drug-Polyvinylpyrrolidone Coprecipitates in Aqueous Solution. Chem. Pharm. Bull. 27, 1223–1230.

Sugimoto, I., Kuchiki, A., Nakagawa, H., Tohgo, K., Kondo, S., Iwane, I., Takahashi, K., 1980. Dissolution and absorption of nifedipine-polyvinylpyrrolidone coprecipitate. Drug. Dev. Ind. Pharm. 6, 137–160.

Takeuchi, H., Handa, T., Kawashima, Y., 1987. Spherical solid dispersion containing amorphous tolbutamide embedded in enteric coating polymers or colloidal silica prepared by spray-drying technique. Chem. Pharm. Bull. 35, 3800–3806.

Yoshinaga, M., Katsuki, S., Miyazaki, M., Liu, L., Kihara, S., Funatsu, K., 2000. Mixing mechanism of three-tip kneading block in twin screw extruders. Polym. Eng. Sci. 40, 168–178.