Improvement of Dissolution Characteristics of a New Chalcone Derivative, SU-740: Comparison between Size Reduction, Solid Dispersion and Inclusion Complexation

Shusei ITO,[a] Miki DEMACHI,[a] Yumiko TORIUMI,[a] Takeshi ADACHI,[a] Shigeru ITAI,[a]
Fumitoshi HIRAYAMA,[b] and Kaneto UEKAMA*,[b]

Research Center, Taisho Pharmaceutical Co., Ltd.,[a] 1–403 Yoshino-cho, Ohmiya-shi, Saitama 330, Japan and Faculty of Pharmaceutical Sciences, Kumamoto University,[b] 5–1, Oe-honmachi, Kumamoto 862, Japan.

Received June 19, 1995; accepted August 14, 1995

Three pharmaceutical techniques, *i.e.*, size reduction, solid dispersion and inclusion complexation, were employed for improvement of the dissolution rate of 4-*tert*-butyl-2′-carboxymethoxy-4′-(3-methyl-2-butenyloxy)chalcone (SU-740). For the size reduction, pulverization was performed using a jet mill. The solid dispersions of SU-740 were prepared with polyethyleneglycol 6000 (PEG) and polyvinylpyrrolidone K29/32 (PVP). The inclusion complexes of SU-740 with three natural cyclodextrins (α-, β-, γ-CyDs) were prepared by the freeze-drying method, or they were isolated according to the B_s type phase-solubility diagram. The dissolution rates of SU-740 from the PVP coprecipitate and the β-CyD complex were much larger than that of the size-reduced form. On accelerated storage (40 °C and 75% relative humidity) for one month, the PVP coprecipitate showed a decrease in the dissolution rate and a change in appearance, whereas the β-CyD complex showed no changes. The present results suggest that inclusion complexation is preferable among the three techniques employed for improving of the dissolution characteristics of SU-740.

Key words SU-740; cyclodextrin; inclusion complex; solid dispersion; size reduction; dissolution rate

4-*tert*-Butyl-2′-carboxymethoxy-4′-(3-methyl-2-butenyloxy)chalcone (SU-740, molecular weight 422.52, see Fig. 1) is a newly developed chalcone derivative with potent anti-ulcer activity. However, the aqueous solubility of SU-740 is very low (about 2.6×10^{-6} M at 25 °C), thus limiting the dosage form design. Therefore, three pharmaceutical techniques, *i.e.*, size reduction, solid dispersion and inclusion complexation, were examined to improve the dissolution rate of SU-740. The reduction of particle size by pulverization is known to be a useful method to enhance the dissolution rate of solid drugs.[1,2] Furthermore, solid dispersions and inclusion complexations are reported to improve the dissolution and bioavailability of poorly water-soluble drugs.[3-8] However, there are few reports on the comparative study of these techniques[9-11] for improving solubilization ability. In this paper, the three above-mentioned techniques were compared to select the most practical way to improve the dissolution rate of SU-740.

Experimental

Materials SU-740 was synthesized by Taisho Pharmaceutical Co., Ltd. (Tokyo, Japan). Polyethyleneglycol 6000 (PEG), polyvinylpyrrolidone K29/32 (PVP) and cyclodextrins (CyDs) (α-, β-, γ-CyDs) were purchased from Sanyo Kasei (Tokyo, Japan), BASF (Germany) and Nihon Shokuhin Kako Co., Ltd. (Tokyo, Japan), respectively. All other materials and solvents were of analytical reagent grade.

pH-Solubility Profile Excess amounts of SU-740 were added to 10 ml of Britton–Robinson buffer of various pHs and shaken for 24 h at 25 °C. An aliquot of the solution was filtered (0.45 μm, DISMIC-3CP, Advantec, Toyo, Tokyo, Japan) and analyzed for SU-740 by high performance liquid chromatography (HPLC) as described below. The pH of the solutions was confirmed to be unchanged before and after the equilibrium (pH change < 0.02).

Size Reduction SU-740 powder was pulverized in a jet mill (Turbo Kogyo, Tokyo, Japan). The air pressure of both the feed and counter injector was set at about 5 kg/cm² for the jet mill, and the powder was supplied in the rate of 1.0 g/10 min. The particle size of SU-740 was determined by the laser diffraction method (Model Microtrac FRA, Nikkiso, Tokyo, Japan) under the following conditions: sampling time 5 s and air pressure 2 kg/cm².

Preparation of Solid Dispersions The solid dispersion of SU-740 with PEG was prepared by the fusion or coprecipitation method, and the solid dispersion with PVP was prepared by the coprecipitation method. The fusion method: the mixtures of SU-740 and PEG in 1 : 5 and 1 : 10 weight ratios were heated at 65 °C until a homogeneous melt was obtained, and the melt was allowed to stand at room temperature for solidification. The solid samples were crushed, pulverized in a mortar, and dried under reduced pressure at room temperature for 24 h. The coprecipitation method: SU-740/PEG or SU-740/PVP in 1 : 5 and 1 : 10 weight ratios was dissolved in chloroform or in ethanol, respectively, and the solvent was evaporated under reduced pressure at 40 °C. The solid powder was pulverized and dried as described above.

Solubility Studies Solubility measurements were carried out according to the method of Higuchi and Connors.[12] SU-740/polymer system: excess amounts (5 mg) of SU-740 were added to a phosphate buffer (10.0 ml, pH 6.5) containing various concentrations (0.01%, 0.1%, 1.0%, 5.0% (w/v)) of PEG or PVP, and the mixture was shaken at 37 °C for 24 h. SU-740/CyD system: excess amounts of SU-740 (10 mg) were added to a phosphate buffer (5.0 ml, pH 6.5) containing various concentration of CyDs, and the mixture was shaken for 5 d at 25 °C. After filtration (0.45 μm, DISMIC-3CP, Advantec, Toyo, Tokyo, Japan), the concentration of SU-740 in solution was measured by HPLC as described below. The complexes of SU-740 with β- and γ-CyD, which precipitated as a microcrystalline powder, were filtered and dried under reduced pressure at room temperature for 2 d. On the other hand, the α-CyD complex was obtained by the freeze-drying method as follows: SU-740 (884 mg) and α-CyD (3.9 g) in a molar ratio of 1 : 2 were dissolved in 0.05% (w/v) ammonia solution and the solution was freeze-dried using a

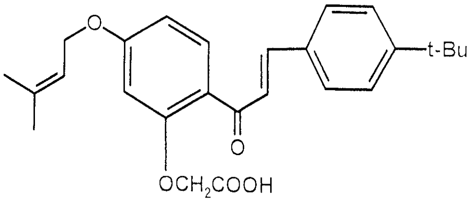

Fig. 1. Chemical Structure of SU-740

---

* To whom correspondence should be addressed.

freeze-drying apparatus (Model Gamma 2-20, B. Braun, Germany).

HPLC Analysis A Jasco HPLC chromatograph (Tokyo, Japan), composed of PU-980 and CO-960 models, was used. The mobile phase (acetonitrile: 0.02 M KH_2PO_4 (pH=3), 13:7, % (v/v)) was delivered at a flow rate of 1.0 ml/min through a TSK-gel ODS 80TM column (4.0 mm by 15 cm; Tohso, Tokyo, Japan) at 50 °C. The detection wavelength for SU-740 was 230 nm. Dicyclohexyl phthalate was used as an internal standard for HPLC (retention time: SU-740 7 min and internal standard 12 min).

Powder X-Ray Diffractometry and Differential Scanning Calorimetry (DSC) The powder X-ray diffraction patterns were measured by an X-ray diffractometer (Rigaku Denki, RAD-3C, Tokyo, Japan). The measuring conditions were as follows: target Cu, monochromator graphite, voltage 40 kV, and current 30 mA. DSC measurement was carried out on a model DSC 7 thermometer (Perkin-Elmer, U.S.A.) at a scanning rate of 10 °C/min under a nitrogen atmosphere, and the sample weight was 2—4 mg.

Dissolution Studies The dissolution test was performed according to the paddle method in Japanese Pharmacopoeia (JP) XII. The sample powders (30 mg as SU-740, < 100 mesh) were weighed and put into the dissolution medium (900 ml, pH 1.2 1st fluid of disintegration test of JP XII, pH 4.0 acetate buffer and pH 6.5 phosphate buffer) and the mixture was stirred (100 rpm) at 37 °C. After filtration (20—30 μm, glass filter G3), the concentration of SU-740 was measured spectrophotometrically at 330 nm.

Stability Test The SU-740 preparations were stored at 40 °C and 75% relative humidity (RH) for one month. The content of SU-740 in the preparations was determined by HPLC as described above, and the change in appearance was observed macroscopically.

Results and Discussion

pH-Solubility Profile The pH-solubility profile of SU-740 is shown in Fig. 2. The solubility of SU-740 increased with increasing pH of the medium, because of the protolytic dissociation of the carboxyl group. The pK_a was calculated to be 4.72 by analyzing the solubility profile, and the solubility of SU-740 was 3.11×10^{-2} mg/ml (7.36×10^{-5} M) at pH 6.99.

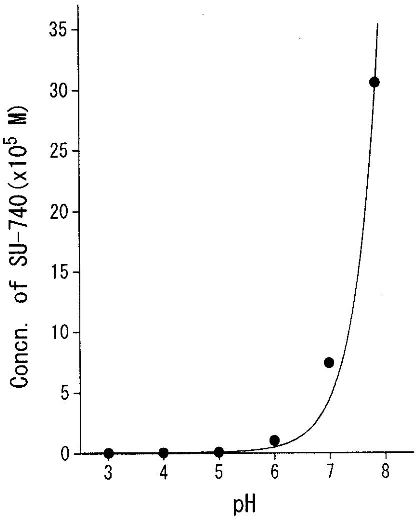

Fig. 2. pH-Solubility Profile of SU-740 at 25 °C

Size Reduction Products Figure 3 shows the dissolution profiles of the pulverized and intact SU-740 in pH 6.5 phosphate buffer at 37 °C. The mean diameters of the intact and pulverized SU-740 were about 18 and 2 μm, respectively, which were determined by the laser diffraction method. The pulverized SU-740 dissolved slightly faster than the intact SU-740 due to an increase in the specific surface area. However, the dissolved amount of the pulverlized SU-740 was only about 2.8×10^{-5} M at 180 min, indicating insufficient improvement of the dissolution rate by means of the size-reduction technique.

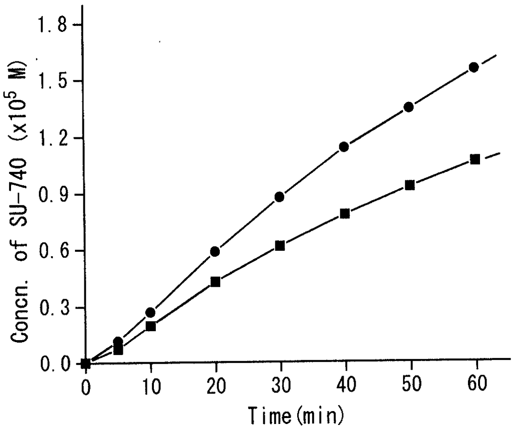

Fig. 3. Dissolution Profiles of Pulverized SU-740 (●, Mean Diameter 2 μm) and Intact SU-740 (■, 18 μm) in pH 6.5 Phosphate Buffer at 37 °C

Solid Dispersion Products Figure 4 shows the powder X-ray diffraction patterns of SU-740/PVP and SU-740/PEG solid dispersions in weight ratios of 1:5 and 1:10 (SU-740:polymer) prepared by the coprecipitation method. The sharp diffraction peaks due to SU-740 crystals disappeared, and only a halo-pattern was observed in the PVP system. In the case of the PEG system, the diffraction peaks at 7°, 13° and 16° disappeared and the diffraction pattern was identical to that of PEG alone. Futhermore, the endothermic peak of 138 °C due to the melting of SU-740 disappeared in DSC thermograms of the solid dispersions (data not shown). Similar results were obtained for the SU-740/PEG dispersions prepared by the fusion method. These results suggest that SU-740 forms homogeneous solid dispersions with PVP and PEG in which SU-740 is in an amorphous state.

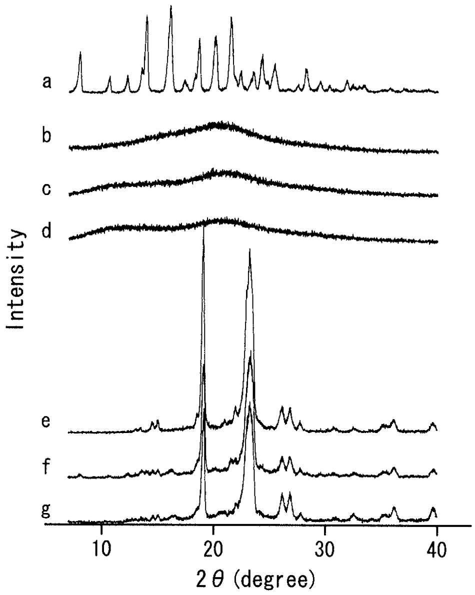

Fig. 4. Powder X-Ray Diffraction Patterns of Intact SU-740 and SU-740/PVP and SU-740/PEG Dispersions Prepared by Coprecipitation Method

a, SU-740 alone; b, PVP alone; c, PVP dispersion (SU-740:polymer=1:5 in weight ratio); d, PVP dispersion (1:10); e, PEG alone; f, PEG dispersion (1:5); g, PEG dispersion (1:10).

Figure 5 shows the dissolution profiles of SU-740/PVP dispersions prepared by the coprecipitation method. The dissolved amount of SU-740 increased with increasing the pH of the media, and the dissolution rates of the 1:10 dispersion were larger than those of the 1:5 dispersion in both pH 1.2 and 4.0 media. The dissolved amount of SU-740 in the pH 4.0 medium decreased after dissolution, which may be due to the dissociation of the PVP dispersion to the free SU-740, followed by recrystallization of SU-740. In the pH 6.5 medium, however, the high concentration of SU-740 after dissolution was maintained due to the protolytic dissociation of SU-740. Figure 6 shows the dissolution profiles of SU-740/PEG dispersions prepared by the coprecipitation and fusion methods. It is apparent that the coprecipitation method is superior to the fusion method in improving the dissolution rate of SU-740. Similar results were reported for the miconazole nitrate/PEG system.[9] When the dissolution behavior was compared between the PVP and PEG dispersions, the dissolution rate of the former was larger than that of the latter (see Figs. 5, 6), because of the higher solubilizing ability of PVP than PEG against SU-740, as is apparent from the solubility diagram of Fig. 7. In addition, other factors such as wettability and dispersibility may be concerned in the rate enhancement of the polymer systems.

Inclusion Complexes Figure 8 shows the phase solubility diagrams of SU-740/α-, β-, γ-CyD systems in pH 6.5 phosphate buffer at 25 °C. A pH of 6.5 was chosen because of convenience of the solubility measurement of SU-740 using HPLC, and pH 6.5 is close to that of the intestinal tract, a main absorption site of SU-740. The α-CyD system showed a typical A$_p$-type diagram, suggesting high order complexation.[12] The 1:2 (SU-740/

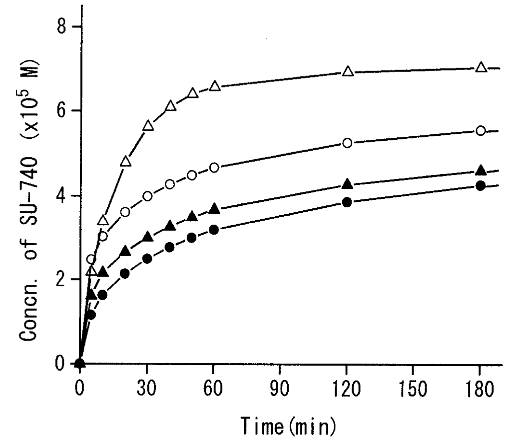

Fig. 6. Dissolution Profiles of SU-740/PEG Dispersions Prepared by Coprecipitation (Open Symbol) and Fusion (Closed Symbol) Methods in pH 6.5 Phosphate Buffer at 37 °C

○, PEG (1:5) coprecipitate; △, PEG (1:10) coprecipitate, ●, PEG (1:5) fused product; ▲, PEG (1:10) fused product.

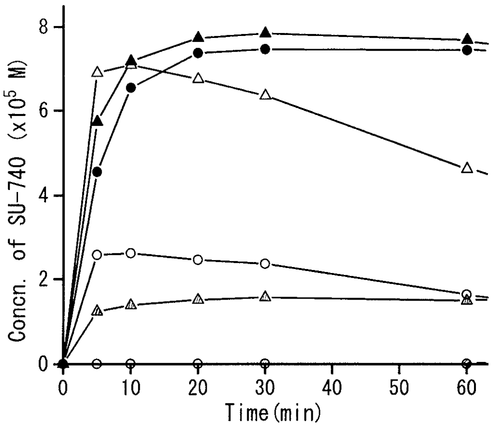

Fig. 5. Dissolution Profiles of SU-740/PVP Dispersions Prepared by Coprecipitation Method in pH 1.2 (Shaded Symbol), pH 4.0 (Open Symbol) and pH 6.5 (Closed Symbol) Fluids at 37 °C

⊘, ○, ●, 1:5 dispersion; ◬, △, ▲, 1:10 dispersion.

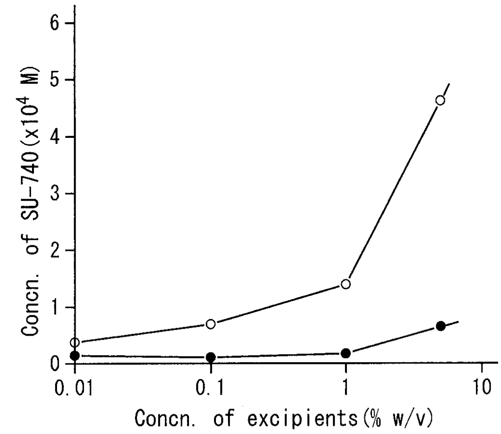

Fig. 7. Phase Solubility Diagrams of SU-740/PVP (○) and SU-740/PEG (●) Systems in pH 6.5 Phosphate Buffer at 37 °C

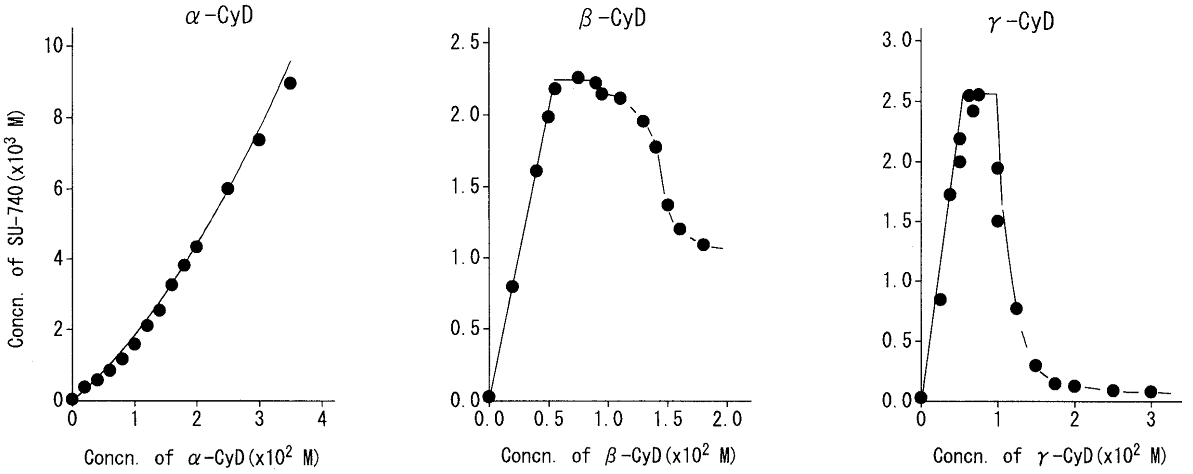

Fig. 8. Phase Solubility Diagrams of SU-740/α-CyD, β-CyD and γ-CyD Systems in pH 6.5 Phosphate Buffer at 25 °C

Table 1. Stability Constants and Stoichiometries of SU-740/CyD Complexes in pH 6.5 Phosphate Buffer at 25 °C

System	Stoichiometry	$K_{1:1}$ (M^{-1})	$K_{1:2}$ (M^{-1})
SU-740/α-CyD	1:2	56	1300
SU-740/β-CyD	1:2	23000	—
SU-740/γ-CyD	1:2	26000	—

α-CyD) stoichiometry was assumed on the basis of the above solubility data as well as the construction of a space filling molecular model. Therefore, the upward curvature of the α-CyD system was analyzed by the iteration method,[13] to obtain stability constants ($K_{1:1}$, $K_{1:2}$) of the 1 : 1 and 1 : 2 complexes. On the other hand, the β-, γ-CyD systems showed typical B_s-type solubility diagrams. The stoichiometry of the β-, γ-CyD complexes was determined to be 1 : 2 (guest : host) on the basis of the chemical analysis of the solid complexes isolated at the descending curvature portion of the diagrams. The apparent 1 : 1 stability constant was calculated from the initial linear portion of the diagram, assuming 1 : 1 complex formation at low concentration of CyDs. The results are listed in Table 1. The binding strength of β-CyD against SU-740 was almost the same as that of γ-CyD. On the other hand, the solubilizing ability of β-CyD in a higher concentration range ($>1.0\times10^{-2}$ M) was higher than that of γ-CyD, because the solubility of the 1 : 2 γ-CyD complex was lower than that of the 1 : 2 β-CyD complex. α-CyD solubilized SU-740 more effectively at higher concentrations ($>1.0\times10^{-2}$ M) than did β-, γ-CyDs, as is apparent from the A_p type solubility curve.

Figure 9 shows the dissolution profiles of the β-CyD complex in pH 1.2, 4.0 and 6.5 media, as well as that of the α-CyD complex in the pH 6.5 medium at 37 °C. The solid complex of SU-740 with β-CyD was prepared on the basis of the phase solubility diagrams, whereas that of α-CyD was prepared by the freeze-drying method in a molar ratio of 1 : 2 (see Experimental). The dissolution behavior of the α-CyD complex was inferior to that of the β-CyD complex, because of the smaller solubilizing ability of the former in a lower concentration range. The dissolution rates of the β-CyD complex in pH 1.2 and 4.0 media were smaller than those of the PVP (1 : 10) dispersion. On the other hand, β-CyD dissolved at a rate similar to that of the PVP (1 : 5) dispersion, the composition ratio of which was almost the same as the β-CyD complex (1 : 2 SU-740/β-CyD molar ratio corresponds to 1 : 5.3 weight ratio). On the other hand, the dissolution rate in the pH 6.5 medium was almost same between the β-CyD complex and the PVP (1 : 10) dispersion.

Stability Tests The SU-740/PVP (1 : 5, 1 : 10) solid dispersion prepared by the coprecipitation method and the SU-740/β-CyD inclusion complex were subjected to stability tests, because both preparations significantly improved the dissolution rate of SU-740. Figure 10 shows the dissolution profiles of the β-CyD complex and the PVP dispersions after storage at 40 °C and 75% RH for one month. No decrease in the SU-740 content was observed under the storage conditions. However, the dissolution rate of the PVP (1 : 5) dispersion decreased significantly, whereas the β-CyD complex and the PVP (1 : 10) dispersion showed no change. The decrease in the dissolution rate may be due to the crystallization of SU-740 in the matrix, although it was difficult to detect the crystallization by powder X-ray diffractometry because of the small crystal size in the crystallization process. Similar phenomena were observed in the nifedipine/PVP system.[14]

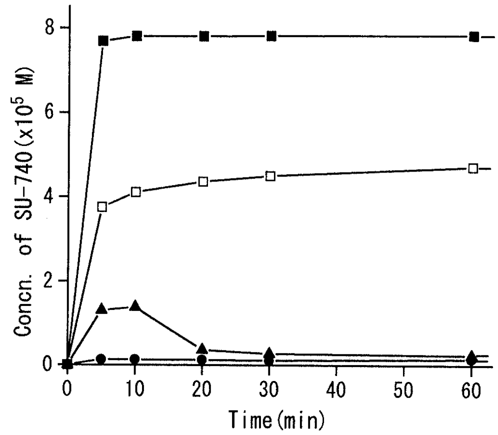

Fig. 9. Dissolution Profiles of SU-740/β-CyD Inclusion Complex in pH 1.2 (●), pH 4.0 (▲) and pH 6.5 (■) Fluids and SU-740/α-CyD Inclusion Complex (□) in pH 6.5 Fluid at 37 °C

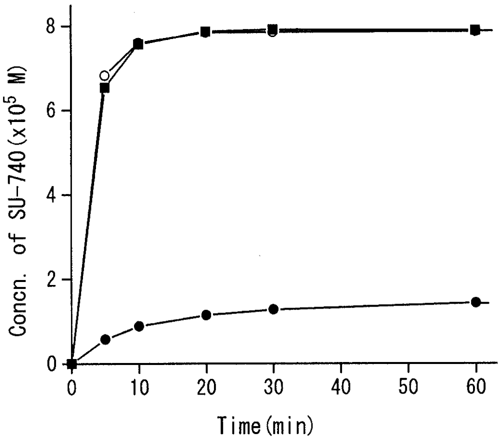

Fig. 10. Dissolution Profiles of SU-740/β-CyD Inclusion Complex (○) and SU-740/PVP Dispersions Prepared by Coprecipitation Method in Weight Ratios of 1 : 10 (■) and 1 : 5 (●), after Storage for One Month at 40 °C, 75% RH

Dissolution medium: pH 6.5 phosphate buffer at 37 °C.

Furthermore, the appearance of both PVP preparations changed during the storage, *i.e.*, the preparation was congealed due to the hygroscopicity of PVP. On the other hand, the β-CyD complex showed no such changes under the experimental conditions.

In conclusion, the solubility and dissolution rate of SU-740 were significantly improved by the formation of inclusion complexes and solid dispersions, whereas the size-reduction technique was less effective. The PVP dispersion was more effective than the PEG dispersion in enhancing the solubility and dissolution of the drug, which may be attributable to the higher solubilizing ability of the former than the latter. From the evaluation of the dissolution after storage, it can be concluded that the

β-CyD complexation is a first choice among three techniques employed for the formulation design of SU-740. This kind of knowledge will be useful for the improvement of oral bioavailability of poorly water-soluble drugs.

References

1) Higuchi W. I., Hiestand E. N., *J. Pharm. Sci.*, **52**, 67 (1963).
2) Brooke D., *J. Pharm. Sci.*, **63**, 344 (1974).
3) Chiou W. L., Riegelman S., *J. Pharm. Sci.*, **60**, 1281 (1971).
4) Sekikawa H., Naganuma T., Fujiwara J., Nakano M., Arita T., *Chem. Pharm. Bull.*, **27**, 31 (1979).
5) Sugimoto I., Kuchiki A., Nakagawa H., Tohgo K., Kondo S., Iwane I., Takahashi K., *Drug Dev. Ind. Pharm.*, **6**, 137 (1980).
6) Lin S., Wouessidijewe D., Poelman M., Duchene D., *Int. J. Pharm.*, **69**, 211 (1991).
7) Uekama K., Horiuchi Y., Kikuchi M., Hirayama F., *J. Incl. Phenom.*, **6**, 167 (1988).
8) Matsuda H., Ito K., Sato Y., Yoshizawa D., Tanaka M., Taki A., Sumiyoshi H., Utsuki T., Hirayama F., Uekama K., *Chem. Pharm. Bull.*, **41**, 1448 (1993).
9) Jafari M. R., Danti A. G., Ahmed I., *Int. J. Pharm.*, **48**, 207 (1988).
10) Utsuki T., Imamura K., Hirayama F., Uekama K., *Eur. J. Pharm. Sci.*, **1**, 81 (1994).
11) Kedzierewicz F., Hoffman M., Maincent P., *Int. J. Pharm.*, **58**, 221 (1990).
12) Higuchi T., Connors K. A., *Adv. Anal. Chem. Instr.*, **4**, 117 (1965).
13) Higuchi T., Kristiansen H., *J. Pharm. Sci.*, **59**, 1601 (1970).
14) Sugimoto I., Kuchiki A., Nakagawa H., *Chem. Pharm. Bull.*, **29**, 1715 (1981).