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Dissolution improvement of RS-8359 by the solid dispersion prepared by the solvent method

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Abstract

Study on dissolution improvement of a water-insoluble compound, RS-8359 ((±)-4-(4-cyanoanilino)-5,6-dihydro-7-hydroxy-7H-cyclopenta[*d*]pyrimidine) was carried out. A hydrochloric acid salt of RS-8359 had much higher solubility than its free form. However, the free form separated out of a neutral buffer solution instantaneously once the salt form was dissolved. We found that the dissolution properties were greatly improved by preparing a solid dispersion of the salt form with a water-soluble polymer mainly because the dissolved water-soluble polymer included in the solid dispersion retarded the precipitation rate of the free form. The crystallinity of the salt form in the solid dispersion did not affect the dissolution properties greatly. Furthermore, the importance of microenvironmental pH in the solid dispersion was suggested by a significant increase in the maximum concentration of RS-8359 in the dissolution process of the solid dispersion as compared with the case that the simple salt form was dissolved in the buffer solution that included the water-soluble polymer.

Keywords: Solid dispersion; Hydrochloric acid salt; RS-8359; Water-soluble polymers

1. Introduction

The following methods are used to improve solubility: (1) increasing the particle surface area available for dissolution by milling (Habib and Attia, 1985), (2) improving the wettability with surfactants or doped crystals (Chow et al., 1995), (3) decreasing crystallinity by preparing a solid dispersion (Flego et al., 1988; Craig and Newton, 1992; Yamaguchi et al., 1992), (4) use of inclusion compounds such as cyclodextrin derivatives (Pitha and Pitha, 1985), (5) use of polymorphisms or solvated compounds (Sekiguchi et al., 1973), (6) use of salt forms. Furthermore, a small amount of

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other compound in a crystal (Chow and Grant, 1989) or crystal habit (Burt and Mitchell, 1980; Femi-Oyewo and Spring, 1994) sometimes affects the dissolution properties. In the case of polymorphism or solvated compounds, a metastable form transits to a stable form when it is dissolved (Ghosh and Grant, 1995). Likewise, in the case of the salt form, the free form which is less soluble than the salt form can precipitate in a buffer solution.

RS-8359 is a basic drug that has inhibitory action of A-type of monoamine oxidase. Dissolution improvement of RS-8359 is necessary to improve bioavailability because the compound is practically insoluble in water. Solid dispersions for the dissolution improvement were studied in this paper. It is practically difficult to prepare a solid dispersion by a solvent method by using a single solvent, because RS-8359 is poorly soluble in organic solvents. Therefore, a mixed solvent is necessary to prepare a solid dispersion. We studied on the dissolution improvement of RS-8359 by preparing a solid dispersion with water-soluble polymers by using a mixed solvent of 1 N hydrochloric acid and methanol, which eventually resulted in a solid dispersion of the salt form.

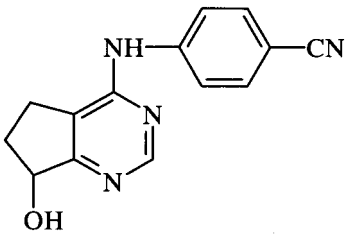
2. Materials and methods

2.1. Materials

RS-8359 is ((±)-4-(4-cyanoanilino)-5,6-dihydro-7-hydroxy-7H-cyclopenta[*d*]pyrimidine) and it was provided by Sankyo. The structural formula is shown in Fig. 1. Hydroxypropylmethylcellulose (Shin-Etsu Chemical, TC-5EW) (abbreviated as HPMC), hydroxypropylcellulose (Nippon Soda, SSL) (abbreviated as HPC), polyvinylpyrrolidone (BASF, K-30) (abbreviated as PVP), and low-substituted hydroxypropylcellulose (Nippon Soda, LH22) (abbreviated as L-HPC) were used as received. A reagent grade of methanol and 1 N hydrochloric acid (abbreviated as HCl) were used.

2.2. Preparation of the HCL salt of RS-8359

A 13-g aliquot of RS-8359 was dissolved in



$C_{14}H_{12}ON_4$

Fig. 1. Structural formula of RS-8359.

180 ml of a mixed solvent of 0.5 N HCl and methanol (13:5, v/v) and crystals were separated out by evaporating the mixed solvent. Then the crystals were filtered and dried at 50°C under reduced pressure. The results of elementary analysis are shown in Table 1. The crystals were found to be a monohydrate hydrochloric acid salt.

2.3. Preparation of solid dispersions

The formulas of the solid dispersions are shown in Table 2(A,B). RS-8359 was dissolved in the mixed solution of HCl and methanol, the water-soluble polymer was dissolved and then L-HPC was suspended. The mixed solvent was removed at 50°C under reduced pressure. The resultant dried mass was dried at 50°C under reduced pressure for 2 h again and sieved through 28-mesh screen. Sample J and K were prepared by the same method but L-HPC was excluded.

Table 1
Elementary analysis of the hydrochloric acid salt of RS-8359

	Monohydrate	
	Theoretical (%)	Assayed (%)
C	54.82	55.33
H	4.93	4.84
N	18.27	18.56
O	10.43	—
Cl	11.56	11.15

Table 2
Formulae of the solid dispersions A–F (A) and G–K (B) and their crystallinity

	(A)						(B)				
Solid dispersion	A	B	C	D	E	F	G	H	I	J	K
Mixing ratio (RS-8359/water-soluble polymer/L-HPC)	1:1:2	1:2:4	1:4:8	1:1:2	1:2:4	1:4:8	1:0:2	1:0:4	1:0:8	1:0.01:0	1:0.02:0
RS-8359 (g)	1.26	1.26	1.26	1.26	1.26	1.26	1.26	1.26	1.26	1.26	1.26
PVP K-30 (g)	1.26	2.52	5.04	—	—	—					
HPC SSL (g)							—	—	—	0.013	0.025
HPMC TC-5EW (g)	—	—	—	1.26	2.52	5.04					
L-HPC LH22 (g)	2.52	5.04	10.08	2.52	5.04	10.08	2.52	5.04	10.08	—	—
1 N HCl (ml)*	10	10	10	10	10	10	10	10	10	10	10
Methanol (ml)*	50	60	60	25	25	25	25	25	25	25	25
Relative crystallinity of RS-8359 HCl salt (%)	88.2	84.0	59.8	75.6	60.0	57.5	72.1	69.8	58.7	87.4	93.4

* These solvents were removed on the drying process.

Table 3
pH profile of solubility of RS-8359 at 20°C

pH	Solubility (μg/ml)
1.2	4750
2.3	366
4.1	12.7
5.1	6.7
6.8	5.0
7.5	7.2

2.4. Dissolution test

The dissolution tests were performed according to the paddle method at 200 rpm as the paddle rotating speed, in accordance with the Japanese Pharmacopoeia XIII, using 500 ml of pH 6.8 phosphate buffer solution including no polymer, 0.02% w/v PVP or 0.02% w/v HPMC at 37°C. The samples were taken out at the predetermined time intervals and filtered through an Ekicrodisc (0.45 μm) (Gelman Sciences Japan), followed by two-fold dilution with a mixed solution of 0.5 N HCl and methanol (1:4, v/v). The concentration of the samples was determined by using high-performance liquid chromatographic analysis with a reversed-phase column.

2.5. Powder X-ray diffraction (PXRD) analysis

Geiger Flex Rint 2200V (Rigaku Denki) was used with Cu-Kα radiation (40 kV/40 mA, $2\theta =$ 5.0–40.0°).

2.6. Measurement of the soluble fraction of L-HPC in the mixed solvent of 0.5 N HCL and methanol and identification test for HPC in the water-soluble fraction

A 10-g aliquot of L-HPC was suspended in 40 ml of the mixed solvent of 0.5 N HCl and MeOH (13:5, v/v), then the suspension was shaken for 30 min to dissolve the soluble fraction in the mixed solution and centrifuged at 3000 rpm for 15 min. The supernatant was filtered through Ekicrodisc (0.45 μm). The filtrate was dried at 70°C under reduced pressure, and then dried at 105°C for 2 h. The residue was weighed. Then, identification test for HPC was performed using the residue in accordance with Japanese Pharmacopeia XIII. One hundred milligrams of the residue was dissolved in 4 ml of water. One milliliter of anthrone TS was added to 2 ml of the above solution, gently, and color development was observed. The other 2 ml of the solution was heated to 70°C to observe turbidity, and then cooled to room temperature to observe the disappearance of the turbidity.

3. Results and discussion

RS-8359 is a practically insoluble drug in water, and dissolution improvement is necessary to improve its bioavailability. One method to improve dissolution properties is the use of a salt form. The pH profile of solubility of RS-8359 is shown in Table 3. The solubility of the compound is high at lower pHs and low at higher pHs. RS-8359 exists as a fully ionized form in the pH 1.2 solution. This suggests that it is possible to increase the solubility of the compound in water when the HCl-salt form is used.

The dissolution profiles of the salt form at pH 6.8 are shown in Fig. 2. In the case of RS-8359 HCl salt, the maximum concentration was 45 μg/ml at the very beginning, and then the amounts of dissolved drug decreased with the lapse of time. The precipitate found in the solution was only the free form of RS-8359 from PXRD analysis. It is known that the anhydrous form of theophylline changes to the hydrous form, which has lower solubility, in an aqueous solution (Smidt et al., 1986). In the case of RS-8359, once the salt form, which has higher solubility, was dissolved, the free form precipitated instantaneously because of its lower solubility. This resulted in the apparent maximum concentration of 45 μg/ml.

When water-soluble polymer, such as HPMC or PVP, was incorporated in the buffer solution, the maximum concentration was increased to 88 or 82 μg/ml, respectively (Fig. 3). The maximum concentration is determined by the sum of positive (dissolution rate) and negative (precipitation rate) effects. The precipitation rate in the buffer solution containing HPMC was significantly

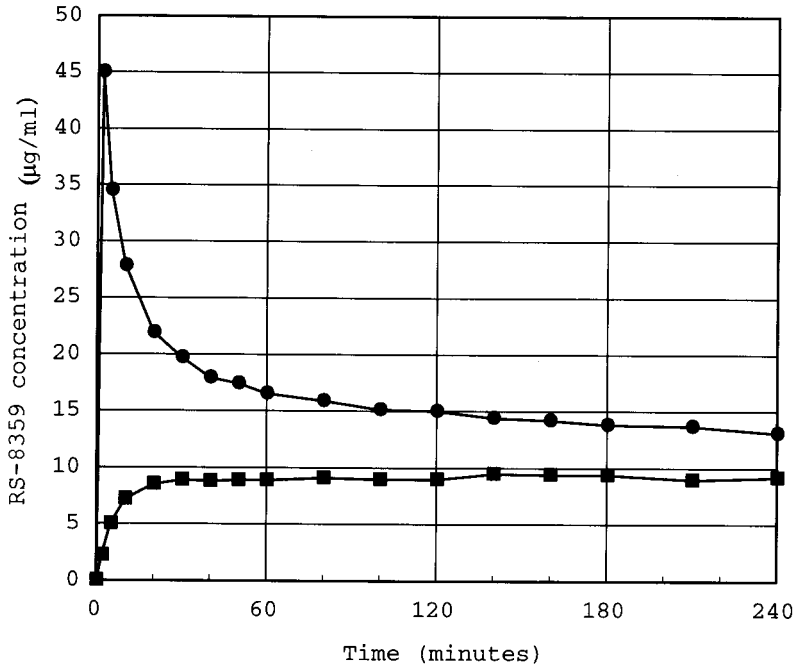


Fig. 2. Dissolution profiles of crystalline RS-8359 in pH 6.8 phosphate buffer solution without water-soluble polymers (100 mg of RS-8359 as the free form in 500 ml of the buffer solution). (■) Free form, (●) HCl salt.

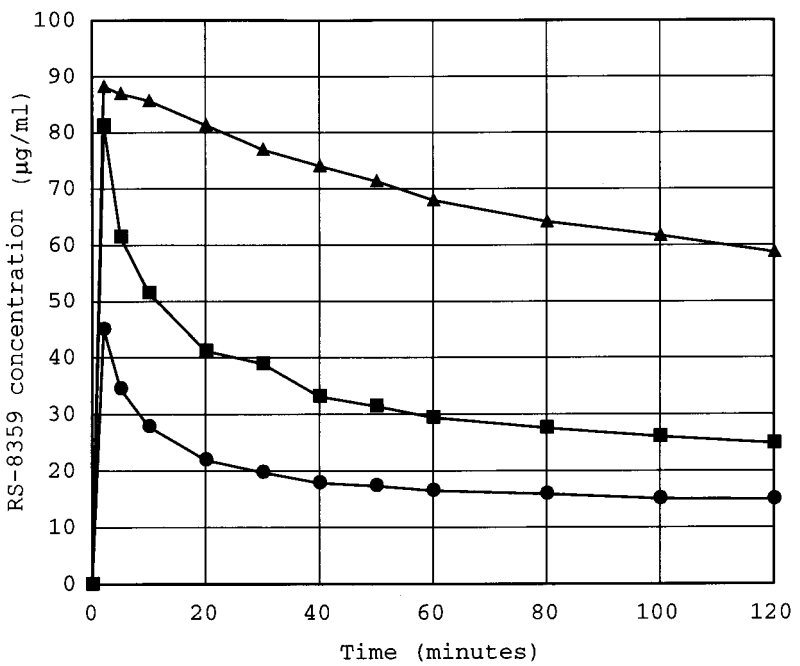


Fig. 3. Dissolution profiles of crystalline RS-8359 HCl salt in pH 6.8 buffer solution including water-soluble polymers (100 mg of RS-8359 as the free form in 500 ml of the buffer solution). (●) Without water-soluble polymers, (■) including 0.02% w/v PVP, (▲) including 0.02% w/v HPMC.

slower than in that containing PVP. This is because HPMC has a greater inhibitory effect on the precipitation of RS-8359 (Usui et al., 1997).

One method to improve dissolution properties is the preparation of a solid dispersion by dissolving the compound and the polymer in an organic solvent(s), and eventually evaporating the solvent(s). In the case of RS-8359, it is poorly soluble in organic solvents. Thus, it is practically difficult to prepare a solid dispersion by the solvent method by using a single solvent. The higher solubility of RS-8359 at a low pH suggests the use of a mixed solvent of an acidic solution with an organic solvent(s). A mixed solvent of 1 N HCl and methanol was selected to prepare the solid dispersion in this experiment, and L-HPC was incorporated as the adsorbent of the solid dispersion. The PXRD profiles of the solid dispersions prepared by using the mixed solvent are shown in Fig. 4. The free form of RS-8359 has characteristic peaks at 9.2, 13.1 and 26.9° and the salt form has them at 11.0, 18.4 and 25.3° as 2θ values. The solid dispersions contained crystalline part, and the crystal incorporated in the solid dispersion was RS-8359 HCl salt, judging from the results of the profiles of the PXRD, because only peaks originating from RS-8359 HCl salt were observed.

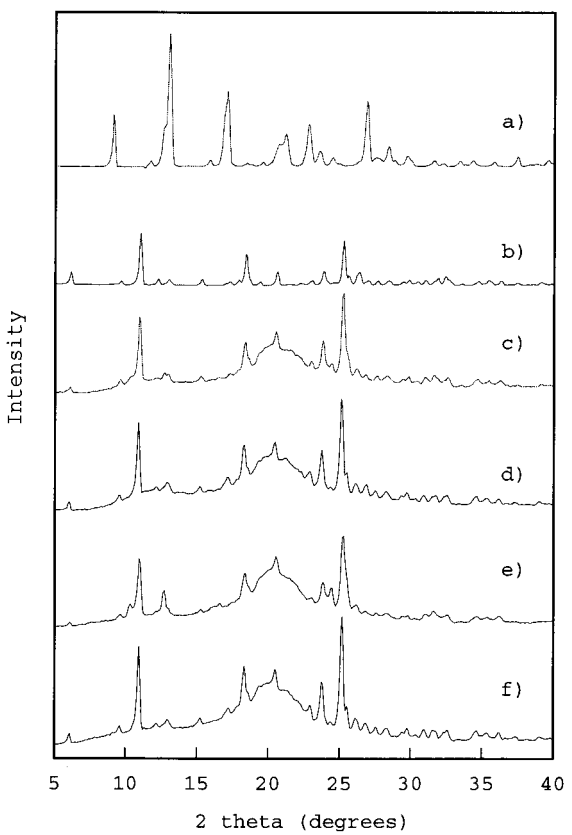


Fig. 4. Powder X-ray diffraction profiles of RS-8359 crystals and solid dispersions and their corresponding physical mixtures. (a) RS-8359 free form, (b) RS-8359 HCl salt, (c) solid dispersion A (RS-8359/PVP/L-HPC = 1:1:2), (d) solid dispersion D (RS-8359/HPMC/L-HPC = 1:1:2), (e) physical mixture A (RS-8359/PVP/L-HPC = 1:1:2), (f) physical mixture D (RS-8359/HPMC/L-HPC = 1:1:2).

The crystallinity of RS-8359 HCl salt in the solid dispersion was determined by comparing the area of the peak ratio of the solid dispersion with that of physical mixture, that is, by Eq. (1) (modified Hermans method, Hermans and Weidinger, 1948), based on the following assumption; the crystallinity of L-HPC and the water-soluble polymers are small enough to neglect.

$$Xcr = \frac{\left(\frac{\int I_{c-sd}(\theta)\mathrm{d}\theta}{\int I_{c-sd}(\theta)\mathrm{d}\theta - \int I_{a-sd}(\theta)\mathrm{d}\theta} \right)}{\left(\frac{\int I_{c-pm}(\theta)\mathrm{d}\theta}{\int I_{c-pm}(\theta)\mathrm{d}\theta - \int I_{a-pm}(\theta)\mathrm{d}\theta} \right)} \times 100 \quad (1)$$

where

Xcr: Relative crystallinity of RS-8359 HCl salt in the solid dispersion (%).

$\int I_{s-sd}(\theta)\mathrm{d}\theta$: Area of the PXRD of the crystalline part of the solid dispersion in the range of 2θ from 5.0 to 40.0°.

$\int I_{a-sd}(\theta)\mathrm{d}\theta$: Area of the PXRD of the amorphous part of the solid dispersion in the range of 2θ from 5.0 to 40.0°.

$\int I_{c-pm}(\theta)\mathrm{d}\theta$: Area of the PXRD of the crystalline part of the physical mixture in the range of 2θ from 5.0 to 40.0°.

$\int I_{a-pm}(\theta)\mathrm{d}\theta$: Area of the PXRD of the amorphous part of the physical mixture in the range of 2θ from 5.0 to 40.0°.

The relative crystallinity of RS-8359 HCl salt in the solid dispersion obtained according to Eq. (1)

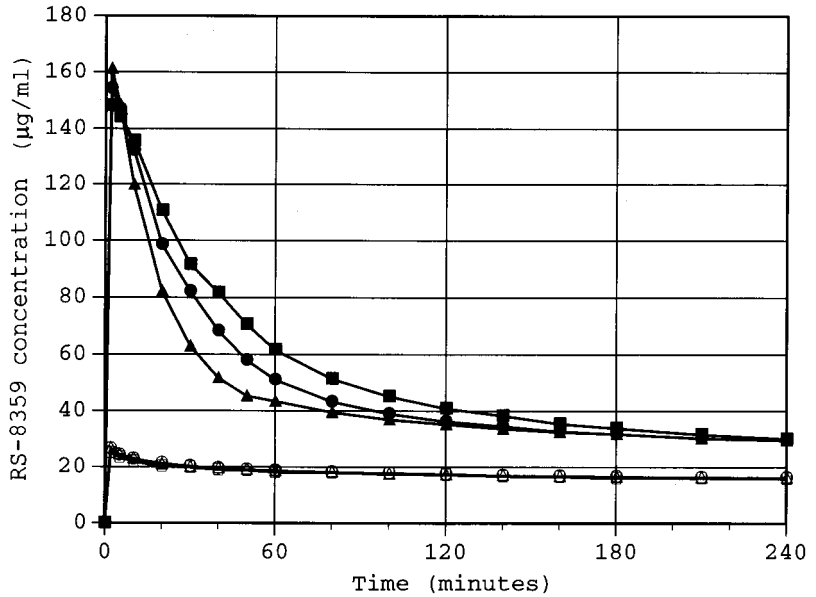


Fig. 5. Dissolution profiles of solid dispersions A, B, C, which include PVP and L-HPC, and their corresponding physical mixtures (100 mg of RS-8359 as the free form in 500 ml of pH 6.8 buffer solution). (■) Solid dispersion A, (□) physical mixture A; (●) solid dispersion B, (○) physical mixture B; (▲) solid dispersion C, (△) physical mixture C.

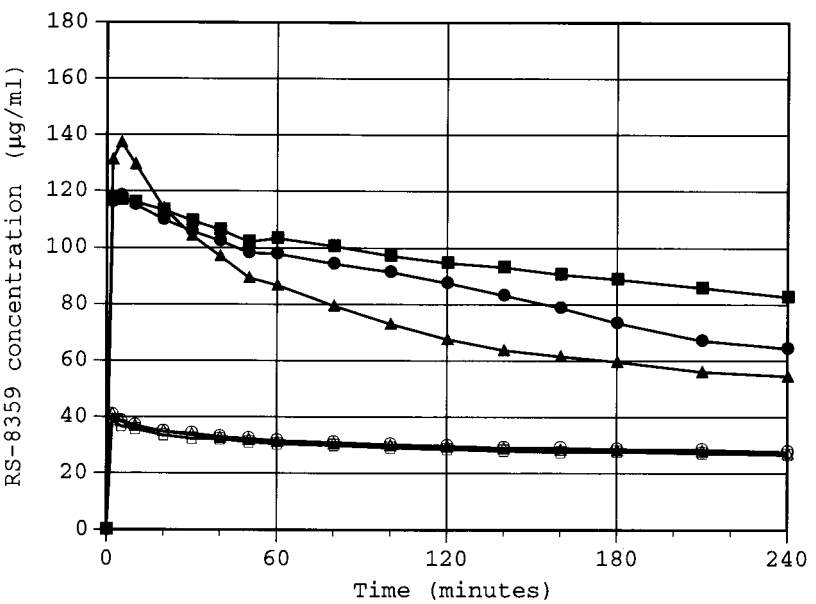


Fig. 6. Dissolution profiles of solid dispersions D, E, F, which include HPMC and L-HPC and their corresponding physical mixtures (100 mg of RS-8359 as the free form in 500 ml of pH 6.8 buffer solution). (■) Solid dispersion D, (□) physical mixture D; (●) solid dispersion E, (○) physical mixture E; (▲) solid dispersion F, (△) physical mixture F.

gives the estimation of the decreased crystallinity as compared with the physical mixture, and is shown in Table 2(A and B). The crystallinity of the salt form decreased as the ratio of the polymers increased. In the case of the solid dispersion including PVP and L-HPC, it decreased from 88

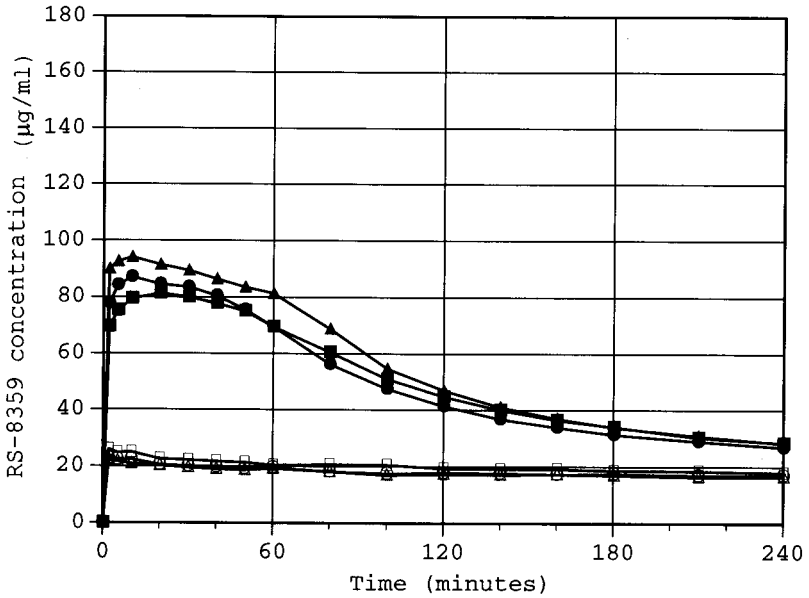


Fig. 7. Dissolution profiles of solid dispersions G, H, I, which include L-HPC and no water-soluble polymer and their corresponding physical mixtures (100 mg of RS-8359 as the free form in 500 ml of pH 6.8 buffer solution). (■) Solid dispersion G, (□) physical mixture G; (●) solid dispersion H, (○) physical mixture H; (▲) solid dispersion I, (△) physical mixture I.

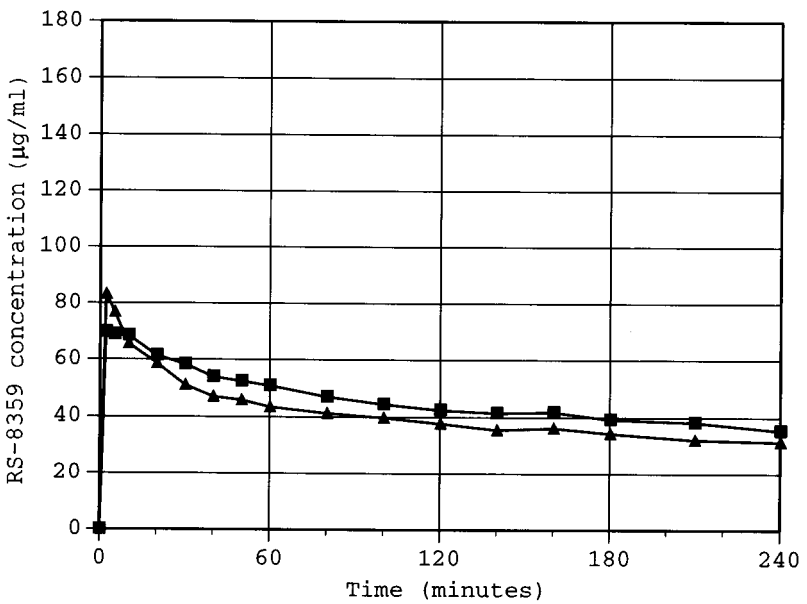


Fig. 8. Dissolution profiles of samples J (▲) and K (■) (100 mg of RS-8359 as the free form in 500 ml of pH 6.8 buffer solution).

to 60%, and in the case of the solid dispersion including HPMC and L-HPC, it decreased from 76 to 58%, as the ratio of the compound to the polymers was changed. Furthermore, in the case of the solid dispersion G, H or I including L-HPC and no water-soluble polymer, the crystallinity

also changed from 72 to 59% as the ratio of the compound to the L-HPC changed from 2 to 8. Base on these results, the amorphous part was increased as the content of the L-HPC increased, and the water-soluble polymers did not give a great impact. Furthermore, no interaction between RS-8359 and L-HPC is expected because no appreciable difference was observed between the IR spectra of solid dispersion G and the corresponding physical mixture (data are not shown).

Kawashima et al. (1993) reported that L-HPC contains water-soluble fraction. We determined the amounts of the soluble fraction of L-HPC in the mixed solvent of 0.5 N HCl and methanol. L-HPC which was used in this experiment, contained 0.8% of the soluble fraction in the mixed solvent in our experiment, and this fraction was also water-soluble. Furthermore, HPC identification test revealed that this fraction contained water-soluble HPC. Samples J and K, which contain small amounts of water-soluble HPC, have higher crystallinity than the other solid dispersions. Thus, the small amounts of water-soluble HPC do not give a great impact on the crystallinity change.

L-HPC swelled when it was suspended in the mixed solvent. It was thought that a partial amount of RS-8359 was sealed in the L-HPC after the drying process, and the sealed part contributed to the production of the amorphous part of RS-8359 HCl salt.

The dissolution profiles of various solid dispersions are shown in Figs. 5–7. The solid dispersion has higher solubility than the physical mixture. The solubility of an amorphous state is usually higher than that of an crystalline state. The maximum concentrations of the solid dispersions are much higher than the physical mixtures. While the crystallinity of RS-8359 HCl salt in the solid dispersion was decreased to 58–88%, the difference in the maximum concentrations among the solid dispersions was very small. It means that higher solubility of the solid dispersion was not induced mainly by the crystallinity change. It is thought that, in the cases of the solid dispersions, the polymer dissolved first and then RS-8359 HCl salt dissolved, because RS-8359 HCl salt existed in the polymer matrix. Thus, the inhibitory effect of the water-soluble polymer on the precipitation of RS-8359 was available. This is also true for the solid dispersions G, H and I. In the cases of these solid dispersions, the soluble fraction, which contains water-soluble HPC, played the same role as HPMC or PVP. Assuming that the water-soluble fraction of L-HPC is mainly composed of water-soluble HPC, we prepared samples J and K. The dissolution profiles are shown in Fig. 8. The precipitation rates of these samples were also slower than the physical mixtures, but slightly faster than solid dispersions G–I. We think that the thin film of HPC was formed on the surface of L-HPC in the cases of solid dispersions G–I, and HPC dissolved faster than the cases of samples J and K.

On the other hand, in the case of the physical mixtures, RS-8359 HCl salt dissolved first and then the polymer dissolved, because RS-8359 HCl salt did not exist in the matrix and the dissolution rate of RS-8359 HCl salt was faster than the polymers. Thus, RS-8359 had precipitated before the polymer effects took place.

The dissolved amounts of the compound from the solid dispersion in 240 min were still higher than solubility of the free form. This is partly because the equilibrium had not been attained at the point, and partly because the polymers have a solubilization effect (Usui et al., 1997).

When the maximum concentrations in Fig. 3 were compared to those in Figs. 5 and 6, the latter ones were higher than the former, that is, the maximum concentration of the solid dispersion in the buffer solution without polymer is higher than that of the salt form that was dissolved in the buffer solution including the polymer. Doherty and York (1989) reported that when a basic drug and an acidic compound were dispersed in a polymer matrix, the solubility of the drug increased by a decrease in the microenvironmental pH. In our experiment, it was thought that when the salt form of RS-8359 dissolved, the microenvironmental pH in the polymer matrix was also lowered, and this increased the solubility of the compound in the matrix and also the maximum concentration, eventually.

In conclusion, the maximum concentration of RS-8359 was increased by decreasing the precipitation rate with the water-soluble polymers in the solid dispersions and by decreasing microenvironmental pH. The solid dispersion has advantages over the simple salt form of RS-8359 to attain higher dissolution, even though the crystallinity is not so lowered.

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