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Dissolution Behavior of Flufenamic Acid dispersed in Cross-linked Insoluble Polyvinylpyrrolidone: Effect of Water-soluble Polymers added as the Third Component[1,2]

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Dissolution profiles of flufenamic acid (FFA) dispersed in cross-linked insoluble polyvinylpyrrolidone (polyvinylpolypyrrolidone, PVPP) were investigated by a dispersed amount method. The concentration of FFA rose very quickly and then decreased gradually, showing a typical supersaturation phenomenon. On the other hand, no supersaturation phenomenon was observed in the case of samples prepared with crystalline cellulose and potato starch as carriers in solid dispersions.

In an attempt to stabilize the supersaturated state, the effects of the addition of water-soluble polymers to solid dispersions of FFA and PVPP were investigated. An adequate stabilization was obtained by the addition of methyl celluloses.

Analysis of factors affecting the dissolution profiles of FFA and prediction of the dissolution behavior of FFA were carried out by a statistical technique. It was found that the penetration rate of water into sample powders, the amount of FFA adsorbed by PVPP, the cohesion tendency of sample powders and the viscosity of the dissolution medium were important in the analysis of dissolution mechanisms and prediction of dissolution profiles of FFA from these systems.

Keywords——cross-linked polyvinylpyrrolidone; flufenamic acid; methyl cellulose; solid dispersion; dissolution; water penetration; adsorption; viscosity; multiple regression analysis

Cross-linked insoluble polyvinylpyrrolidone (polyvinylpolypyrrolidone, PVPP) obtained by proliferous polymerization of *N*-vinylpyrrolidone exhibits a high swelling pressure.[3] For that reason, PVPP is especially useful as a disintegrating agent in pharmaceutical formulations. Sorption and desorption properties of numerous drugs with PVPP were also studied by Frömming *et al.*, and the possible interactions of PVPP with various drugs were investigated in detail.[4] On the other hand, many studies have been carried out on the enhancement of the solubility and dissolution rate of slightly soluble drugs by means of a solid disperison or molecular dispersion in various polymers such as polyethyleneglycol,[5] polyvinylpyrrolidone[6] and crystalline cellulose.[7]

One of the purposes of the present research was to evaluate PVPP as a carrier compound in a solid dispersion system with flufenamic acid (FFA), a non-steroidal antiinflammatory drug, in comparison with crystalline cellulose, potato starch and carboxymethyl cellulose calcium, which are all insoluble polymers generally used as additives in pharmaceutical formulations. Moreover, the effects of water-soluble polymers added as the third component in the preparation of FFA/PVPP solid dispersion samples on the dissolution of FFA were investigated by a statistical technique.

Experimental

Materials——FFA, generously supplied by Taisho Pharmaceutical Co., Ltd., was used after recrystallization from ethanol–water. PVPP was generously supplied by BASF Japan Ltd. Crystalline cellulose of JP X grade was purchased from Asahi Kasei Co., Ltd. Potato starch of JP X grade was purchased from

Yoshida Pharmaceutical Co., Ltd. Carboxymethyl cellulose calcium of JP X grade was generously supplied by Sankyo Co., Ltd. These water-insoluble polymers were used after passage through a 100 mesh sieve. Twenty-five water-soluble polymers used are listed in Table I. Locust bean gum and guar gum were generously supplied by Sansho Co., Ltd. Other polymers used were the same commercial products as described in the previous paper.[8]

Preparation of Solid Dispersion Samples——Chart 1 shows the method for dispersion of FFA in PVPP, crystalline cellulose, potato starch and carboxymethyl cellulose calcium. FFA and each polymer in various weight ratios were dissolved or suspended in ethanol and a suitable amount of water-soluble polymer was added. The mixture was agitated well at about 70°C, then the residue was dried *in vacuo* at room temperature for 24 h, ground well in a mortar and sieved. The fraction retained on a 200 mesh sieve and passing a 100 mesh sieve was used in the following experiments.

Identification of Compounds——Powder X-ray diffractometry and differential scanning calorimetry were employed in the same way as described in the previous paper.[9]

Procedure for Dissolution Study——The dissolution profiles of FFA from sample powder was determined by a dispersed amount method. Using a dissolution cell similar to that described by Sekiguchi *et al.*,[10] a certain excess of sample powder (equivalent to five times the saturated concentration of FFA) was weighed accurately and put in the dissolution cell, which was kept at 37°C by circulating constant temperature water

Table I. Water-soluble Polymers used in This Study

Methyl cellulose (13—18 cP)[a] (MC-I)
Methyl cellulose (20—30 cP)[a] (MC-II)
Methyl cellulose (80—120 cP)[a] (MC-III)
Methyl cellulose (350—550 cP)[a] (MC-IV)
Methyl cellulose (1200—1800 cP)[a] (MC-V)
Methyl cellulose (4000 cP)[a] (MC-VI)
Methyl cellulose (7000—10000 cP)[a] (MC-VII)
Polyvinylpyrrolidone K-30 (PVP K-30)
Polyvinylpyrrolidone K-90 (PVP K-90)
Dextran T-40
Dextran T-70
Hydroxypropyl cellulose-S (HPC-SL)
Hydroxypropyl cellulose-L (HPC-L)
Hydroxypropyl cellulose-H (HPC-H)
Polyvinyl alcohol (2000)[b] (PVA)
Polyethyleneglycol-4000 (PEG)
Carboxymethyl cellulose sodium (1050)[b] (CMC-Na)
Sodium alginate
Carrageenan
Gum arabic
Gum tragacanth
Locust bean gum
Guar gum
Gelatin (J.I.S. first grade)
Pectin

a) Data in parentheses indicate the viscosity of 2 % aqueous solution at 20°C, supplied by Tokyo Kasei Industrial Co., Ltd.

b) Data in parentheses indicate the degree of polymerization, supplied by Tokyo Kasei Industrial Co., Ltd.

FFA 1 g

1) add water-insoluble polymer
2) add water-soluble polymer
3) dissolve or suspend in 100 ml of ethanol
4) agitate well for 5 min at 70°C
5) remove the solvent *in vacuo* at 70°C
6) dry *in vacuo* at room temperature for 24 h
7) grind in a mortar
8) sieve (100—200 mesh)

sample

Chart 1. Preparative Method for Sample Powder in the outer vessel. To this was added 50 ml of 1/15 M phosphate buffer solution (pH 6.4), which had previously been brought to 37°C. Immediately after the addition, stirring (500 rpm) was begun with a magnetic stirrer. The solution was sampled at appropriate intervals and filtered through a Toyo TM-2 membrane filter (0.45 μm). The concentration of FFA in the filtrate was determined by the ultraviolet (UV) absorption method after dilution with 1/15 M phosphate buffer solution (pH 6.4).

Procedure for Determination of Factors affecting the Dissolution of FFA——The following factors, based on the physico-chemical properties of sample powder or water-soluble polymers added as the third component, were selected as possible factors affecting the dissolution of FFA from these systems.

1) Penetration of Water into Sample Powder (*PW*): One hundred mg of each powder was packed in a graduated glass tube (inner diameter 2.52 mm) whose bottom had been covered with Toyo No. 5B filter paper by tapping mechanically several times to give 8.0 cm height. The glass tube was placed perpendicularly in the thermostat. From the time at which 0.2 ml of 1/15 M phosphate buffer solution (pH 6.4) was put on the packed powder, the decreasing length of the solution was followed at 37°C. As a linear relation was observed between the amount of the solution penetrated and the square root of time, the slope was used as a measure of penetration of water into sample powder.

2) Amount of FFA adsorbed by PVPP in Water-soluble Polymer Solution (*AA*): One hundred mg of PVPP and 10 ml of 0.3 g/l FFA in 1/15 M phosphate buffer solution (pH 6.4) containing 1.5 g/l water-soluble polymers were put into a 25 ml test tube and kept in the thermostat for 48 h at 37°C. The solution was filtered through a Toyo TM-2 membrane filter (0.45 μm). The concentration of FFA in the filtrate was determined by the UV absorption method after dilution with the buffer solution.

3) Hardness of Compressed Tablet of Sample Powder (*HT*): A tablet consisting of 100 mg of sample powder (diameter 10 mm), which had been compressed directly under 200 kg/cm^2, was tested in a Kiya hardness tester.

4) Angle of Repose of Sample Powder (*AR*): *AR* was determined by means of a hand-made apparatus able to determine the angle of repose of a small amount of sample powder (2—3 g).

5) Solubility or Insolubility of Water-soluble Polymers in Ethanol (*SI*): Three hundred mg of water-soluble polymer was suspended in 100 ml of ethanol, and the solution was agitated well at 70°C for 5 min. The water-soluble polymers were assigned the scores 1 and 0 according to whether they were soluble in ethanol as judged with the naked eye, or not, respectively.

Determinations of the following factors, based on the physico-chemical properties of water-soluble polymers, were carried out as described in the previous paper:[8] 6) thickness of gel formed on the polymer disk surface (*GF*), 7) pH of polymer solution (*PP*), 8) viscosity of polymer solution (*VP*), and 9) apparent dissolution rate of polymers (*DP*).

Results and Discussion

Dissolution Behavior of FFA dispersed in PVPP

Figure 1 shows the powder X-ray diffraction patterns of FFA/PVPP solid dispersion systems which were prepared at various weight ratios. Several sharp diffraction peaks attributed to FFA crystals gradually decreased with increase in the concentration of PVPP, and peaks completely disappeared at ratios of 1:1—1:5. In the case of a physical mixture of FFA and PVPP, sharp peaks attributed to FFA crystals were apparent. In differential scanning calorimetry, no endothermic peak accompanying the melting of FFA crystals was observed at the above ratios (1:1—1:5). Therefore, FFA was considered to be in amorphous state in PVPP at these weight ratios. The dissolution properties of FFA from these systems as determined by the dispersed amount method are shown in Fig. 2. The concentration of FFA rose very quickly and then decreased gradually, showing typical supersaturation phenomena at weight ratios of 1:2—1:5. These results coincide well with the disappearance FFA crystals in sample powders. The decrease of FFA concentration was due to phase transition to stable forms accompanied by crystallization. The increase of PVPP in samples might have resulted in retardation of phase change, but its effect was not great. Figure 3 shows the powder X-ray diffraction patterns of FFA dispersed in crystalline cellulose, potato starch and carboxymethyl cellulose calcium, which are generally used as additives in pharmaceutical formulations. In all cases, the sharp diffraction peaks attributed to FFA crystals were still seen, in contrast to the case of PVPP. No supersaturation phenomenon was observed when these sample powders were dispersed under the same conditions, except for the case of carboxymethyl

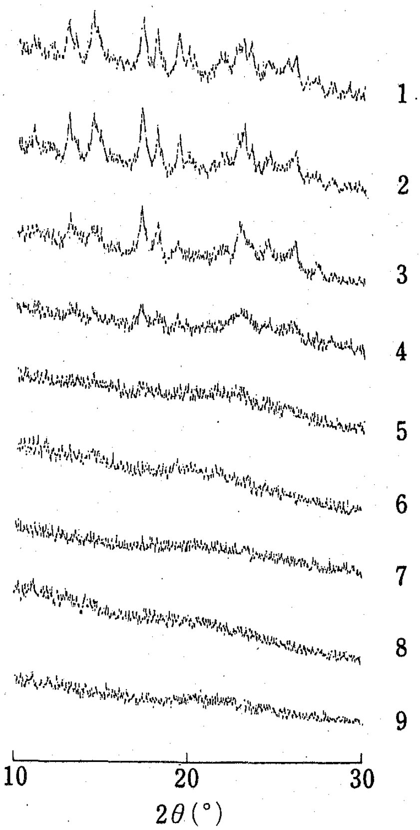

Fig. 1. Powder X-Ray Diffraction Patterns of FFA/PVPP Solid Dispersion Samples with Various Weight Ratios

1, 5:1; 2, 4:1; 3, 3:1; 4, 2:1; 5, 1:1; 6, 1:2; 7, 1:3; 8, 1:4; 9, 1:5.

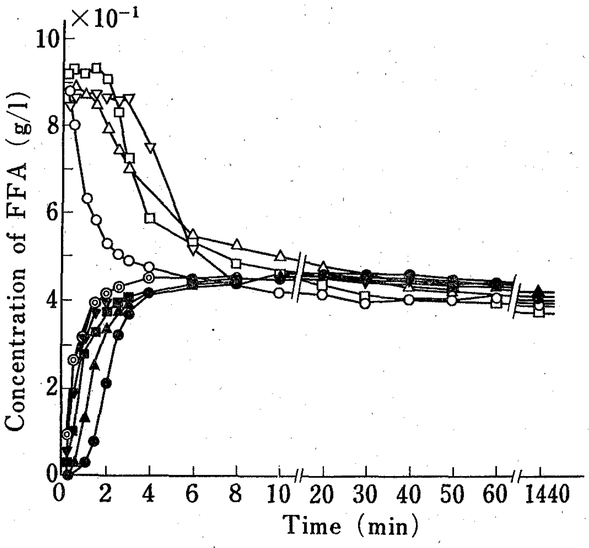

Fig. 2. Dissolution Profiles of FFA/PVPP Solid Dispersion Samples with Various Weight Ratios in 50 ml of pH 6.4 Phosphate Buffer Solution (at 37°C, 100 rpm)

●, 5:1; ▼, 4:1; ■, 3:1; ▼, 2:1; ◎, 1:1; ○, 1:2; △, 1:3; □, 1:4, ▽, 1:5.

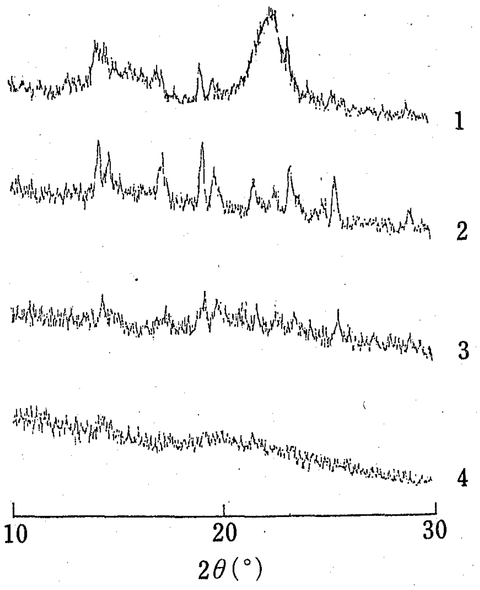

Fig. 3. Powder X-Ray Diffraction Patterns of FFA dispersed in Various Water-insoluble Polymers

1, crystalline cellulose; 2, potato starch; 3, carboxymethyl cellulose calcium; 4, PVPP.

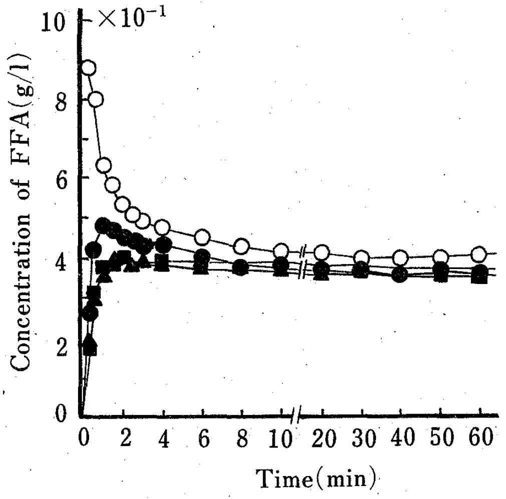

Fig. 4. Dissolution Profiles of FFA dispersed in Various Water-insoluble Polymers in 50 ml of pH 6.4 Phosphate Buffer Solution (at 37°C, 500 rpm)

▲, crystalline cellulose; ■, potato starch; ●, carboxymethyl cellulose calcium; ○, PVPP.

cellulose calcium as shown in Fig. 4. A slight supersaturation was observed with carboxymethyl cellulose calcium, but the maximum concentration attained was not as great as with PVPP.

These results indicate that the disappearance of FFA crystals essentially occurs only in the case of PVPP as an insoluble carrier for solid dispersion systems of FFA.

Stabilization of Supersaturation State

The stabilization of the supersaturation state of FFA affords a high dissolution rate for a prolonged period and an increase of bioavailability when the samples are administered orally.[11] As shown in Fig. 2, the crystallization of FFA dispersed in PVPP (1: 2—1: 5) was relatively rapid and the concentrations of FFA almost coincided with the solubility of intact FFA after 10 min in all cases. For the stabilization of the supersaturation state, the effects of addition of water-soluble polymers to a sample of FFA/PVPP (1: 2) were investigated. As an example, the effects of methyl celluloses (MCs) are shown in Figs. 5 and 6. A marked stabilization of the supersaturation state was observed in all cases, but no great differences among the kinds of MCs and with various amounts of MCs added were apparent under the present limited range of experimental conditions. The effects of other water-soluble polymers are also shown in Table II. The dissolution profile of FFA from each sample was expressed as the maximum concentration of FFA (C_m), the time at the maximum concentration (T_m), the area under the dissolution curve (*AUDC*), and the apparent crystallization rate constant (k_r) which was calculated according to the reported equation,[12] $k_r = \ln(C_t - C_s)/t$, where C_t is the concentration at time t and C_s the equilibrium concentration. These dissolution parameters were used in the statistical analysis described later. C_m and T_m were scarcely affected by diverse water-soluble polymers. On the other hand, *AUDC* and k_r were changed significantly. In particular, good retardation of the crystallization process of FFA was obtained with a series of MCs.

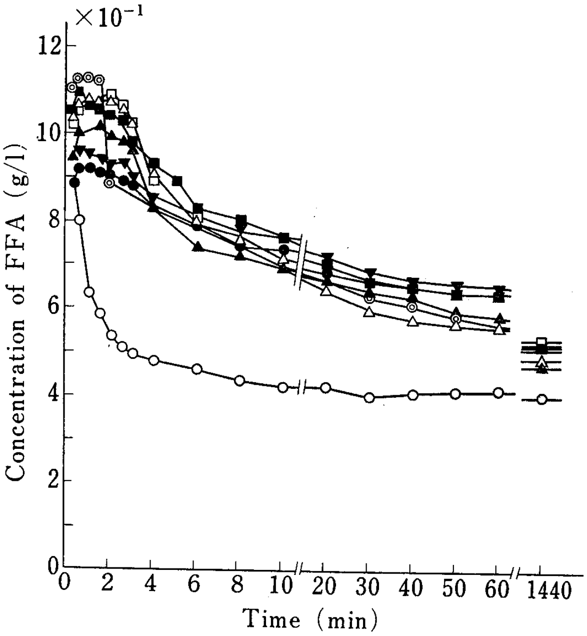

Fig. 5. Dissolution Profiles of FFA/PVPP/MCs (1 : 2 : 0.3) Solid Dispersion Samples in 50 ml of pH 6.4 Phosphate Buffer Solution (at 37°C, 500 rpm)

●, MC-I; ▲, MC-II; ▼, MC-III; ◎, MC-IV; △, MC-V; ■, MC-VI: □, MC-VII; ○, FFA/PVPP (1: 2) solid dispersion sample (reference).

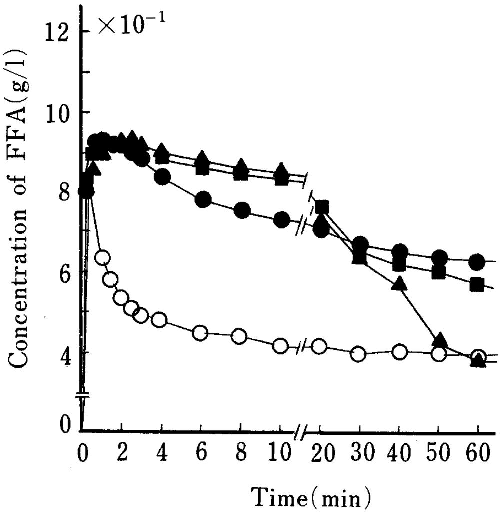

Fig. 6. Dissolution Profiles of FFA/PVPP/MC-I Solid Dispersion Samples in 50 ml of pH 6.4 Phosphate Buffer Solution (at 37°C, 500 rpm)

●, FFA/PVPP/MC-I (1: 2: 0.3); ■, FFA/PVPP/MC-I (1: 2: 0.6); ▲, FFA/PVPP/MC-I (1: 2: 0.9); ○, FFA/PVPP (1: 2) solid dispersion sample (reference).

Table II. Dissolution Parameters of FFA/PVPP/Water-soluble Polymer Systems

Water-soluble polymer	$C_m \times 10^{-1}$ (g/l)	T_m (min)	$AUDC \times 10^{-2}$ (g·min/l)	$k_r \times 10^2$ (min^{-1})
Not added	8.76	0.25	2.51	21.6
MC-I	9.21	0.50	4.11	4.78
MC-II	10.2	1.50	3.97	5.33
MC-III	9.61	0.50	4.24	4.86
MC-IV	11.2	1.00	3.95	6.25
MC-V	10.8	1.00	3.86	6.96
MC-VI	11.0	0.50	4.27	6.81
MC-VII	10.8	2.00	4.19	8.66
PVP K-30	11.3	2.00	3.23	14.4
PVP K-90	10.1	2.00	3.47	8.19
Dextran T-40	8.85	1.00	2.81	16.0
Dextran T-70	9.17	0.50	2.56	21.1
HPC-SL	9.25	0.50	2.63	14.4
HPC-L	8.16	1.50	2.44	13.8
HPC-H	8.95	1.00	3.11	9.27
PVA	8.67	0.50	2.81	9.60
PEG	6.98	0.25	2.61	14.8
CMC-Na	9.47	0.50	2.10	10.8
Sodium alginate	9.75	0.25	2.71	18.3
Carrageenan	8.67	0.50	2.75	12.7
Gum arabic	8.40	1.00	2.96	14.7
Gum tragacanth	9.45	1.00	2.86	17.2
Locust bean gum	9.07	0.25	2.39	23.2
Guar gum	8.67	0.50	3.01	11.8
Gelatin	9.15	0.50	2.31	23.8
Pectin	9.31	0.25	2.57	20.2

Each datum is the mean of two determinations. C_m means maximum concentration of FFA. T_m means time at C_m. $AUDC$ means area under the dissolution curve (0—60 min). k_r means apparent crystallization rate constant.

Statistical Approach for Analysis of Factors affecting *AUDC* and k_r

Scarcely any variations of both C_m and T_m were observed with diverse water-soluble polymers, as described above, so $AUDC$ and k_r were used as dependent variables. Nine factors (PW, AA, HT, AR, SI, GF, PP, VP and DP) initially selected as predictors of $AUDC$ and k_r are listed in Table III. The scatter diagrams of some factors with $AUDC$ are shown in Fig 7. A parabolic relation between PW and $AUDC$ was observed clearly, and the series of MCs lay near the maximum positions in Fig. 7a, giving high values of $AUDC$. AA was negatively related and AR was positively related with $AUDC$, as shown in Fig. 7b and 7c. Moreover, a parabolic relation between log VP and $AUDC$ was also observed, though the relation was relatively weak, as shown in Fig. 7d. Therefore, it seemed appropriate to

Table III. Physico-chemical Properties selected as Predictors

Water-soluble polymer	$PW^{a)} \times 10^2$ (ml/$\sqrt{\text{min}}$)	$AA^{a)} \times 10^2$ (g/g)	$AR^{b)} \times 10^{-1}$ (°)	$VP^{c)} \times 10^{-2}$ (cP)	$HT^{c)}$ (kg)	PP	$DP^{c)}$ (mg/min)	$CF^{b)}$ (mm)	SI
Not added	7.99	1.24	5.36	——	2.02	——	——	——	—
MC-I	4.81	1.17	6.22	0.0234	2.64	6.58	2.02	0.554	0
MC-II	3.74	1.23	7.04	0.0235	2.76	5.31	1.76	0.970	0
MC-III	3.84	1.20	6.38	0.117	2.17	4.96	3.61	0.704	0
MC-IV	4.00	1.15	6.98	0.198	2.57	5.23	3.11	0.524	0
MC-V	3.21	1.30	6.42	0.248	2.08	5.40	2.88	1.06	0
MC-VI	4.44	1.43	6.34	0.432	2.68	5.42	4.08	1.19	0
MC-VII	4.99	1.63	6.40	0.704	2.45	5.63	3.25	1.02	0

Water-soluble polymer	$PW^{a)}\times 10^2$ (ml/$\sqrt{\text{min}}$)	$AA^{a)}\times 10^2$ (g/g)	$AR^{b)}\times 10^{-1}$ (°)	$VR^{c)}\times 10^{-2}$ (cP)	$HT^{c)}$ (kg)	PP	$DP^{c)}$ (mg/min)	$CF^{b)}$ (mm)	SI
PVP K-30	5.09	1.43	5.66	0.00802	3.13	4.56	4.35	0.718	1
PVP K-90	3.53	1.60	5.94	0.0230	3.53	6.07	2.64	0.824	1
Dextran T-40	7.38	1.68	6.40	0.00815	3.87	7.34	5.72	0.618	0
Dextran T-70	7.53	1.63	6.32	0.00840	2.94	7.72	3.61	1.11	0
HPC-SL	1.93	1.63	5.90	0.0137	2.15	5.66	2.61	0.632	1
HPC-L	1.95	1.63	5.80	0.0186	2.00	6.87	1.05	0.768	1
HPC-H	1.84	1.75	6.20	1.04	3.24	5.93	0.492	0.868	1
PVA	6.74	1.45	6.08	0.0140	2.38	6.35	1.68	0.620	0
PEG	6.69	1.42	5.44	0.00824	1.33	6.19	25.7	0.455	1
CMC-Na	0.666	1.82	5.92	0.210	2.74	6.79	1.78	1.80	0
Sodium alginate	1.67	1.77	5.46	2.13	2.42	7.33	1.58	1.78	0
Carrageenan	0.576	1.33	5.50	4.01	2.72	9.00	1.26	2.15	0
Gum arabic	7.28	1.28	5.88	0.0112	2.94	4.90	4.11	1.11	0
Gum tragacanth	1.01	1.42	5.80	1.40	3.02	5.13	1.76	1.59	0
Locust bean gum	0.347	1.67	6.02	0.642	2.41	6.67	1.84	0.682	0
Guar gum	1.07	1.35	6.82	19.4	2.41	6.40	2.13	0.442	0
Gelatin	6.83	1.66	6.16	0.0103	2.20	6.11	8.25	0.450	0
Pectin	1.33	1.69	5.60	0.0864	2.29	3.77	2.79	0.876	0

a) Each datum is the mean of two determinations. *b*) Each datum is the mean of five determinations. *c*) Each datum is the mean of three determinations. *PW* means the value of penetration of water into sample powder. *AA* means the amount of FFA adsorbed by PVPP in water-soluble polymer solution. *AR* means the angle of repose of sample powder. *VP* and *PP* mean the viscosity and pH of 1 % water-soluble polymer solution. *HT* means the hardness of a compressed tablet of sample powder. *DP* means the dissolution rate of water-soluble polymer. *GF* means the thickness of gel formed on the polymer disk surface. *SI* means the solubility (1) or insolubility (0) of water-soluble polymers in ethanol; see text p. 3703.

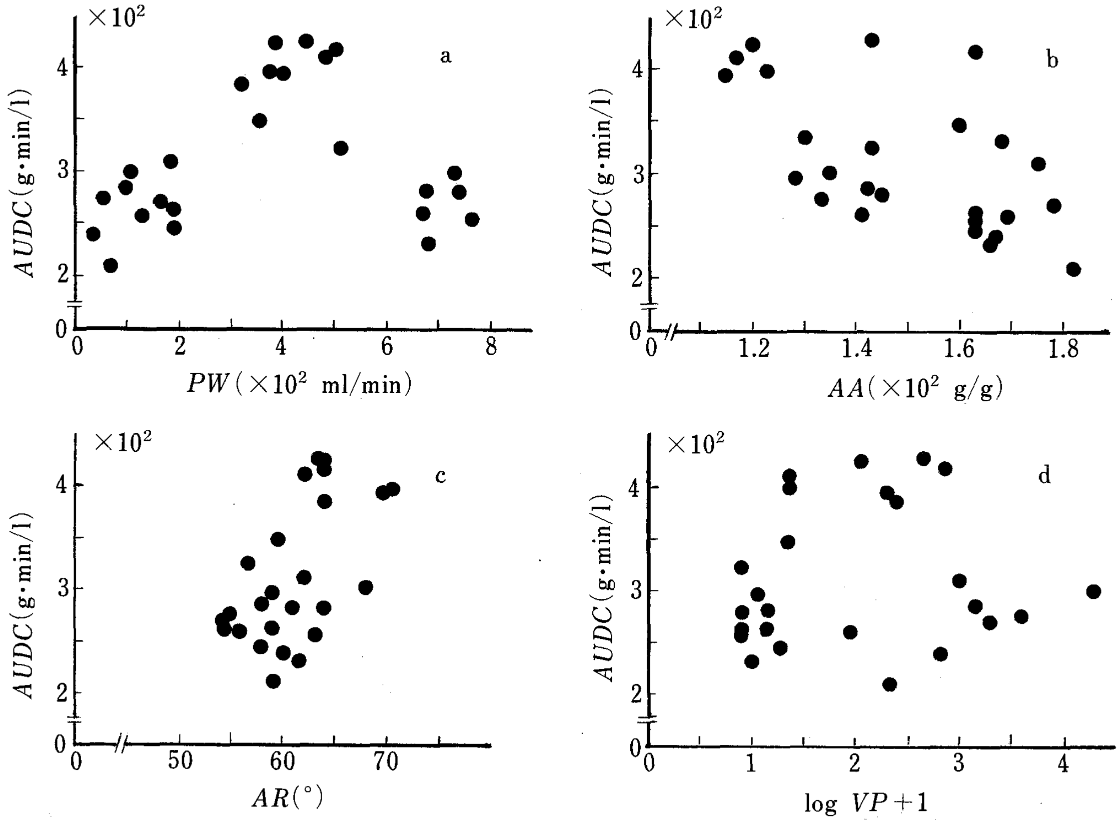

Fig. 7. Scatter Diagrams between *AUDC* and Various Factors

a, PW; b, AA; c, AR; d, log VP.
The abbreviations are defined in Experimental.

include the square terms of *PW* and log*VP* as predictors of *AUDC*. The values of the correlation matrix among the factors are shown in Table IV; multi-colinearity among the factors does not arise, because each correlation coefficient is relatively small except for those of the squares of *PW* and log*VP*.

Table IV. Correlation Matrix among the Factors

	PW^2	PW	AA	AR	$(\log VP)^2$	$\log VP$	HT	PP	DP	GF	SI
PW^2	1										
PW	0.972	1									
AA	−0.092	−0.193	1								
AR	0.088	0.173	−0.408	1							
$(\log VP)^2$	−0.536	−0.595	−0.011	0.073	1						
$\log VP$	−0.675	−0.705	0.005	0.090	0.940	1					
HT	0.126	0.102	0.142	0.160	−0.006	−0.027	1				
PP	0.061	−0.058	0.247	−0.158	0.279	0.168	0.105	1			
DP	0.473	0.463	−0.066	−0.250	−0.268	−0.366	−0.440	−0.040	1		
GF	−0.348	−0.419	0.176	−0.377	0.362	0.457	0.199	0.357	−0.272	1	
SI	−0.104	−0.046	0.236	−0.370	−0.263	−0.327	−0.043	−0.089	0.295	−0.287	1

Abbreviations are defined in Experimental.

Regression equations for *AUDC* were calculated by stepwise multiple regression analysis,[13] and are listed in Table V. *PW*, *AA*, *VP* and *HT* were selected as the optimum factors for the prediction of *AUDC*, and these factors (equation 4), gave quite good coincidence, with statistical significance, between the experimental and calculated values as shown in Fig. 8. The other factors were not important for the prediction of *AUDC*. In particular, the fact that *SI* was not included in the optimum equation obtained by stepwise development of the regression equation suggests that *AUDC* was not much affected by the situation of water-soluble polymers in sample powders. It is not easy to explain the contribution of *PW* to *AUDC*, because the value of *PW* depends on complicated relationships among factors such as wetting, pore size and pore length of sample powder, and gelation and swelling of water-soluble polymers added as the third component. A possible explanation is as follows. The penetration of water is a necessary condition for the diffusion of FFA molecules, but crystallization is also accelerated with increase of the amount of water penetrating into and around particles of sample powders. In fact, *PW* took the greatest value when water-soluble polymer was not added to the sample preparation, and the value of *AUDC* was relatively small, as shown in Tables II and III. In any case, the value of *PW* can be measured easily, so it was considered that *PW* was the most important factor for the prediction of *AUDC*. A contribution of *VP*

Table V. Stepwise Development of Regression Equation for *AUDC*

Equation	$AUDC=-aPW^2+bPW-cAA-d(\log VP)^2+e\log VP+fHT+\text{constant}$										
	a	b	c	d	e	f	const.	n	s	r	F
1	0.118 (±0.031)[a]	0.983 (±0.249)					1.75 (±0.40)	25	0.410	0.819	22.4
2	0.0973 (±0.0286)	0.797 (±0.236)	1.19 (±0.66)				3.81 (±1.20)	25	0.349	0.878	23.7
3	0.0906 (±0.0225)	0.857 (±0.189)	1.04 (±0.49)	0.157 (±0.107)	0.732 (±0.316)		2.81 (±0.96)	25	0.245	0.948	33.6
4	0.0916 (±0.0193)	0.853 (±0.161)	1.14) (±0.42)	0.158 (±0.091)	0.719 (±0.270)	0.235 (±0.140)	2.40 (±0.86)	25	0.209	0.964	39.7

[a] The data in parentheses indicate 95% confidence intervals. Abbreviations are defined in Experimental.

to *AUDC* may be explained in terms of the balance between its inhibiting effects on crystallization and diffusion of FFA from the surface of sample powder. The sign of *AA* in the regression equation is minus, indicating that the crystallization of FFA on PVPP solid surface in the dissolution medium may be accelerated with increase of the amount of FFA adsorbed on PVPP. Both the hardness of compressed tablet and the angle of repose of sample powder have a relation to the cohesion tendency of mutal sample powders though the angle of repose was not included in the optimum regression equation for *AUDC*.

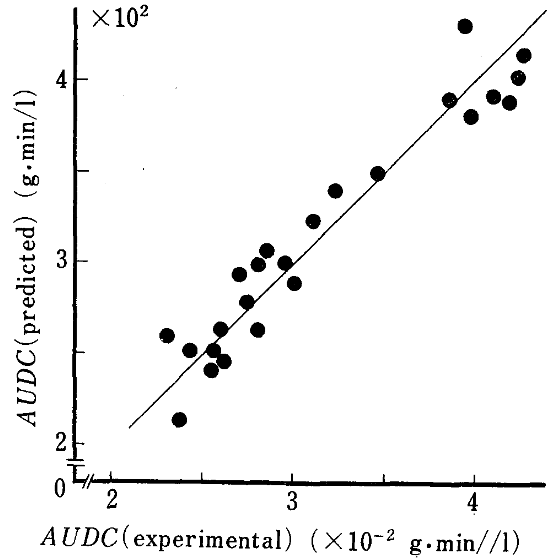

Fig. 8. Relationship between Experimental and predicted Values of *AUDC*

Equations for the apparent crystallization rate constant (k_r) are also listed in Table VI. *PW*, *AA* and *AR* were selected as the optimum factors for the prediction of k_r. The presence of the various factors in the optimum regression equation can be explained in essentially the same way as in the case of *AUDC*, though *VP* and *HT* did not remain in the optimum equation. The statistical significance is not as good as in the case of *AUDC*. One reason may be that the values of k_r do not adequately reflect the crystallization of FFA in the dissolution medium, because the value was derived on the assumption that the crystallization process is first order. More detailed investigations should be carried out in order to determine how water-soluble polymers affect the dissolution of FFA from these systems.

Table VI. Stepwise Development of Regression Equation for k_r

Equation	$\log k_r = aPW^2 - bPW + cAA - dAR + \text{constant}$								
	a	*b*	*c*	*d*	const.	*n*	*s*	*r*	*F*
5	0.0344 (±0.0110)[a]	0.275 (±0.089)			1.41 (±0.14)	25	0.147	0.751	14.2
6	0.0273 (±0.0105)	0.212 (±0.086)	0.407 (±0.247)		0.709 (±0.438)	25	0.128	0.828	15.2
7	0.0247 (±0.0100)	0.189 (±0.083)	0.326 (±0.237)	0.126 (±0.106)	1.56 (±0.83)	25	0.119	0.859	14.1

a) The data in parentheses indicate 95% confidence intervals. Abbreviations are defined in Experimental.

From the viewpoint of the systematic design of pharmaceutical formulations, it may be possible to utilize some of the factors investigated in this paper in conjunction with statistical treatment to estimate the efficiency of PVPP as a possible carrier for solid dispersion systems with various water-soluble polymers as the third component.

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References and Notes

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