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Dissolution Kinetics for Coprecipitates of Indomethacin with Polyvinylpyrrolidone[1,2]

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Dissolution profiles of indomethacin/polyvinylpyrrolidone (PVP) coprecipitates (involving a crystallization process) were investigated kinetically by the dispersed amount and rotating disk methods in comparison with those of physical mixtures. The dissolution rate constant, k_t, the rate constant of the crystallization process, k_r, and saturated concentrations before and after the crystallization, C_{SM} and C_{SO}, were calculated from the dissolution data by a curve fitting procedure. The effects of the content and molecular weight of PVP in the coprecipitates on these dissolution parameters were also investigated in detail.

It was found that increase of the content and the molecular weight of PVP correlated well with retardation of the crystallization process. In order to obtain desirable dissolution patterns, we attempted to estimate the optimum content of PVP in the coprecipitates by analysis of the dissolution parameters.

Keywords——coprecipitate; indomethacin; polyvinylpyrrolidone; dissolution rate; saturated concentration; crystallization process; rotating disk method; dispersed amount method

Many studies have been carried out on enhancement of the solubility and dissolution rate of slightly soluble drugs by the utilization of coprecipitates with water-soluble materials such as urea,[4] bile acids,[5] polyethyleneglycol,[6] and polyvinylpyrrolidone (PVP).[7] However, there are few reports on the dissolution kinetics of coprecipitates.[7] Moreover, the optimum ratio of drugs and water-soluble materials in the coprecipitates has been obtained empirically.

The present study was carried out to investigate kinetically the dissolution profiles of the coprecipitate of indomethacin (IMC), a slightly soluble non-steroidal antiinflammatory drug, with PVP.

In order to obtain desirable dissolution patterns (to increase the bioavailability) of IMC, we attempted to estimate the optimum content of PVP in the coprecipitate by analysis of the dissolution parameters.

Experimental

Materials——IMC supplied by SS Pharmaceutical Co., Ltd., was used after recrystallization from diethylether. PVP marketed as "PVP K-15," "PVP K-30," and "PVP K-90" was used without further treatment.

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Preparation of IMC/PVP Coprecipitate——IMC and PVP at a suitable weight ratio were dissolved in ethanol at about 70°, then the solvent was removed *in vacuo* in a rotary evaporator at about 70°. The residue was dried *in vacuo* at room temperature for 24 hr, ground well in a mortar and stored in a desiccator.

Preparation of IMC Amorphous Form——IMC was melted at about 160°, then cooled at room temperature. The glassy mass thus produced was ground well in a mortar and stored in a desiccator.

Identification of the Compounds——Powder X-ray diffractometry and differential scanning calorimetry were employed in the manner described in the previous paper.[8]

Procedure for Dissolution Study——a) Dispersed Amount Method: Following the previous paper,[9] a certain excess of sample powder which contained 100 mg of IMC was dispersed in 50 ml of pH 6.0, 1/15 M phosphate buffer solution. Sampling was done with a two ml pipette, and the solution was filtered with a Toyo TM-2 membrane filter (0.45 μm). The concentration of IMC in the filtrate was determined by the ultraviolet (UV) absorption method after dilution with 1/15 M phosphate buffer solution at pH 6.0.

b) Rotating Disk Method: The procedure employed was the same as in the previous paper.[10] Every experiment was carried out under the following conditions: 30 ml of 1/15 M phosphate buffer solution at pH 6.0 at 37°; disk velocity, 50, 100, 300, and 600 rpm; disks of 1.3 cm diameter compressed under 200 kg/cm^2. When the samples were compressed to make the disks, no phase transition due to the pressure was observed. At appropriate intervals, 1 ml samples were taken, and the volume was kept constant by adding the same amount of fresh dissolution medium of the same temperature. The concentration was determined by the UV absorption method.

Results and Discussion

Dissolution Behavior of the Coprecipitates

Figure 1 shows the powder X-ray diffraction patterns of IMC/PVP K-30 (1 : 1) coprecipitate. Upon coprecipitation with PVP, the sharp diffraction peaks attributed to IMC crystals disappeared. In the measurements by differential scanning calorimetry, the endothermic peak accompanying the melting of IMC crystals was not seen in the coprecipitates. Therefore, IMC might be present without crystalline structure in the coprecipitates.

When the coprecipitates were dispersed in aqueous solution according to the dispersed amount method, the concentration of IMC rose very quickly and then decreased gradually, showing typical supersaturation phenomena. Similar dissolution patterns are well known in the cases of polymorphs,[11] solvates[12,13] and complexes.[9,14] The decrease of IMC concentration might be due to phase transition to more stable forms accompanied by crystallization. Actually, crystallization was obvious throughout the dissolution of the coprecipitate, as shown in Fig. 1. Therefore, the crystallization process is one of the factors which is likely to control the dissolution rate of the coprecipitate.

If it is assumed that the surface area and the diffusivity of IMC from the coprecipitates are almost constant under these experimental conditions, the crystallization rate of IMC in the coprecipitate will be proportional to the degree of supersaturation and will be of first order with respect to the concentration term of IMC in the saturated layer, and thus the crystallization rate of IMC in the saturated layer might be expressed as[13]

$$-\frac{dC_i}{dt} = k_r(C_i - C_{SO}) \qquad (1)$$

where C_i is the effective concentration on the solid surface, t is the time, k_r is the crystallization rate constant, and C_{SO} is the saturated concentration after the crystallization. Since $C_i = C_{SM}$ (C_{SM} is the saturated concentration before the crystallization) at $t=0$, equation (1) can be integrated to yield equation (2).

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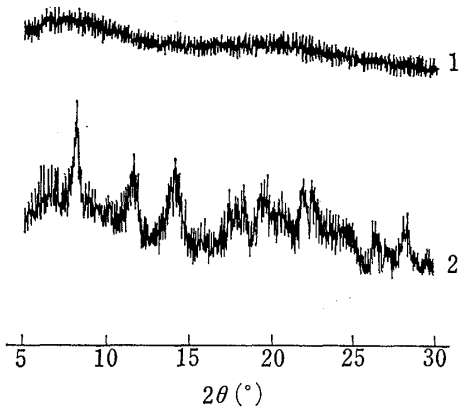

Fig. 1. Powder X-Ray Diffraction Patterns of IMC/PVP K-30 (1: 1) Corecipitate before and after Dissolution by the Disperesed Amount Method

1: before the dissolution experiment.
2: at 2 hr after the start of the dissolution experiment.

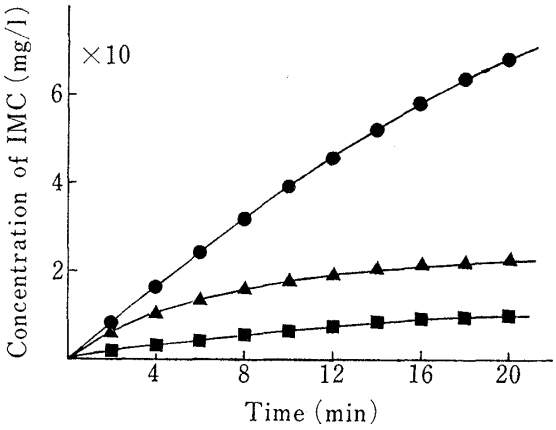

Fig. 2. Dissolution Profiles of IMC/PVP K-30 (1: 1) Coprecipitate (●), Amorphous IMC/PVP K-30 (1: 1) Physical Mixture (▲), and IMC Form I (■), Determined by the Rotating Disk Method (37°, 100 rpm)

Each point is the mean of three determinations.

$$C_t = C_{SM} \cdot \exp(-k_r t) + C_{SO}[1-\exp(-k_r t)] \quad (2)$$

The dissolution rate can be expressed as described in the previous paper,[13,14]

$$\frac{dC}{dt} = k_t\{C_{SM} \cdot \exp(-k_r t) + C_{SO}[1-\exp(-k_r t)] - C\} \quad (3)$$

$$C = k_t(C_{SM}-C_{SO})[\exp(-k_r t) - \exp(-k_t t)]/(k_t-k_r) + C_{SO}[1-\exp(-k_r t)] \quad (4)$$

where, k_t is the dissolution rate constant and C is the concentration at time t in the bulk liquid. These equations can be applied to the analysis of the dissolution patterns of the coprecipitates by the rotating disk method under the non-sink condition.[13]

As an example, the dissolution properties of IMC/PVP K-30 (1: 1) coprecipitate, amorphous IMC/PVP K-30 (1: 1) physical mixture, and IMC form I (the most stable form)[11] as

Table I. Dissolution Parameters of IMC/PVP Coprecipitates Determined by the Rotating Disk Method (37°, 100 rpm)

	Content of PVP (%)	$k_t \times 10^3$ (min^{-1})	$k_r \times 10^2$ (min^{-1})	$C_{SM} \times 10^{-2}$ (mg/l)	$C_{SO} \times 10^{-2}$ (mg/l)
PVP K-15	16.7	7.93	4.41	5.01	2.26
	33.3	8.13	4.44	5.01	2.34
	50.0	8.01	4.29	4.93	2.45
	66.7	7.94	4.11	5.25	2.58
PVP K-30	16.7	7.74	4.64	4.97	2.21
	33.3	7.90	3.44	5.22	3.20
	50.0	7.72	2.66	5.08	3.62
	66.7	7.66	1.87	5.29	4.37
PVP K-90	16.7	7.67	4.24	4.63	2.28
	23.1	7.11	3.69	4.40	2.80
	33.3	7.44	3.31	4.79	3.32
	41.2	7.05	2.81	4.68	3.46
	50.0	6.39	1.72	4.50	4.34

determined by the rotating disk method are shown in Fig. 2.

The dissolution parameters in equations 3 and 4 for the coprecipitates were calculated by a curve fitting procedure[15] from the dissolution data in Fig. 2, and are summarized in Table I.

Even if the content of PVP in the coprecipitate is changed, all of the dissolution parameters are unchanged in the case of IMC/PVP K-15 coprecipitate, and the values of k_t and C_{SM} are hardly changed in the cases of IMC/PVP K-30 and IMC/PVP K-90 coprecipitates, as shown in Table I. However, in the cases of IMC/PVP K-30 and IMC/PVP K-90 coprecipitates, k_r is decreased and C_{SO} is increased with increase in the content of PVP. These results indicate that both PVP K-30 and K-90 inhibit the crystallization process of IMC during the dissolution of the coprecipitate, but they appeared to have little effect on the diffusivity of IMC or on the saturated concentration before crystallization.

Effect of Disk Velocity on the Dissolution Parameters of Coprecipitate

The effects of the rotational velocity of the disk on the dissolution parameters of IMC/PVP K-30 (1: 0.5) coprecipitate are shown in Table II. The value of k_t increased with increase of the disk velocity, and was proportional to the 1/2 power of the rotational velocity of the disk, as shown in Fig. 3. The other parameters were hardly affected by changes in the stirring conditions. In paticular, the finding that the value of k_r did not change indicates that the use of equations 3 and 4 is reasonable for analysis of the dissolution phenomena of the coprecipitates, because equations 3 and 4 were derived on the assumption that the crystallization process occurred in the saturated layer.[13]

Table II. Effect of Rotational Velocity on the Dissolution Parameters of IMC/PVP K-30 (1: 0.5) Coprecipitate Determined by the Rotating Disk Method at 37°

Rotational velocity (rpm)	$k_t \times 10^3$ (min^{-1})	$k_r \times 10^2$ (min^{-1})	$C_{SM} \times 10^{-2}$ (mg/l)	$C_{SO} \times 10^{-2}$ (mg/l)
50	6.00	3.05	4.71	3.46
100	7.90	3.44	5.22	3.20
300	13.0	3.07	5.23	3.33
600	20.0	3.28	5.13	3.51

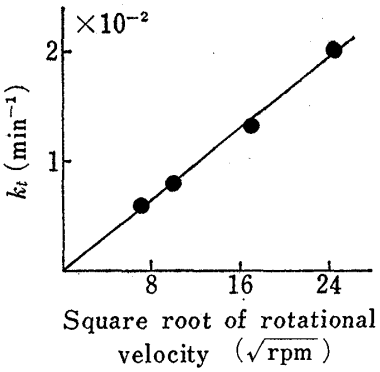

Fig. 3. Relation between k_t of IMC/PVP K-30 (1: 0.5) Coprecipitate and Rotational Velocity of the Disk at 37°

Comparison of Coprecipitate with Physical Mixture

The dissolution parameters of a physical mixture of amorphous IMC prepared by the fusion method and PVP K-30 were calculated in the same way as in the case of the coprecipitate, and are summarized in Table III. The value of k_r for the physical mixture was considerably larger than that of the coprecipitate. In contrast, the value of C_{SO} for the physical mixture was much smaller than that of the coprecipitate. These results indicate that the retardation effect on the crystallization of IMC was insufficient in the case of the physical mixture. A possible interpretation is that the dissolution surface of IMC was covered entirely by the high concentration of PVP in the case of the coprecipitate, whereas the covering effect of PVP was only partial in the case of the physical mixture.

15) This calculation was carried out on a TOSBAC series 7/10 computer with a program written by the authors.

Relation between PVP Content and Dissolution Parameters of Coprecipitate

The effects of the content of PVP on the crystallization process of the coprecipitates are shown in Fig. 4. The value of k_r is inversely proportional to the content of PVP. The order of the values of the negative slope of the regression line between k_r and the content of PVP was as follows: PVP K-90>PVP K-30>PVP K-15, indicating that the crystallization is strongly affected by the degree of polymerization of the PVP. Therefore, it might be suggested that the value of the slope in Fig. 4 can be used as a parameter of the degree of retardation of the various carrier polymers on the crystallization process of drugs in the coprecipitates.

Table III. Dissolution Parameters of IMC/PVP K-30 Coprecipitates and Amorphous IMC/PVP K-30 Physical Mixture Determined by the Rotating Disk Method (37°, 100 rpm)

	Content of PVP (%)	$k_t \times 10^3$ (min^{-1})	$k_r \times 10^2$ (min^{-1})	$C_{SM} \times 10^{-2}$ (mg/l)	$C_{SO} \times 10^{-2}$ (mg/l)
Coprecipitate	16.7	7.74	4.64	4.97	2.21
	33.3	7.90	3.44	5.22	3.20
	50.0	7.72	2.66	5.08	3.62
	66.7	7.66	1.87	5.29	4.37
Physical mix.	16.7	8.02	23.9	5.62	0.473
	33.3	8.36	14.5	5.19	0.591
	50.0	7.37	20.4	5.00	0.670
	66.7	7.45	15.3	4.59	1.23

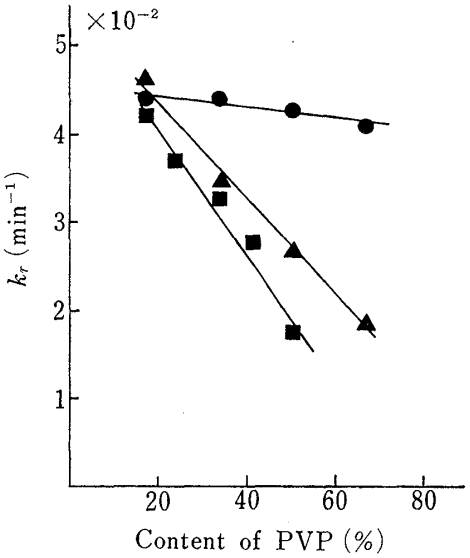

Fig. 4. Relation between k_r and Content of PVP in Coprecipitates

—●—: PVP K-15, —▲—: PVP K-30, —■—: PVP K-90.

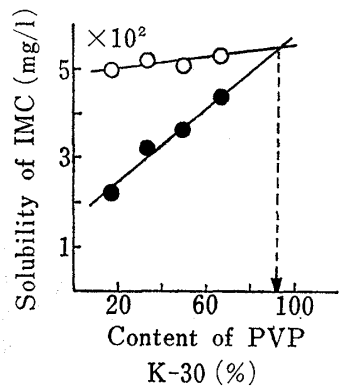

Fig. 5. Estimation of the Optimum Content of PVP K-30 in Coprecipitate

—○—: C_{SM}, —●—: C_{SO}.

Table IV. Estimation of the Optimum Content of PVP in Coprecipitates

PVP	Optimum content (%)
K-15	—[a]
K-30	90.7
K-90	57.4

a) An optimum content was not obtained for this coprecipitate.

Figure 5 shows the relation between the content of PVP K-30 and the saturated concentrations before and after the crystallization process of IMC in the coprecipitates. The values of C_{SM} and C_{SO} are both proportional to the content of PVP K-30. Linear relations were also observed in the case of PVP K-15 and PVP K-90. The value of the slope of the regression line of C_{SO} against PVP content is larger than that of C_{SM}, indicating that the content of PVP strongly affects the saturated concentration after the crystallization process under these experimental conditions. These results indicate that the phase change of the coprecipitate was reduced to a minimum at the content of PVP corresponding to the point of intersection of the two regression lines in Fig. 5, *i. e.*, this is the theoretical optimum content of PVP in the coprecipitate. These values are summarized in Table IV. From the standpoint of retardation of the crystallization process, it was considered that PVP K-90 was the most suitable polymer for use as a carrier in this coprecipitate.

In order to obtain desirable dissolution properties, it may be possible to utilize some of the values obtained in this paper for estimation of the optimum content and of the efficiency of various polymers as carriers in other coprecipitate systems.

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