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Analysis of Interfacial Transfer of Indomethacin following Dissolution of Indomethacin/Polyvinylpyrrolidone Coprecipitates[1,2]

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For the analysis of interfacial transfer of indomethacin (IMC) following the dissolution of IMC coprecipitates with polyvinylpyrrolidone (PVP), a new equation based on the crystallization of IMC was derived and found to fit the results reasonably well. Therefore, the crystallization process of IMC in coprecipitates with PVP is an important factor in the analysis of interfacial transfer phenomena as well as in the analysis of dissolution behavior. The new equation might be suitable for prediction of the bioavailability of drugs in the coprecipitate system on the basis of the results of *in vitro* experiments.

Keywords——coprecipitate; indomethacin; polyvinylpyrrolidone; interfacial transfer; dissolution; crystallization

In the previous paper,[3] the authors reported the dissolution kinetics of indomethacin (IMC)/polyvinylpyrrolidone(PVP) coprecipitates in detail. IMC was considered to be in an amorphous state in the coprecipitates. Consequently, the dissolution properties of IMC from the coprecipitates could not be explained by the Noyes–Whitney dissolution equation[4] due to phase transition of IMC to more stable forms. We have found that equation 1 is suitable to explain the unusual dissolution profiles of these systems, because it was derived by taking into account the crystallization process.[3]

$$\frac{dC}{dt} = k_t\{C_{sm}\exp(-k_r t)+C_{so}[1-\exp(-k_r t)]-C\} \quad (1)$$

C_{sm} and C_{so} are the saturated concentrations before and after the crystallization of IMC, respectively, k_t is the dissolution rate constant, k_r is the crystallization rate constant, and C is the concentration at time t in the bulk liquid.

For prediction of the bioavailability of drugs on the basis of *in vitro* experiments, Uekama *et al.* used a rotating disk dissolution apparatus with an organic phase, and the following equations were applied to analyze the interfacial transfer from the phosphate buffer to dichloroethane following the dissolution of drugs such as benzoic acids and barbiturates.[5]

$$\frac{dC_w}{dt} = k(C_s-C_w) - k_f C_w + k_b C_o \quad (2)$$

$$\frac{dC_o}{dt} = k_f C_w - k_b C_o \quad (3)$$

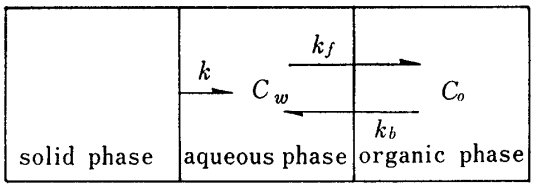

Fig. 1. A Model for Interfacial Transfer of Drugs following Dissolution

C_w and C_o represent the concentrations of drugs in the aqueous phase and in the organic phase, k_f and k_b are the apparent first-order rate constants for forward and back transfer, respectively, k is the dissolution rate constant, and C_s is the saturated concentration of drugs in the aqueous phase. Equations 2 and 3 express the rate of change of drug concentration in the aqueous and organic phases, respectively. The relations among these parameters are illustrated in Fig. 1.

However, the direct application of these equations to coprecipitates is not possible because of their unusual dissolution behavior. Thus, in this study, equation 4 was applied instead of equation 2 to analyze the dissolution of IMC from its coprecipitates with PVP taking account of interfacial transfer.

$$\frac{dC_w}{dt} = k_t\{C_{sm}\exp(-k_r t)+C_{so}[1-\exp(-k_r t)]-C_w\} - k_f C_w + k_b C_o \qquad (4)$$

Equation 4 is easily derived from equation 1, and the values of C_w and C_o can be estimated with quite high accuracy by the application of equations 3 and 4.

Experimental

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

Preparation of IMC/PVP Coprecipitate——IMC and PVP were dissolved in 1: 1 weight ratio in ethanol at about 70°C. The solvent was removed *in vacuo* using a rotary evaporator at about 70°C, then the residue was dried *in vacuo* at room temperature for 24 h, ground well in a mortar and stored in a desiccator.

Identification of Compounds——Powder X-ray diffractometry and differential scanning calorimetry were employed in the same way as described in a previous paper.[6]

Determination of Interfacial Transfer following Dissolution——Interfacial transfer following dissolution of each coprecipitate was determined by means of the apparatus shown in Fig. 2. The aqueous phase and organic phase consisted of 30 ml of 1/15 M, pH 6.5 phosphate buffer solution and 30 ml of chloroform, respectively. These solutions were mutually saturated prior to the experiments. Disks (solid phase) of 1.3 cm diameter were prepared by compressing coprecipitate powders under 200 kg/cm² in a Shimadzu hydraulic press for preparing KBr tablets for infrared spectroscopy.

The rotation speed of the disks and stirring rate of the organic phase were both 100 rpm. No disturbance of the interface was observed under these conditions. At appropriate intervals, 1 ml samples of aqueous and organic phases were taken, and the volumes of both phases in the apparatus were kept constant by adding the same amounts of fresh media of the same temperature. The concentration was determined by the UV absorption method.

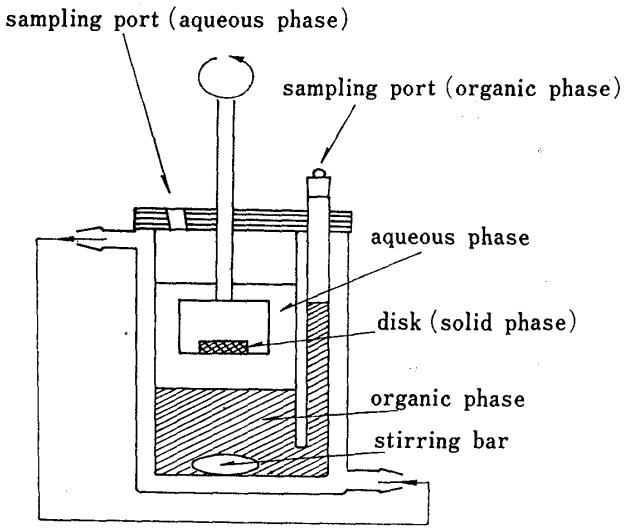

Fig. 2. Apparatus for Determination of Interfacial Transfer following Dissolution

Determination of Dissolution Behavior——Dissolution behavior of IMC from the coprecipitates was determined by means of the apparatus shown in Fig. 2 without the organic phase. The dissolution medium consisted of 30 ml of 1/15 M, pH 6.5 phosphate buffer solution previously saturated with chloroform. The other conditions were the same as in the above experiment.

Determination of Interfacial Transfer——Interfacial transfer of IMC was determined by means of the apparatus shown in Fig. 2 without the disk (solid phase). The aqueous phase consisted of 30 ml of 1/15 M, pH 6.5 phosphate buffer solution containing 0.20 g/l of IMC and various concentrations of PVP, which had been saturated with chloroform previously. The organic phase consisted of 30 ml of chloroform saturated with the buffer solution. The other conditions were the same as in the above experiment.

Results and Discussion

Determination of Dissolution and Interfacial Transfer Parameters

Figure 3 shows the dissolution behavior of IMC/PVP coprecipitates in the buffer solution saturated with chloroform. The values of k and C_s in equation 2 were obtained from Fig. 3

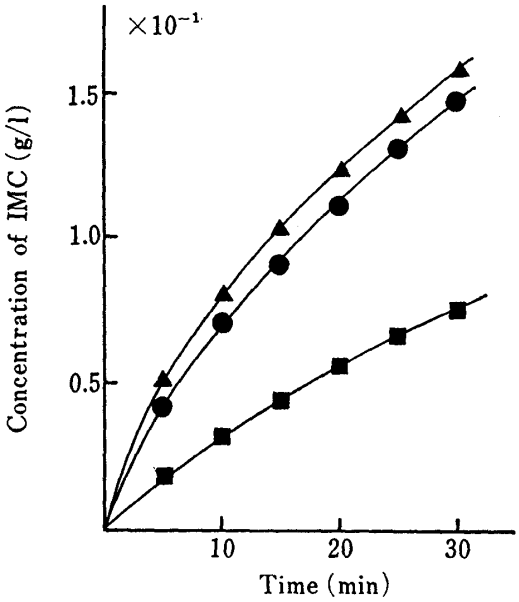

Fig. 3. Dissolution Profiles of IMC/PVP K-15 Coprecipitate (●), IMC/PVP K-30 Coprecipitate (▲) and IMC/PVP K-90 Coprecipitate (■) in 30 ml of 1/15 M, pH 6.5 Phosphate Buffer Solution saturated with Chloroform at 37°C

Each point is the mean of three determinations.

on the assumption that the dissolution of coprecipitates could be explained by Noyes–Whitney equation.[4] On the other hand, the values of k_t, k_r, C_{sm} and C_{so} in equation 4 were computed by the non-linear least-squares method[7] according to equation 1 on the assumption that the crystallization of IMC occurred following dissolution. The details of this dissolution mechanism were reported in a previous paper.[3] The values of these parameters are summarized in Table I. It was shown that the data were better fitted by equation 1 than by the Noyes–Whitney equation.

The interfacial transfer parameters (k_f and k_b) were calculated by the method of Schumacher *et al.*,[8] and are summarized in Table II. PVP added to the aqueous phase had no effect. Therefore, the mean values of k_f and k_b were used for the analysis of interfacial transfer following the dissolution of coprecipitates.

Estimation of Interfacial Transfer following Dissolution

Interfacial transfer phenomena from the phosphate buffer layer to the chloroform layer following dissolution of IMC/PVP coprecipitates are shown in Fig. 4. Solid lines indicate the theoretical values of C_w and C_o computed by the Runge–Kutta method[7] from equations 3 and 4. Dotted lines indicate the results obtained by using equations 2 and 3. Quite a good fit was obtained by the use of equation 4. Therefore, the crystallization process of IMC in its coprecipitates with PVP seems to be an important factor in the analysis of the interfacial transfer phenomena as well as in the analysis of the dissolution behavior.

Based on the above considerations, equation 4 might be applicable for the prediction of the bioavailability of drugs in a coprecipitate system on the basis of *in vitro* experiments of the type described in this paper.

Table I. Dissolution Parameters obtained from the Noyes–Whitney Equation and Equation 1

System	$k \times 10^2$ (min^{-1})	$C_s \times 10$ (g/l)	$S_e \times 10^2$	$k_t \times 10^3$ (min^{-1})	$k_r \times 10$ (min^{-1})	C_{sm} (g/l)	$C_{so} \times 10$ (g/l)	$S_e \times 10^3$
IMC/PVP K-15	4.17	2.05	1.07	8.00	2.71	1.53	5.86	5.68
IMC/PVP K-30	5.29	1.96	1.49	8.16	2.89	1.90	5.91	1.98
IMC/PVP K-90	3.14	1.23	1.08	7.25	1.17	0.598	3.03	5.67

S_e is standard error of estimate.

Table II. Parameters for Interfacial Transfer of IMC

Concentration of PVP	$k_f \times 10^2$ (min^{-1})	$k_b \times 10^3$ (min^{-1})
No addition of PVP	2.19	1.90
PVP K-15 (0.20 g/l)	2.12	1.91
PVP K-30 (0.21 g/l)	2.23	1.91
PVP K-90 (0.20 g/l)	2.14	1.92

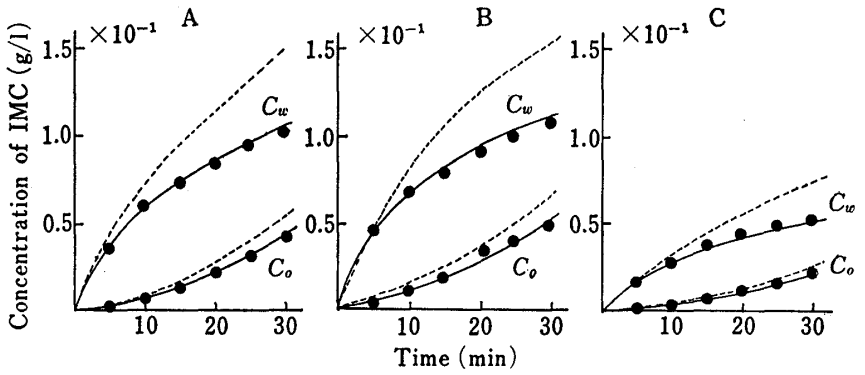

Fig. 4. Interfacial Transfer of IMC following Dissolution of IMC/PVP Coprecipitates at 37°C

A: IMC/PVP K-15 coprecipitate, B: IMC/PVP K-30 coprecipitate, C: IMC/PVP K-90 coprecipitate.
-●-: experimental data (each point is the mean of three determinations).
——: theoretical curve obtained from equations 3 and 4.
----: theoretical curve obtained from equations 2 and 3.

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References and Notes

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Kinin-inactivating Enzyme from the Mushroom *Tricholoma conglobatum*. VI. Actions on Angiotensins I and II[1)]

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A potent kinin-inactivating enzyme from the mushroom *Tricholoma conglobatum*, Shimeji kininase, liberated angiotensin II and the dipeptide, H–His–Leu–OH, from angiotensin I. Thus, this enzyme was considered to have both kininase and angiotensin I converting activities like kininase II (angiotensin I converting enzyme, EC 3.4.15.1), which is widely distributed in mammals of various species.

On the other hand, this enzyme had angiotensinase activity in addition to angiotensin