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Solubility Parameter and Dissolution Behavior of Cefalexin Powders with Different Crystallinity

Hiroaki EGAWA,[1a)] Shuei MAEDA,[1b)] Etsuo YONEMOCHI, Toshio OGUCHI, Keiji YAMAMOTO,* and Yoshinobu NAKAI[1b)]

Faculty of Pharmaceutical Sciences, Chiba University, 1–33 Yayoicho, Chiba 260, Japan. *Received September 10, 1991*

The dissolution behavior and the solubility parameters of cefalexin powders of different crystallinity were determined. The maximum concentration of cefalexin in water at 35 °C increased with decreasing the crystallinity. Partial solubility parameters of cefalexin were determined as $\delta_d=8.3$, $\delta_s=10.2$ (cal/cm^3)$^{1/2}$ for intact cefalexin and $\delta_d=9.6$, $\delta_s=12.0$ (cal/cm^3)$^{1/2}$ for the amorphous. The partial solubility parameters of intact samples were the smallest among those of different crystallinity samples. The variation of δ_s with crystallinity was significantly greater than that of δ_d. For the estimation of the interaction with water, the interaction radii were calculated, and the effectiveness of this value was confirmed.

Keywords solubility parameter; cefalexin; solubility; crystallinity; grinding; amorphous; interaction radius

It is known that the solubility levels of calcium gluceptate varied with the crystallinity.[2)] A constant solubility for an amorphous state was not acceptable, as it is impossible to determine a definite chemical potential to the amorphous state. We have paid attention to solubility parameters, which are one of the indexes of solubility, and we have already determined solubility parameters of some medicinals and excipients.[3)]

On the basis of the Snyder and Karger interaction model, Kesselring proposed the method to obtain partial solubility parameters of a solid from adsorption energies determined by gas-solid chromatography.[4,5)] In this work the solubility parameters of cefalexin powders of varied crystallinity were determined by the chromatography method. We also investigated the application of the interaction radius to elucidate the apparent solubility levels of various cefalexin samples of different crystallinity.

Experimental

Materials Cefalexin was obtained from Shionogi & Co., Ltd. and was used without further purification. Organic solvents, sodium dihydrogenphosphate and caffeine were of reagent grade.

Preparation of Low Crystallinity Cefalexin Cefalexin was ground by the vibrational mill (Heiko, TI-200). Cefalexins of different crystallinity were prepared by changing the grinding times. An alternative aqueous solution of cefalexin (0.01 g/ml) was frozen at −196 °C and was lyophilized by a freeze dryer (Yamato NEO COOL). The freeze dried cefalexin powder was obtained by grinding the lyophilized sample in an agate mill.

Determination of Crystallinity The crystallinity of cefalexin was determined by the Hermans' method.[6)] Powder X-ray diffraction patterns were measured by using X-ray diffractometer (Rigaku Denki, 2027) as reported previously.[3)] The X-ray diffraction patterns between $2\theta=5.0°$ and 30.0° were used to calculate the crystallinity.

Dissolution Studies 400 mg of Cefalexin was suspended in 10 ml of distilled water in an L-tube at 35 °C. The suspensions were shaken at 60 strokes/min. The aliquots were filtered through a Millipore filter (0.22 μm) and were diluted. The concentrations of cefalexins were determined by the high performance liquid chromatographic (HPLC) method. Caffeine was used as an internal standard.

Determination of Solubility Parameter The solubility parameters were determined using a gas chromatograph (Shimadzu GC-12A) as reported previously.[3,7)] The adsorption energies on cefalexin samples of *n*-octane, *n*-nonane, *n*-decane, benzene, toluene and tetrahydrofuran were used to evaluate the solubility parameters.

Results and Discussion

Estimation of Crystallinity of Cefalexin It was reported that the crystallinity of cefalexin decreased with increased grinding time and that cefalexin became amorphous by freeze drying.[8,9)] Figure 1 shows the changes of X-ray diffraction patterns of cefalexin by grinding and freeze drying. By using Hermans' method, the crystallinity (X_{cr}) of each sample was determined as 88.6% for intact cefalexin, 36.7% for a 1 min ground sample and 20.8% for a 10 min ground sample, respectively. The crystallinity of freeze dried cefalexin was estimated as 0%. As the water content of the freeze dried sample which was used for the solubility parameter measurement was determined to be more than 4.9% by the Karl-Fischer method, the freeze dried sample was considered as the cefalexin monohydrate.

Changes of Cefalexin Concentration in Water Figure 2 shows the dissolution behavior of cefalexin samples in distilled water at 35 °C. The concentration of 3.50×10^{-2} M

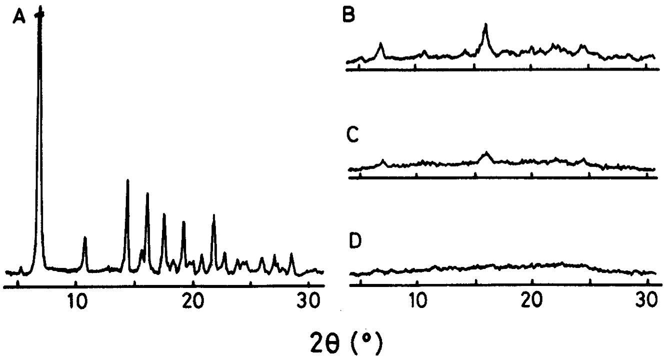

Fig. 1. X-Ray Diffraction Patterns of Cefalexin Powders

A) intact; B) ground for 1 min; C) ground for 10 min; D) freeze dried.

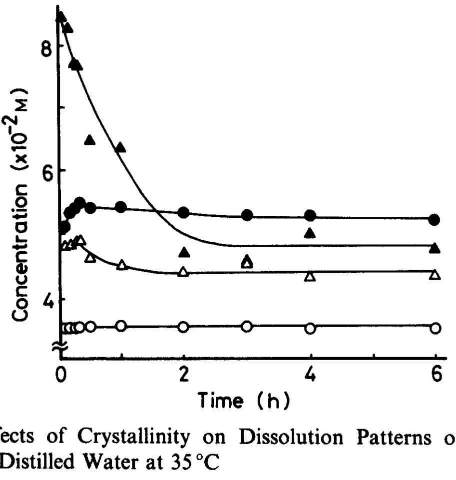

Fig. 2. Effects of Crystallinity on Dissolution Patterns of Cefalexin Powders in Distilled Water at 35 °C

○, $X_{cr}=88.6\%$; △, $X_{cr}=36.7\%$; ●, $X_{cr}=20.8\%$; ▲, $X_{cr}=0\%$.

was observed as the solubility of cefalexin in water at this condition. The ground samples showed high concentrations of cefalexin constantly from the initial to 6 h plots of dissolution; 4.39×10^{-2} M for $X_{cr} = 36.7\%$ and 5.27×10^{-2} M for $X_{cr} = 20.8\%$. The supersaturation levels were found to be stable within 6 h. These high concentrations, however, returned to the solubility level when crystalline cefalexin powders were added to the test suspensions. The freeze dried cefalexin showed a higher concentration of 8.48×10^{-2} M at 5 min and the value decreased gradually to 6.46×10^{-2} M at 30 min. This pattern was significantly different from other dissolution curves, indicating some different crystalline properties.

Solubility Parameters Table I shows adsorption energies of molecular probes on various cefalexin samples obtained by the gas chromatography method. It was observed that intact cefalexin had low adsorption energies compared to the ground and freeze dried samples. It was also found that the variations of adsorption energies of *n*-alkanes on samples were smaller than those of other organic solvents.

TABLE I. Adsorption Energies on Cefalexins

Molecular probe	Adsorption energy (kcal/mol) Crystallinity of cefalexin (%)			
	88.6	36.7	20.8	0
n-Octane	9.7	12.1	11.1	11.5
n-Nonane	11.6	13.8	13.1	13.1
n-Decane	13.2	14.5	14.2	14.6
Benzene	6.9	9.8	10.8	10.1
Toluene	8.9	11.7	11.3	10.8
Tetrahydrofuran	9.8	12.6	12.1	10.8

TABLE II. Partial Solubility Parameters of Cefalexins

Crystallinity of cefalexin (%)	δ_d	δ_s (cal/cm^3)$^{1/2}$	δ_t
88.6	8.3	10.2	13.2
36.7	9.9	15.8	18.6
20.8	9.6	15.6	18.3
0	9.6	12.0	15.4

TABLE III. Apparent Solubility of Cefalexin and Interaction Radius with Water

Crystallinity of cefalexin (%)	Apparent solubility at 35 °C ($\times 10^{-3}$ M)	Interaction radius (cal/cm^3)$^{1/2}$
88.6	3.50	13.2
36.7	4.39	10.3
20.8	5.27	10.0

Table II shows partial solubility parameters of various cefalexins calculated by multilinear regression from six adsorption energies shown in Table I, where the subscripts d and s show dispersion and specific cohesion, respectively. Both of the partial solubility parameters of intact cefalexin were smaller than those of lower crystallinity cefalexins. The values of δ_d varied from 8.3 to 9.9 (cal/cm^3)$^{1/2}$, but δ_s showed much greater variation, that is, from 10.2 to 15.8 (cal/cm^3)$^{1/2}$. The difference of total solubility parameters seemed to be due to the great variation of δ_s values which related to hydrogen bonding and polar interactions.

Calculation of Interaction Radius δ_d *vs.* δ_s plots were known to be useful to obtain information concerning the solvent–solute interaction. Solubility of the solute was usually correlated with the distance on the coordinates between the two points of corresponding solvent and solute. This distance, interaction radius (r), was expressed by the following equation.[10)]

$$r^2 = 4 \times (\delta_d^i - \delta_d^j)^2 + (\delta_s^i - \delta_s^j)^2$$

Superscripts of ^{i} and ^{j} show the solute and solvent, the values of δ_d and δ_s of distilled water are known as 6.0 and 22.6 (cal/cm^3)$^{1/2}$, respectively. Table III shows apparent solubility of different cefalexins and the interaction radius with water. Good correlation was observed between two values, that is, the solubility levels increased with decreasing the values of interaction radius. It was suggested that estimating r value from partial solubility parameters was useful for predicting solubility levels. For freeze dried cefalexin, however, an observed maximum concentration of cefalexin had no dependency on the calculated r value. The freeze dried cefalexin could differ from the ground cefalexin in physicochemical properties, even when both powders showed similar low crystallinity or X-ray diffraction patterns.

References and Notes

1) Present Address: *a) Shionogi & Co., Ltd., 5-12-4 Sagisu, Fukushima-ku, Osaka 553, Japan; b) Tsumura & Co., 3586 Yoshiwara, Amimachi, Inashiki-gun, Ibaraki 300-11, Japan.*
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