

Dissolution studies in organic solvents for evaluating hydrogen-bond matrix of cellulose in the ground mixture

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Abstract

Benzoic acid crystals were ground with microcrystalline cellulose. In order to evaluate the hydrogen-bond matrix of cellulose in the ground mixture, dissolution experiments were carried out using organic solvents as dissolution media. With prolongation of grinding, benzoic acid was gradually amorphized and the dissolution of benzoic acid from the ground sample was significantly suppressed in cyclohexane. This result was considered to be due to the dispersion of benzoic acid molecules in the hydrogen-bond matrix of cellulose through the grinding process. From experiments using a series of organic solvents, it was found that the amount of benzoic acid dissolved was correlated to the polarity of solvents. On the other hand, moisture in the solvent and primary hydroxyl groups in solvent molecules were considered to be effective factors for enhancing the dissolution of benzoic acid from the ground mixture.

Keywords: Dissolution; Ground mixture; Cellulose; Hydrogen bonding; Solid dispersion; Organic solvent

1. Introduction

Cellulose, the most widely distributed polysaccharide in nature, has long been receiving attention due to its excellent utility. Particularly in pharmaceutical technology, cellulose is one of the most important materials as a tablet excipient and a raw material for the synthesis of coating bases. Cellulose molecules have a large number

of hydroxyl groups which form intermolecular and intramolecular hydrogen-bond structures. Because of its fundamental interest and practical importance, a number of investigations aimed at characterizing the hydrogen bond have been carried out (Kroon-Batenburg et al., 1990; Zhbakov, 1992).

Solid dispersions have been applied in pharmaceutical technology for enhancing and/or controlling the dissolution of medicinals (Chiou and Riegelman, 1971; Saers et al., 1993; Yuasa et al., 1993). We have investigated the molecular state of drugs in ground mixtures with microcrystalline cellulose by means of infrared (Nakai et al., 1980;

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Nakai, 1986), photoacoustic (Nakai et al., 1987), and fluorometric spectrometry (Yamamoto et al., 1994) and have demonstrated that the spectroscopic approach appears to be informative. We should take into account the correspondence of the spectral data to the physico-chemical properties, such as dissolution (Nakai et al., 1977b), sublimation (Nakai et al., 1978), and chemical stability (Nakai et al., 1982). In the present study, we investigated the dissolution behavior of benzoic acid from the ground mixture with microcrystalline cellulose using organic solvents as dissolution media to characterize the hydrogen-bond matrix of cellulose.

2. Experimental

2.1. Materials

Benzoic acid (BA, Koso Chemical Co., Ltd) was of special reagent grade. Microcrystalline cellulose (MCC, Avicel® PH-101, Asahi Chemical Ind. Co., Ltd) was dried for 3 h at 110°C in a vacuum before use. Cyclohexane, *n*-hexane, 2-propanol, acetonitrile, methanol and ethanol (Nacalai Tesque) were all special reagent grade. Molecular sieves 3A (Nacalai Tesque) were used for drying of 2-propanol.

2.2. Preparation of ground mixture

A 2.0 g physical mixture of MCC (97.0%) and BA (3.0%) was ground by means of a vibrational mill (Heiko Seisakusho TI-200) made of tungsten carbide.

2.3. Powder X-ray diffraction

A Rigaku Denki 2027 X-ray diffractometer was used. The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 30 kV; current, 5 mA; scintillation counter.

2.4. Dissolution study

Cyclohexane, *n*-hexane, 2-propanol, acetonitrile, methanol and ethanol were used as dissolu-

tion media. A powdered sample (500 mg) of ground mixture was put into 500 ml of each organic solvent thermostated at 25°C. The suspended solution was vigorously stirred (200 rpm) by means of a magnetic stirrer. At definite intervals, 5 ml of solution was pipetted and filtered out through a membrane filter (Millipore®, 0.2 μm), and the concentration of BA was determined spectrophotometrically at 255 nm.

2.5. Measurement of water content in dissolution media

The water content of each solvent was determined by the Karl-Fisher method using a Hiranuma AQ-6 aquacounter.

3. Results and discussion

3.1. Dissolution profiles of benzoic acid from ground mixtures of microcrystalline cellulose

A mixture of benzoic acid (BA; 3%) and microcrystalline cellulose (MCC; 97%) was ground by means of a vibrational mill. The powder X-ray diffraction pattern of the mixture was changed as a result of the grinding process as shown in Fig. 1. The intensities of the diffraction peaks at about $2\theta = 15$ and 22° , due to crystalline regions of cellulose, decreased corresponding to amorphization of cellulose by grinding. A diffraction peak of BA crystals was observed at $2\theta = 7.8^\circ$ before

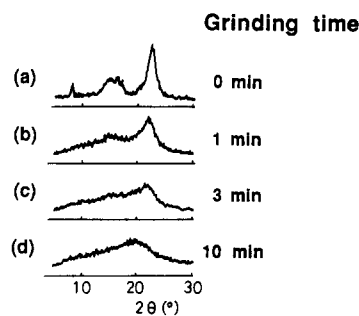


Fig. 1. Changes in powder X-ray diffraction pattern of benzoic acid (BA, 3%)-microcrystalline cellulose (MCC, 97%) system on grinding. A physical mixture of BA and MCC (a) was ground for 1 (b), 3 (c) and 10 min (d).

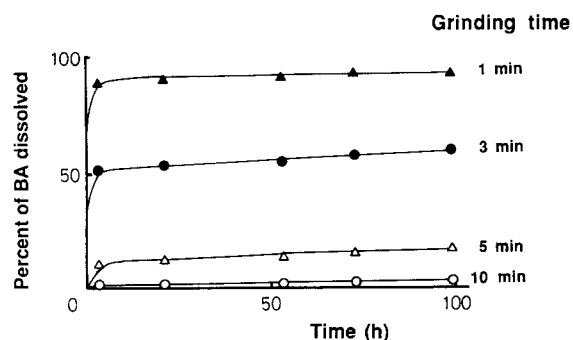


Fig. 2. Effects of grinding on BA dissolution from the ground mixture with MCC in cyclohexane. The samples were prepared by grinding for 1 (▲), 3 (●), 5 (△) and 10 min (○).

grinding, and the disappearance of the peak implies that BA crystals were also amorphized by co-grinding with MCC.

Dissolution experiments for the ground mixtures were carried out by use of organic solvents as dissolution media. Fig. 2 depicts the dissolution curves of BA from the samples ground for 1, 3, 5 and 10 min in cyclohexane at 25°C. The dissolution of BA was found to be suppressed with the duration of grinding, and almost all the proportion of BA in the 10 min ground mixture remained stable against dissolution. Nakai (1986) demonstrated by infrared spectroscopy that drug molecules in the amorphous state were dispersed molecularly in the hydrogen-bond network formed among cellulose molecules in the ground mixture. The results of the dissolution study, e.g., the suppression of BA dissolution, should be correlated to such a change in the molecular states of BA by co-grinding. Accordingly, we believe that

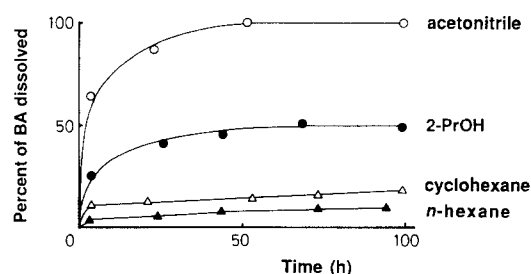


Fig. 3. Dissolution curves of BA from the ground mixture with MCC (ground for 5 min) in acetonitrile (○), 2-propanol (●), cyclohexane (△) and *n*-hexane (▲).

the dissolution study, in which organic solvents were used as dissolution media, can be a great help in evaluating the molecular state of drugs and in characterizing the hydrogen-bond network of cellulose in the ground mixture as well as spectroscopic approaches.

Dissolution experiments were carried out by use of several organic solvents. Fig. 3 shows dissolution curves of BA from the 5 min ground mixture into *n*-hexane, 2-propanol and acetonitrile as well as cyclohexane at 25°C. Benzoic acid is highly soluble in each solvent, and the BA concentration of 100% dissolved is much lower than the level of saturation. The dissolution patterns were significantly different among different solvent systems, and the level of final concentration of BA seems to relate to the polarity of the solvents. In the dissolution curves from the 10 min ground mixture shown in Fig. 4 the dissolution of BA was appreciably suppressed in each

Table 1
Percent of BA dissolved after 100 h and properties of solvents

Solvent	Percent dissolved after 100 h		ϵ^a	δ^b	P^c
	Ground for 5 min	Ground for 10 min			
Water	100	100	78.3	21.0	10.2
Methanol	100	100	32.6	14.4	5.1
Ethanol	100	100	24.6	12.7	4.3
Acetonitrile	100	34.8	36.0	11.7	5.8
2-Propanol	49.0	8.7	19.9	11.5	3.9
Cyclohexane	17.8	5.5	2.0	8.2	-0.2
<i>n</i> -Hexane	9.4	4.2	1.9	-	0.1

^a Relative electric constant at 25°C.

^b Hildebrand's solubility parameter (Hildebrand and Scott, 1962).

^c Snyder's polarity parameter (Snyder, 1974).

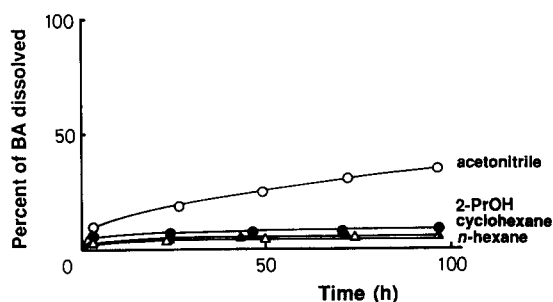


Fig. 4. Dissolution curves of BA from the ground mixture with MCC (ground for 10 min) in acetonitrile (○), 2-propanol (●), cyclohexane (△) and *n*-hexane (▲).

solvent system, i.e., the final percentages dissolved were less than 10% except for that in acetonitrile.

The amounts of BA dissolved after 100 h and some parameters characteristic of the polarities of the solvents are listed in Table 1. It is clearly evident that the dissolution of BA was significantly suppressed by 10 min grinding rather than by 5 min grinding. The amount of BA dissolved increased with increasing solvent polarity in both ground mixtures, suggesting a correlation between the dissolution of BA and the polarity of the dissolution media.

3.2. Effect of moisture in dissolution media on dissolution profiles

Nakai et al. (1977a) reported that for measurement of the specific surface area of amorphous cellulose, the water vapor adsorption method resulted in a considerably larger value of the specific surface area than the nitrogen gas adsorption method. Yamamoto et al. (1976) reported that immediate dissolution and supersaturation were observed in the dissolution test of relatively insoluble drugs from the ground mixture with microcrystalline cellulose. These results were considered to indicate that water molecules have a strong ability to destroy hydrogen-bond networks in cellulose matrix. Therefore, the effects of water molecules in the solvents should be studied. Water contents were determined for the four solvents used in the present dissolution experiments as shown in Table 2 from the Karl-

Table 2
Water contents in organic solvents

Solvent	Water content (ppm) ^a
Acetonitrile	231
2-Propanol	140
Cyclohexane	12.1
<i>n</i> -Hexane	28.5

^a Water contents were determined by the Karl-Fisher method.

Fisher method. The water content was found to increase with the polarity of the solvent. In order to investigate the effects of moisture in greater detail, dissolution tests were carried out using 2-propanol containing different amount of water. Fig. 5 shows plots of the amount of BA dissolved from 5 min ground mixture after 100 h vs initial water content of 2-propanol. The results indicated that an increase in water content in 2-propanol led to enhancement of the dissolution of BA by water.

The variation in water content accompanying the dissolution process was investigated using a large amount, as much as 8.0 g, of 5 min ground mixture in 500 ml of 2-propanol which contained 4.80% of water. As shown in Fig. 6, a decrease in water content in 2-propanol was observed during the dissolution process. These results suggested that water molecules were adsorbed on the cellulose matrix during the process of dissolution. Nakai (1977a) reported that the specific surface area of ground cellulose was estimated to be as great as 361 m²/g by water vapor adsorption

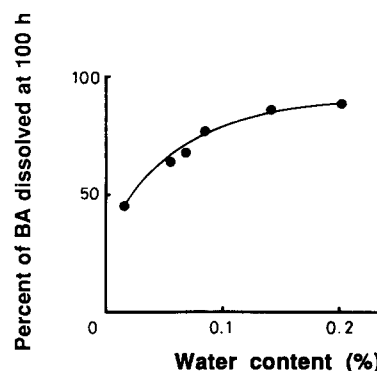


Fig. 5. Dependence of percent BA dissolved after 100 h on the water content in 2-propanol.

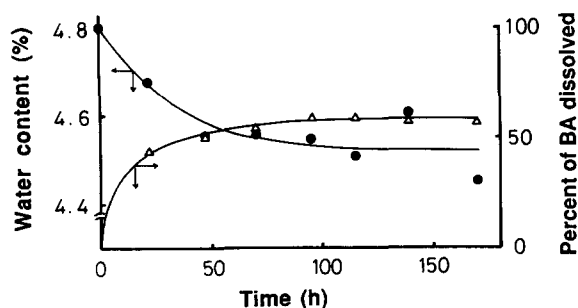


Fig. 6. Variation of water content in 2-propanol during dissolution process. The experiment was carried out by putting 8.0 g of the ground mixture in 500 ml of 2-propanol containing 4.8% of water.

although the low value of $1.0 \text{ m}^2/\text{g}$ was obtained via nitrogen gas adsorption. By assuming 6.2 \AA^2 as the molecular area of water and the monomolecular layer adsorption, the amount of water which can adsorb on 8 g of ground cellulose was calculated to be approx. 1.3 g. In Fig. 6, the decrease in water content during the dissolution experiment was found to be approx. 0.3% in 500 ml of solvent. This amount corresponded to 1.5 g of water and indicated good agreement with the calculated value. Therefore, it appears reasonable to consider that water molecules affected the dissolution of BA from the ground mixture through the ability to adsorb on the cellulose matrix and to destroy hydrogen bonds.

Fig. 7 demonstrates the effects of water content on the amount of BA dissolved from 10 min

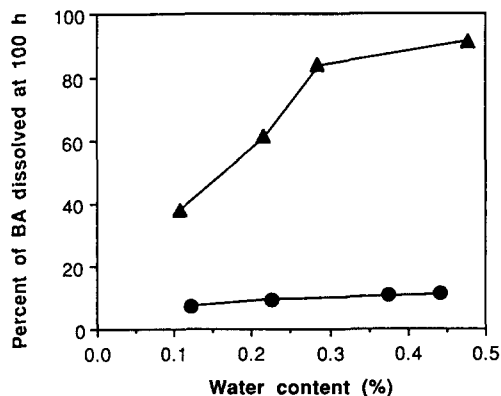


Fig. 7. Dependence of percent BA dissolved from 10 min ground mixture with MCC on the water content in 2-propanol (●) and acetonitrile (▲).

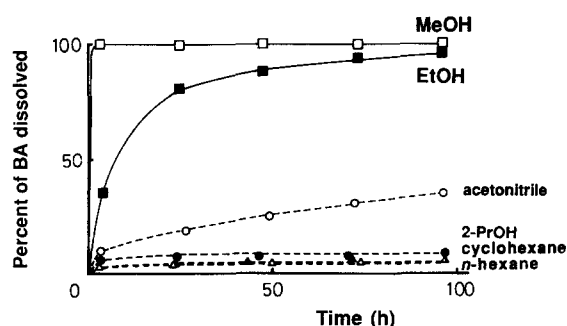


Fig. 8. Dissolution curves of BA from 10 min-ground mixture with MCC in ethanol (■) and methanol (□).

ground mixture into 2-propanol and acetonitrile over a period of 100 h. The dissolution of BA was dependent on the water content in 2-propanol to some extent and significantly so in acetonitrile. The great difference in the dissolved amount between acetonitrile and 2-propanol containing the same level of moisture could be explained based on the difference in polarity of the dissolution media.

3.3. Methanol and ethanol as dissolution media

Methanol and ethanol were used as dissolution media. Fig. 8 shows dissolution curves from 10 min ground mixture in methanol and ethanol superimposed on the results of four other solvents. BA dissolution took place sufficiently in both ethanol and methanol, but differed from that in the other solvents. For example, the magnitudes of the dielectric constants of the solvents used conformed to the following order: acetonitrile > methanol > ethanol > 2-propanol > cyclohexane > *n*-hexane. For methanol and ethanol, the dissolution results did not correlate with the dielectric constant. These properties of methanol and ethanol could be assumed to result from the hydroxy groups which have strong hydrogen-bond forming ability, and steric factors should also be taken account, since such marked dissolution was not observed in 2-propanol.

In the field of liquid chromatography, several parameters characterizing the strength of solvents were proposed to describe the elutropic series, such as the Macek and Prochazka series (Haris

and Macek, 1963), solvent strength on alumina (ϵ^0) (Snyder, 1961), Hildebrand's solubility parameter (δ) (Hildebrand and Scott, 1962), and Snyder's polarity parameter (P') (Snyder, 1974). The δ and P' values for water, methanol, ethanol, acetonitrile, 2-propanol, cyclohexane and *n*-hexane are listed in Table 1. A good correlation is evident between the dissolution results, involving both the final level of BA dissolved and the dissolution rate, and Hildebrand's solubility parameters in which the factor of hydrogen bonding was implied as well as dispersion interaction and permanent dipole-permanent dipole interaction.

Relatively polar solvents (especially alcohols) usually show anomalous behavior on chromatography, and the order of eluting power of the solvents cannot necessarily be represented by these parameters. This anomaly is referred to as the 'selectivity' or 'secondary effect' (Snyder, 1961) of solvent, indicating that these solvents play complicated roles. In the present dissolution experiment as well, the behavior of methanol and ethanol seems to be anomalous if it is assumed that BA dissolution from cellulose matrix is dependent on the polarity of the solvent. We may consider that both methanol and ethanol, to a great extent, have the ability to destroy the hydrogen bonds of the cellulose matrix as a result of the primary hydroxyl groups, followed by sufficient dissolution of BA from the ground mixture with MCC.

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References

- Chiou, W.L. and Riegelman, S., Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, 60 (1971) 1281–1302.
- Haris, I.M. and Macek K., *Bibliography of Paper Chromatography*, Academic Press, 1963, p. 115.
- Hildebrand, J.H. and Scott, R.L., *Regular Solutions*, Prentice-Hall, NJ, 1962.
- Kroon-Batenburg, L.M., Kroon, J. and Northolt, M.G., Theoretical studies on $\beta(1 \rightarrow 4)$ glucose oligomers as models for native and regenerated cellulose fibres. *Papier*, 44 (1990) 640–647.
- Nakai, Y., Molecular behavior of medicinals in ground mixtures with microcrystalline cellulose and cyclodextrins. *Drug Dev. Ind. Pharm.*, 12 (1986) 1017–1039.
- Nakai, Y., Fukuoka, E., Nakajima, S. and Hasegawa, J., Crystallinity and physical characteristics of microcrystalline cellulose. *Chem. Pharm. Bull.*, 25 (1977a) 96–101.
- Nakai, Y., Fukuoka, E., Nakajima, S. and Iida Y., Effects of grinding on physical and chemical properties of crystalline medicinals with microcrystalline cellulose: II. Retention of volatile medicinals in ground mixture. *Chem. Pharm. Bull.*, 26 (1978) 2983–2989.
- Nakai, Y., Fukuoka, E., Nakajima, S. and Yamamoto, K., Effects of grinding on physical and chemical properties of crystalline medicinals with microcrystalline cellulose: I. Some physical properties of crystalline medicinals in ground mixture. *Chem. Pharm. Bull.*, 25 (1977b) 3340–3346.
- Nakai, Y., Nakajima, S., Yamamoto, K., Terada, K. and Konno, T., Effects of grinding on physical and chemical properties of crystalline medicinals with microcrystalline cellulose: IV. Comparison of the IR spectra of medicinals in the solid state and in solution. *Chem. Pharm. Bull.*, 28 (1980) 652–656.
- Nakai, Y., Nakajima, S., Yamamoto, K., Terada, K., Suenaga, M. and Kudoh, T., Effects of grinding with or without microcrystalline cellulose on the decomposition of *p*-aminosalicylic acid. *Chem. Pharm. Bull.*, 30 (1982) 734–738.
- Nakai, Y., Yamamoto, K., Terada, K. and Sakai, M., Measurement of acid strength of excipients by photoacoustic spectroscopy. *Chem. Pharm. Bull.*, 35 (1987) 4255–4262.
- Saers, E.S., Nyström, C. and Aldén, M., Physicochemical aspects of drug release: XVI. The effect of storage on drug dissolution from solid dispersions and the influence of cooling rate and incorporation of surfactant. *Int. J. Pharm.*, 90 (1993) 105–118.
- Snyder, L.R., Classification of the solvent properties of common liquids. *J. Chromatogr.*, 92 (1974) 223–230.
- Snyder, L.R., Linear elution adsorption chromatography: II. Compound separability with alumina as adsorbant. *J. Chromatogr.*, 6 (1961) 22–52.
- Yamamoto, K., Nakano, M., Arita, T., Takayama, Y. and Nakai, Y., Dissolution behavior and bioavailability of phenytoin from a ground mixture with microcrystalline cellulose. *J. Pharm. Sci.*, 65 (1976) 1484–1488.
- Yamamoto, K., Oguchi, T., Yonemochi, E., Matsumura, Y. and Nakai, Y., Fluorometric study on the molecular states of 2,5-diphenyloxazole in ground mixture with γ -cyclodextrin. *Pharm. Res.*, 11 (1994) 331–336.
- Yuasa, H., Ozeki, T., Kanaya, Y. and Oishi, K., Application of the solid dispersion method on the controlled release of medicine: IV. Precise control of the release rate of a water soluble medicine by using the solid dispersion method applying the difference in the molecular weight of a polymer. *Chem. Pharm. Bull.*, 41 (1993) 933–936.
- Zhbankov, R.G., Hydrogen bonds and structure of carbohydrates. *J. Mol. Struct.*, 270 (1992) 523–539.