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Changes of Surface Area in the Dissolution Process of Crystalline Substances

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A series of experiments was conducted to evaluate the changes of surface area during the dissolution process of sieved crystalline particles. The dissolution of some paraben derivatives was followed under the sink condition. Whole particles were collected at intervals during the dissolution measurements. The mean diameter and surface area of the gathered particles were estimated by geometrical and projected area measurements on photomicrographs, and with a LUZEX image analyzer. A fairly good correlation between the surface area (S_H) estimated from Heywood's diameter and the projected area was obtained in spite of the gradual change of particle shape. The dissolution rate constants of sieved paraben crystals were very similar, even though the original particle sizes were different. Dissolution measurements of binary systems mixed at various ratios of the sieved samples were carried out. These dissolution profiles were simulated based on the changes of surface area in the dissolution process of the sieved components by the use of S_H . The simulated dissolution curves estimated from S_H coincided well with those measured over almost the whole dissolution process. The evaluation of dissolution behavior based on the measurement of particle size or particle surface area appears to be useful to estimate or predict the dissolution process.

Keywords—alkyl *p*-hydroxybenzoate; paraben; crystalline particle; dissolution; rotating disk method; mixed system; simulation; change of surface area; image analyzer

Introduction

The dissolution process is an important factor which influences the bioavailability of sparingly soluble drugs. Dissolution behavior is affected by many properties of the particle, such as effective surface area, size, size distribution, shape and so on. There have been many reports on the dissolution of drugs. In most of them, the treatment was based on constant surface area,¹⁾ initial particle size distribution,²⁾ or mean particle size,³⁾ and few have considered the changes of surface area. Dissolution behavior of powder or a tablet which easily disintegrates depends on the particle size, and hence the particle surface area. When the dissolution rate constant is estimated on the base of unit surface area, the rate constant obtained should be a characteristic value for the substance, independent of the initial particle size, and the dissolution process of a polydisperse system might be predictable.

Here, the dissolution characteristics of some paraben derivatives were measured and the value of dissolution rate constant per unit area obtained by measuring the changes of surface area of the particles during the dissolution process of sieved samples was used to simulate the dissolution processes of mixed binary systems.

Experimental

Materials—Parabens such as methyl, ethyl, *n*-propyl and *n*-butyl *p*-hydroxybenzoate (extra pure reagent grade, Kanto Chemical Co., Ltd.: abbreviated as Me-PHBA, Et-PHBA, Pr-PHBA, Bu-PHBA) were used after being

sieved.

Measurements of Particle Size and Surface Area—Particle size and surface area of the particles were estimated from the geometrical and projected area in photomicrographs, and by using a LUZEX-500 image analyzer (NIRECO Co., Ltd.). Specific surface area was measured by an air permeation method by the use of a type SS-100 specific surface area meter (Shimadzu Ind. Co.).

Measurement of Solubility—Suitable amounts of water and sample were added to capped test tubes and solubilities at 25°C were determined by the following two methods for each sample. 1) A saturated solution was obtained by shaking for 10 d in 25°C in a thermocontrolled room. A small amount of solution was sampled every 24 h to check the concentration. 2) A small excess of crystals was added to a solution prepared at $50 \pm 1^\circ\text{C}$ and the mixture was stored at 25°C in a thermocontrolled room to make a saturated solution at 25°C. The concentration was estimated from the absorbance at 255 nm of the filtered sample solution, measured with a type 200-20 spectrophotometer (Hitachi Ind. Co.).

Measurement of Density—Density of samples used was measured by the use of a helium-air pycnometer (type 1302, Simadzu-Micromeritics Co.).

Dissolution by Rotating Disk Method—A suitable amount of sample (1.50 g) was compressed at a pressure of 3 t by means of a type TCM-5000C multipurpose compressor (Shinko Tsushin) to make a model tablet (2.0 cm diameter). The model tablet was fixed on a rotating holder and placed in a dissolution apparatus (type NTR-VS, Toyama Sangyo Co., Ltd.) coupled to a flow cell set in a type 200-20 spectrophotometer *via* a pump. The dissolution test was carried out in 1000 ml of water at a rotation speed of 250 rpm at 25°C. The dissolution measurements were carried out five times.

Dissolution of Crystalline Particles—A suitable amount of sieved sample (equivalent to one-twentieths of the solubility) was added to the dissolution apparatus. The solution was sampled to determine the concentration, and all the particles that remained were collected to determine the surface area (S_H , described later) after a given dissolution time. These dissolution and surface area measurements were carried out four times under the same conditions as described above.

Sieved samples mixed at various ratios were also used for dissolution measurements. Their dissolution processes were simulated based on the changes of surface area obtained for the component samples.

Results and Discussion

Solubility

The concentration of the solution remained almost the same after two days in method 1. Solubility values determined by the two method showed very little difference from each other and the mean values are listed in Table I.

Dissolution by the Rotating Disk Method

Dissolution profiles obtained are shown in Fig. 1.

The dissolution rate (dC/dt) given by Nernst⁴⁾ is expressed by Eq. 1:

$$dC/dt = (DS/V\delta)(C_s - C) \quad (1)$$

where D is the diffusion constant, S is the effective surface area, V is the amount of solvent, δ is the thickness of the diffusion layer, C_s is the solubility and C is the concentration in the dissolution process.

TABLE I. Properties of Alkyl Parabens

	Solubility (g/l)	Dissolution rate constant k' (cm/min)	Density ρ (g/cm ³)	Particle size D_H (mm)	Dissolution rate constant k (cm/min)
Me-PHBA	2.110	0.081			
Et-PHBA	0.806	0.080			
Pr-PHBA	0.330	0.077	1.28	0.134 (L) 0.048 (S)	0.122 0.115
Bu-PHBA	0.213	0.065	1.23	0.103 (L) 0.026 (S)	0.121 0.133

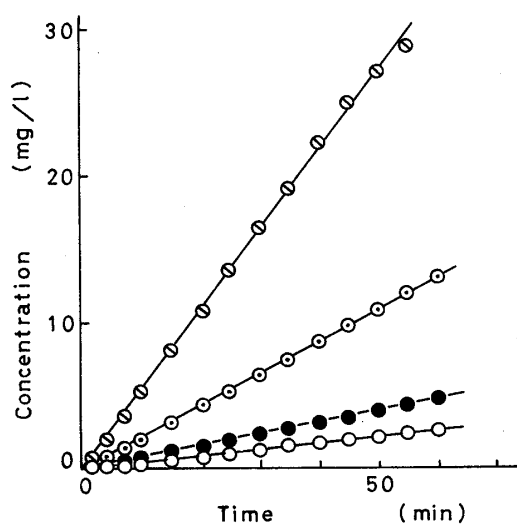


Fig. 1. Dissolution Curves of Alkyl Parabens Obtained by the Rotating Disk Method

⊙, Me-PHBA; ○, Et-PHBA; ●, Pr-PHBA; ○, Bu-PHBA.

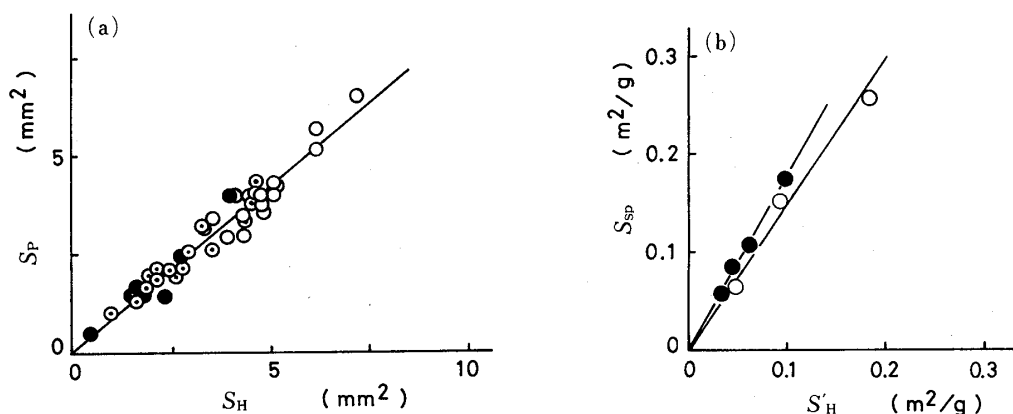


Fig. 2. Relationship between Surface Areas Estimated by Different Methods

(a) Bu-PHBA (L): ○, original; ⊙, after 4 h; ●, after 6 h. (b) ○, Bu-PHBA; ●, Pr-PHBA.

Compared with C_s , C is small enough to consider that the dissolution is carried out under the sink condition, and Eq. 1 can be simplified to Eq. 2. Equation 3 was obtained by integration of Eq. 2.

$$dC/dt = (k'S/V)Cs \quad (2)$$

$$C = (k'S/V)Cst \quad (3)$$

Here, $k' = D/\delta$ and is the dissolution rate constant per unit area.

Fairly good linear relationships were obtained between concentration and dissolution time, as shown in Fig. 1. According to Eq. 3, k' was estimated from the slope of the straight line, and the values obtained are listed in Table I.

The value of k' decreased with increasing side chain length of parabens.

Particle Size and Surface Area

Surface area expressed by S_H was calculated on the basis of a spherical particle using Heywood's diameter and the projected area (S_p) was obtained from projected areas for several directions measured from photomicrographs and by using a LUZEX image analyzer. The correlation between S_H and S_p of Bu-PHBA is shown in Fig. 2a, and relationships between specific surface area obtained by the air permeation method (S_{sp}) and that estimated from Heywood's diameter ($S'_H = 6/\rho D_H$) are shown in Fig. 2b. The value of D_H was evaluated by

using about 20 mg of sieved samples in this case, and the results are listed in Table I.

Considering the changes of particle shape with dissolution time, values for original particles and particles at a given dissolution time were shown altogether. As can be seen in Fig. 2a, there is a fairly good correlation between S_H and S_p in spite of the gradual change of particle shape. In regard to specific surface area, good linear relationships between S_{sp} and S'_H can be seen in Fig. 2b. From these results, it seems that surface area can be evaluated in terms of S_H , when a suitable coefficient is introduced in each relationship. Thus, S_H might reflect proper surface areas, and S_H was used for the following treatments of the results.

Dissolution of Crystalline Particles

Dissolution profiles of Pr-PHBA obtained for different initial particle size samples are shown in Fig. 3.

When surface area changes with dissolution time under the sink condition, Eq. 2 can be transformed to Eq. 4 by the use of $S(t)$ in place of S .

$$dC/dt = kS(t)Cs/V \quad (4)$$

Here, k is dissolution rate constant per unit area, and is distinct from k' in Eq. 2.

When k , Cs and V are constant as in this case, a linear relationship between dC/dt and $S(t)$ should exist. Figure 4 shows this relationship. Here, dC/dt was estimated from the tangent line at the measured point in Fig. 3 and surface area at the time $S(t)$ was obtained as S_H measured directly at the same point.

As shown in Fig. 4, the relationship between dC/dt and S_H exhibited good linearity, and the k value was estimated from the slope of each straight line. The k values for Bu-PHBA were estimated in the same manner and are also listed in Table I. According to Eq. 4, only one straight line should occur in the relationship between dC/dt and S_H , even if the original particle sizes are different. Comparing the results in Fig. 1 and Table I, the k values of the parabens are very similar. On the other hand, the dissolution rate constant obtained by the crystalline particle dissolution method is larger than that obtained by the rotating disk method, as seen in Table I, although they were expected to give similar values.

The change of surface area of Pr-PHBA with time is shown in Fig. 5. The dotted line obtained by calculation using the k value and Eq. 4 showed fairly good agreement with the measured results. However, the calculated values tended to be larger than those measured at the final stage of the dissolution process. This difference was supposed to be caused by a lack

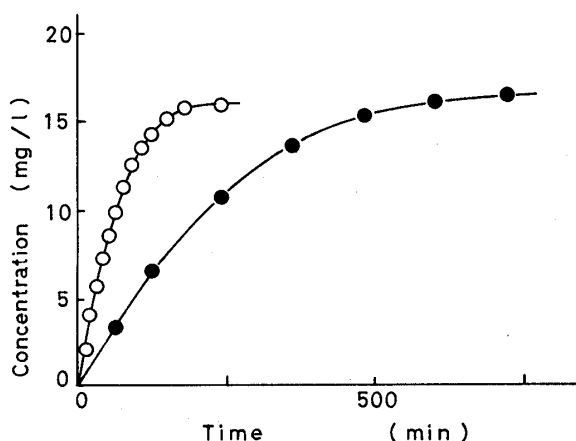


Fig. 3. Dissolution Curves of Pr-PHBA

Amount of Pr-PHBA, 16 mg; ●, Pr-PHBA (L); ○, Pr-PHBA (S).

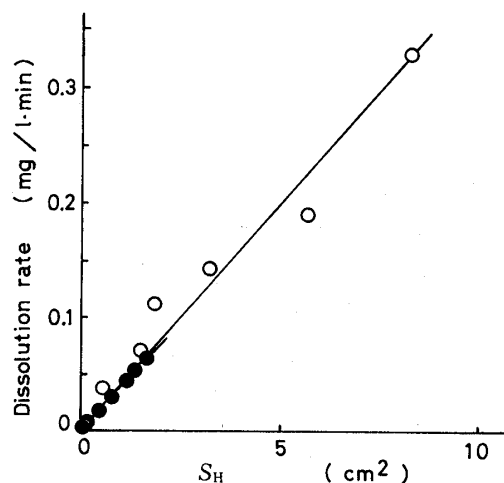


Fig. 4. Relationship between Dissolution Rate and S_H

●, Pr-PHBA (L); ○, Pr-PHBA (S).

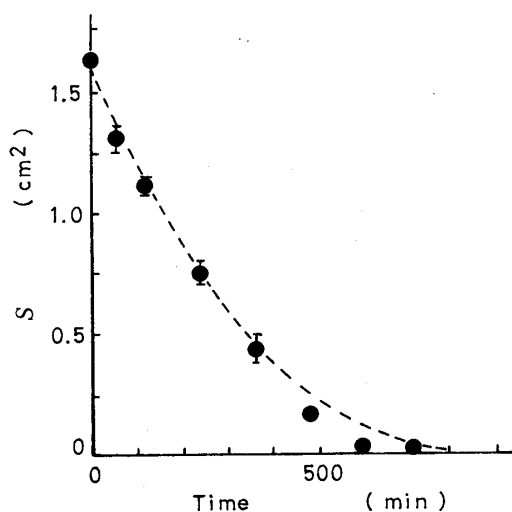


Fig. 5. Relationship between Surface Area and Dissolution Time for Pr-PHBA (L)

●, S_H ; ----, $S(t)$ calculated by using Eq. 4.

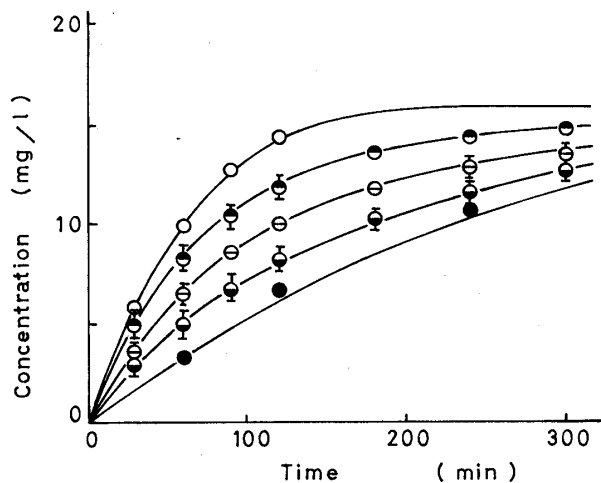


Fig. 6. Dissolution and Simulation Curves for Mixed Binary Systems of Pr-PHBA

Mixing weight ratio (S)/(L): ○, 1/0; ●, 3/1; ⊙, 1/1; ⊙, 1/3; ●, 0/1. —, Calculated by using Eq. 6.

of consideration of the solubility of relatively small particles in the sieved sample besides the difficulty in the estimation of S_H .

Dissolution and Simulation Curves for Mixed Binary Systems

The dissolution results for binary systems consisting of various weight ratios of sieved, different-particle-size samples of Pr-PHBA are shown in Fig. 6. The simulated curves shown by solid lines in Fig. 6 were obtained as follows. By integrating Eq. 4, Eq. 5 was obtained.

$$C = (kC_s/V) \int_0^t S(t) dt \quad (5)$$

The value of $\int_0^t S(t) dt$ was obtained by graphical integration using the values given by the dotted line in Fig. 5. The value of C was calculated by the use of Eq. 5 for each component, i.e., C_S and C_L . Then, C in the mixed binary system at time t was obtained by means of Eq. 6 as the summation of the contributions of the components.

$$C = X_S C_S + X_L C_L \quad (6)$$

Here, X_S and X_L are the mixing weight ratios of Pr-PHBA (S) and (L) respectively. The simulated dissolution curves estimated by Eq. 6 coincided well with those measured over almost the whole range as shown in Fig. 6.

As described above, the dissolution process of mixed binary systems can be well estimated by a treatment based on the measurement of particle size or particle surface area of each component, and the method should be useful to estimate or predict the dissolution processes of mixed systems.

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