Chem. Pharm. Bull. 37(5) 1362—1365 (1989)

Changes of Surface Area in the Dissolution Process of Crystalline Substances. III. Dissolution and Simulation Curves for Symmetrical Particle-Size-Distributed Model Systems

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Received September 29, 1988

The dissolution of sieved *n*-propyl *p*-hydroxybenzoate crystalline particles mixed at various weight ratios devised to give symmetrical particle size distributions was conducted under the sink condition. These dissolution processes were simulated on the basis of the change of surface area estimated for the component samples. The mixed ternary systems were converted into several imaginary symmetrical particle-size-distributed systems, and the dissolution processes of the original mixed systems were simulated with the imaginary systems by making use of the relationship between the surface-producing rate constant and the initial particle size. The validity of the simulation on the bases of the surface-producing rate constant and the introduction of imaginary particles was also examined. The simulated values showed fairly good coincidence with those measured. The values simulated by the use of the changes of surface area during the dissolution, obtained by graphical integration for the components, were closer to the measured values than those simulated by the use of the relationship between the surface-producing rate constant and the initial particle size. However, the latter simulation method was thought to be more useful than the former, because the surface area produced during the dissolution is given by a generalized function of the initial particle size and the dissolution behavior of mixed systems was predictable when the initial particle size of the components were defined in advance.

Keywords paraben; *n*-propyl *p*-hydroxybenzoate; crystalline particle; dissolution; surface area; image analyzer; mixed system; imaginary system; simulation

Introduction

The dissolution process is an important factor which influences the bioavailability of sparingly soluble drugs. Dissolution behavior of a powder or a tablet which easily disintegrates depends on the particle size, and hence, the particle surface area. Hence, a method to evaluate or predict the dissolution process in terms of the surface area was sought. In the previous paper, the changes of surface area during the dissolution process were measured, and the relationship between the surface-producing rate constant and the initial particle size of the sieved sample was estimated. Then the dissolution of ternary systems mixed to have various surface areas was conducted to estimate the effect of the components on the simulation of the dissolution behavior, and to examine the validity of the treatment.[1)]

In this paper, the dissolution of mixed system devised to have symmetrical particle-size distributions was carried out, and the dissolution processes were simulated following the method described in the previous paper.[1)] The surface producing rate constant was given as a function of the initial particle size, and the samples sieved before use should be composed of various particle sizes, even if it were narrow ranges. Hence, the dissolution processes of the mixed systems were also simulated assuming some equivalent imaginary symmetrical particle-size-distributed systems on the basis of the relationship between the surface-producing rate constant and the initial particle size of sieved samples.

Experimental

Materials The samples reported in the previous paper[1b)] were used. *n*-Propyl *p*-hydroxybenzoate (extra pure reagent, Kanto Chemical Co., Ltd.) 14/20, 20/28 and 28/35 mesh fractions, separated by the use of J. I. S. sieves, were abbreviated as Pr-PHBA(L), Pr-PHBA(M) and Pr-PHBA(S), respectively; their Heywood's diameters measured by using a LUZEX-500 image analyzer (NIRECO Co., Ltd.) were 0.134, 0.104 and 0.076 cm, respectively.

Dissolution of Mixed Systems A suitable amount of sieved samples (equivalent to one-twentieth of the solubility) mixed at various weight ratios to have a symmetrical particle size distribution was used. The dissolution test was carried out following the method described in the previous paper.[1b)] The measurement carried out twice gave similar values, and data are presented as the mean values.

Results and Discussion

Dissolution and Simulation Curves for Mixed Systems

The dissolution rate (dC/dt) given by Nernst[2)] is expressed by Eq. 1:

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

where D is the diffusion constant, S is the effective surface area for dissolution, δ is the thickness of the diffusion layer, V is the volume of solvent, C_s is the solubility and C is the concentration in the dissolution process. When C is small enough to consider that the dissolution is occurring under the sink condition, and the surface area changes with dissolution time, Eq. 1 can be transformed to Eq. 2 by the use of $S(t)$ in place of S, and Eq. 3 is obtained by integrating Eq. 2:

$$dC/dt=(kC_s/V)\cdot S(t) \qquad (2)$$

$$C=(kC_s/V)\cdot \int_0^t S(t)dt \qquad (3)$$

where $k=D/\delta$ and is the dissolution rate constant.

Equation 3 was treated as follows in the previous paper.[1b)] 1) The surface area produced during the dissolution process ($\int_0^t S(t)dt$) was obtained by graphical integration using the values obtained from the surface area *versus* time curves for sieved samples. 2) The surface-producing rate constant (α) was evaluated following the method of Nogami *et al.*[3)] 3) The relationship between the α-value and the initial Heywood's diameter ($D_{H,o}$) was examined, and the following equation was obtained.

$$\alpha=7.650\times 10^4/D_{H,o} \qquad (4)$$

4) According to Eq. 3, the maximum surface area produced during the dissolution, $\int_0^\infty S(t)dt$ is independent of particle

size, and is given when all the sample has dissolved. Hence, denoting by M_o the amount of sample used for the dissolution, $\int_0^\infty S(t)\mathrm{d}t = M_o/kC_s$. 5) As a result, Eq. 5 was deduced.

$$C=(1/V)M_o(1-e^{-\alpha t}) \tag{5}$$

Therefore, the concentration during the dissolution can be calculated by the use of Eqs. 4 and 5 when the particle size and the amount of the sample are given.

Mixed systems used for dissolution measurement were devised to have symmetrical particle size distributions. Examples of particle size distributions and a dissolution profile are shown in Figs. 1 and 2. The simulation curves shown in Fig. 2 were obtained by two methods.[1b] 1) The concentration of the mixed system at time t, *i.e.*, C_σ, was evaluated by means of Eq. 6 as the summation of the contributions of all the components:

$$C_\sigma=\sum X_i C_i \tag{6}$$

where X_i is the mixed weight ratio of component i and C_i is the concentration of component i at time t calculated by means of graphical integration of the surface area *versus* time curve and Eq. 3. The values obtained are shown by the broken line. 2) The concentration of the mixed system at time t, *i.e.*, C_α, was evaluated by Eq. 7 as the summation of the concentration calculated by Eqs. 4 and 5 for all of the components:

$$C_\alpha=(1/V)\sum w_{i,o}(1-e^{-\alpha_i t}) \tag{7}$$

where α_i and $w_{i,o}$ are the α-value and the initial amount of component i, respectively. The values obtained are shown by the solid line. The C_σ and C_α values thus obtained are also shown in Fig. 3 to clarify the correlation with the measured value (C).

The broken line shown in Fig. 3 is the line that should be obtained when C_σ and/or C_α are equal to C. The simulated values show fairly good coincidence with the measured values. Then the validity of the simulations was assessed as described in the previous paper.[1b] The ratios of C_σ and C_α to C, *i.e.*, C_σ/C $(=R_\sigma)$ and C_α/C $(=R_\alpha)$, were calculated, and the validity of the simulations was estimated from the mean value ($\bar{R}_\sigma$ and $\bar{R}_\alpha$) and standard deviation (S. D.). The results obtained for the mixed systems are summarized in Table I.

The results were broadly similar to those described in the pervious paper.[1b] Compared with the measured value, the simulated values were a little higher in the initial stage and a little lower in the middle stage of the dissolution, and the C_σ value is closer to the measured value than the C_α value, as can be seen in Figs. 2 and 3. The results summarized in Table I show that the mean values, *i.e.*, $\bar{R}_\sigma$ and $\bar{R}_\alpha$, for all the systems deviate slightly. The values thus simulated show fairly good coincidence with those measured, and both methods are thought to be useful to simulate or predict the dissolution behavior of mixed systems. However, the C_σ value relies on the evaluation of surface area produced during the dissolution for each component. Also, the C_σ value can be calculated only when the surface producing properties of components are known. On the other hand, the C_α value seemed to be less affected by a particular

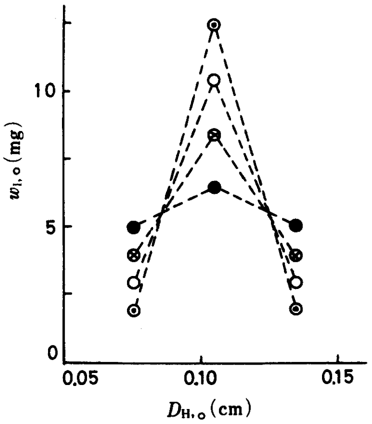

Fig. 1. Particle Size ($D_{H,o}$) and Amount ($w_{i,o}$) of Components for Mixed Systems

⊙, system I; ○, system II; ⊗, system III; ●, system IV.

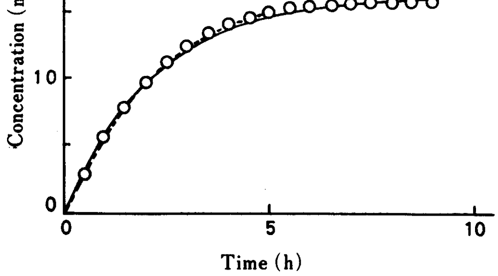

Fig. 2. Dissolution and Simulation Curves for Mixed System II

------, C_σ; ——, C_α.

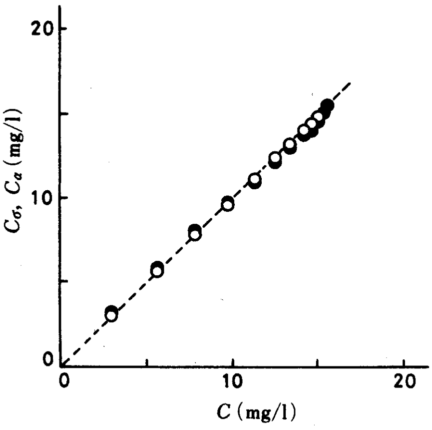

Fig. 3. Relationship between Measured Value (C) and Simulated Values (C_σ and C_α) for Mixed System II

○, C_σ; ●, C_α; ------, C_σ and/or $C_\alpha=C$.

Table I. Evaluation of Simulated Values for Mixed Systems

Mixed system	Amount of Pr-PHBA (mg)			$\bar{R}_\sigma\pm$S.D.	$\bar{R}_\alpha\pm$S.D.
	(S)	(M)	(L)		
I	2.0	12.4	2.0	0.997±0.025	0.997±0.038
II	3.0	10.4	3.0	0.999±0.023	0.998±0.037
III	4.0	8.4	4.0	0.980±0.022	0.990±0.036
IV	5.0	6.4	5.0	0.988±0.023	0.993±0.037

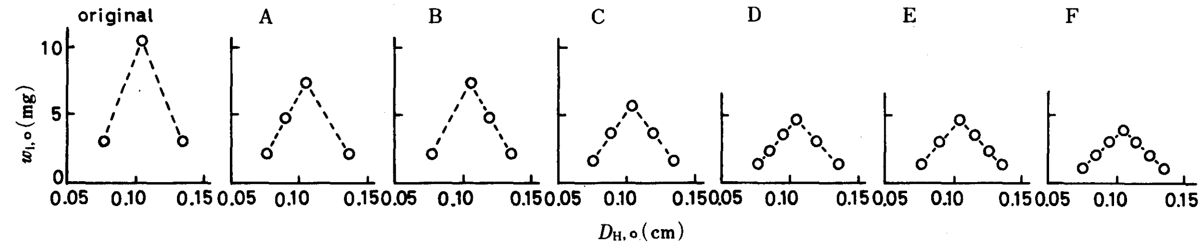

Fig. 4. Original and Imaginary Systems for Mixed System II

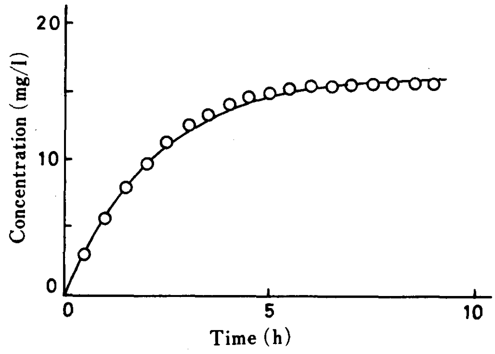

Fig. 5. Simulation Curve Evaluated from Type F Imaginary System for Mixed System II

——, C_x.

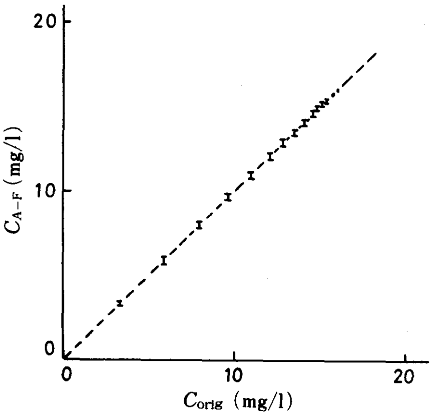

Fig. 6. Relationship between the Values Simulated from Imaginary Systems (C_{A-F}) and Those of Original System (C_{orig}) for Mixed System II

------, $C_{A-F}=C_{orig}$. The upper and lower values of each point are obtained from the type A and B imaginary systems, respectively.

component and might be calculated just by knowing the particle sizes of components, because the surface-producing property of each component is given as a generalized value as a function of initial particle size. Hence, the simulation method by the use of Eq. 7 is thought to be more useful than the method by the use of Eq. 6.

Simulation Curves for Mixed Systems Estimated from Imaginary Symmetrical Particle-Size-Distributed Systems In the previous section, it was shown that the surface-producing rate constant can be expressed in terms of the particle sizes, and the equations suggest that the change of surface area of any particle size sample is predictable by the use of the surface-producing rate constant. Hence, the dissolution behavior of mixed systems is expected to be predictable when the particle size distribution properties are known. The applicability of the equations was examined by simulating the dissolution of a mixed system by the use of several imaginary particle-size-distributed systems.

The samples were sieved before use, however they should be composed of various sizes of crystalline particles, even if it were narrow range. Therefore, the mixed system should contain various particle sizes, even though the mixed system was prepared from three sieved components. Hence, some imaginary components were chosen as the middle, one-third and two-thirds particle sizes between Pr-PHBA (S) and (M) or Pr-PHBA (M) and (L) to simulate the dissolution behavior of the mixed ternary systems. To avoid complexity, the amount of each component was calculated along the broken line shown in Fig. 1, neglecting possible deviation from the real particle size distribution in the mixed system. The original and imaginary systems (type A—F) for the mixed ternary system II thus obtained are shown in Fig. 4 as an example. Thus, the system consisting of three components was transformed to one of four to seven components, and the applicability or validity of Eq. 7 was examined. The simulation curve obtained by the use of the imaginary system is shown in Fig. 5; the simulated values obtained for all the imaginary systems were close to each other, and the values are compared with those of the original three-component system in Fig. 6. The upper and lower values of each point are obtained from the type A and B imaginary systems, respectively. The values obtained from the type C and F imaginary systems are very close to those of the original system.

Table II. Evaluation of Values Simulated from Imaginary Systems

Type	$\bar{R}_x \pm$ S.D.			
	System I	System II	System III	System IV
Original	0.997±0.038	0.998±0.037	0.990±0.035	0.993±0.037
A	1.011±0.044	1.012±0.043	1.002±0.037	1.004±0.040
B	0.982±0.035	0.984±0.033	0.977±0.035	0.979±0.034
C	0.996±0.038	0.998±0.036	0.989±0.035	0.991±0.035
D	1.005±0.041	1.006±0.040	0.996±0.035	0.999±0.037
E	0.989±0.036	0.990±0.034	0.981±0.035	0.983±0.033
F	0.997±0.038	0.998±0.036	0.988±0.034	0.991±0.035

The ratio of simulated value to measured value was used to estimate the validity of the simulation in the same manner as described in the previous section, and the mean value of the ratio and standard deviation are summarized in Table II. The mean values for all the systems deviated only slightly from unity, showing that the simulated values coincide well with the measured values. Comparing the simulated values with those of the original mixed system, the simulated value became a little higher or lower in accordance with the introduction of imaginary components to emphasize the smaller particle size region (types A and D) or the larger particle size region (types B and E). When imaginary components were chosen suitably (types C and F) to reflect the original particle size distribution pattern, the simulated values coincided well with those of the original system. In general, the simulated values for imaginary systems deviated only a few percent from those of the original system and the measured values, as can be seen in Fig. 6 and Table II.

Hence, when the relationship between the surface-producing rate constant and the initial particle size is obtained, the dissolution properties can be estimated by the use of particle size (Eq. 4), and the dissolution behavior of a sample whose particle size distribution is known might be predicted (Eq. 7). Also, the simulated values for type F component system and those of other component systems were similar. Therefore, the dissolution behavior of a sample composed of various particle-size particles might be predicted by picking some particle sizes and amounts and converting the original system into a simple imaginary system.

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