[Chem. Pharm. Bull. 30(8)2958—2963(1982)]

Crystal Habits and Dissolution Behavior of Aspirin[1)]

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(Received February 8, 1982)

Aspirin crystals having different types of habits were prepared by recrystallization of commercial products from various solvents. The difference in crystal habits was investigated crystallographically and optically by the use of a polarizing microscope to measure habit parameters a, b, and c. The dissolution behavior of these crystals was studied in an artificial gastric juice, and the dissolution constants were calculated by means of the Noyes-Whitney equation using the specific surface areas obtained from the habit parameters.

It was found that the dissolution constants of crystals with different habits were not constant, and it seems that the values depend upon the ratio of the area of (001) to the sum of the areas of the remaining faces. It was also found that aspirin dissolved more easily when it was powdered than would be expected from the increased surface area. This phenomenon might be a result of the distortion of crystals which was observed under the polarizing microscope.

Keywords——aspirin; crystal habit; dissolution behavior; polarizing microscope; specific surface area; habit parameters

It was believed among physicians in Japan many years ago that there was a slight difference in bioavailability between domestic and imported aspirin products. One of the authors of this paper, A. Watanabe, previously investigated with S. Watanabe of Tohoku University[2)] the various kinds of commercial aspirin products by morphological and optical crystallographic methods. They confirmed then that there was no essential difference in crystallographic properties and no polymophs among the commercial preparations of aspirin, though a remarkable difference in crystal habit was observed between the domestic aspirins and the imported Bayer aspirin. Tawashi[3)] reported the existence of polymorphs in recrystallized crystals of aspirin from ethanol or *n*-hexane, and stated that there was a remarkable difference in dissolution behavior between the two types of crystals. However, polymorphism of aspirin was not observed in the subsequent studies of Pheiffer,[4)] Mitchell[5)] or Schwarzman.[6)] Nevertheless, there remains evidence that the crystals of aspirin show different dissolution behavior when they are recrystallized from different types of solvents. Nogami[7)] and Kato *et al.*[8)] studied the absorption and excretion behavior of various commercial products of aspirin as well as various recrystallized crystals obtained from these products, and found that both the recrystallized thin crystals and the commercial leaflet crystals showed better dissolution and excretion behavior than other Japanese commercial products.

The present author prepared various kinds of aspirin crystals, which showed different crystal habits, by recrystallization using various kinds of solvents, and investigated the nature of the crystal habits quantitatively using the habit parameters measured by means of the polarizing microscope. Next, the dissolution behavior of each crystal was studied in an artificial gastric juice. It was found that the dissolution velocity of aspirin crystals depends not only upon the surface area of the crystal powder but also upon the crystal habit. In other words, it depends upon the ratio of the area of (001) to the sum of the areas of the remaining planes. Moreover, it was also found that the dissolution behavior of aspirin crystals is affected by the distortion of crystals caused by crushing. Therefore, the factors which affect the dissolution behavior of aspirin are the surface area of crystals, the crystal habits, and the

distortion of crushed crystal powder. The resulting complexity of dissolution behavior of aspirin crystals probably accounts at least in part for the rather complicated bioavailability behavior of aspirin preparations.

Experimental

Materials——Aspirin, J.P. IX, manufactured by Shioe-Seiyaku Co. Ltd. in Osaka, was purchased from Nakarai Chemicals Ltd. The solvents, extra pure grade, used for recrystallization of aspirin were also purchased from Nakarai Chemicals Ltd.

Instruments——A binocular polarizing microscope, Olympus BHA with photographic attachments, was used.

Measurement of Refractive Indices——A commercial kit of immersion oils[9] was used. The measurement was carried out by the immersion method described in the previous paper.[1b]

Measurement of Dissolution Velocity——1.0 g of aspirin crystals was added to 500 ml of artificial gastric juice of pH 1.2 (No. 1 Liquid of J.P. X), stirred at 400 rpm in a thermostat at 37°C. A definite quantity of the solution was pipetted after a definite time and filtered with cotton, and then the amount of aspirin was assayed by a spectrophotometer observing the UV absorption at 278 nm and 308 nm. The concentration of aspirin (C_a) was obtained by the following equation:

$$C_a = (A_{278} - \varepsilon^s_{278} \times C_s)/\varepsilon^a_{278} + (C_s - C^0_s),$$

where ε^s_{278} and ε^a_{278} are the molar extinction coefficient of salicylic acid and aspirin respectively, C_s is the concentration of salicylic acid of the test solution ($C_s = A_{308}/\varepsilon^s_{308}$) and C^0_s is the initial concentration of salicylic acid.

Results and Discussion

I. Various Habits of Aspirin Crystals and Their Quantitative Determination from Habit Parameters

Aspirin was crystallized as monoclinic plates[2] as shown in Fig. 1(a). The domestic commercial aspirin crystals used in this study show almost the same habit as that in Fig. 1(a); photomicrographs are shown in Fig. 2(a). Recrystallization of the commercial aspirin product from different types of solvents gave various crystal habits of aspirin. By using ethanol, mathanol or acetone as the solvent, aspirin could be crystallized as small plates or prisms as shown in Fig. 1(b) and Fig. 2(b). From water, aspirin crystallized as thin plates or leaflets as shown in Fig. 1(c) and Fig. 2(c), and from dioxane or *n*-heptane, it crystallized as thin needles or elongated prisms as shown in Fig. 1(d) and Fig. 2(d) or (d').

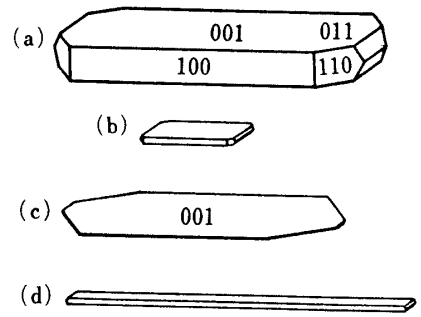

Fig. 1. Various Habits of Aspirin Crystals

Table I. Refractive Indexes of Aspirin

Face	n_1	n_2	Extinction	Elongation
001	1.562	1.652	Parallel	+
100	1.573	1.652	Parallel	+
101	1.640	1.652	Parallel	+

These crystal habits were investigated by means of the polarizing microscope using the immersion method as described in the previous paper.[1b] To identify the face which lay parallel to the microscope stage, the key refractive indexes were measured, and by comparing the data with the values shown in Table I the face (001) or (100) could be easily discriminated. In most aspirin crystals, the face (001) was predominant and lay parallel to the stage. Thus, average-size crystals were selected in the microscope field, and the approximate average surface area of (001) was measured from the habit parameters, a and b, as shown in Fig. 3. Then the other habit parameter c, the thickness of the face (001), was calculated from the relative retard-

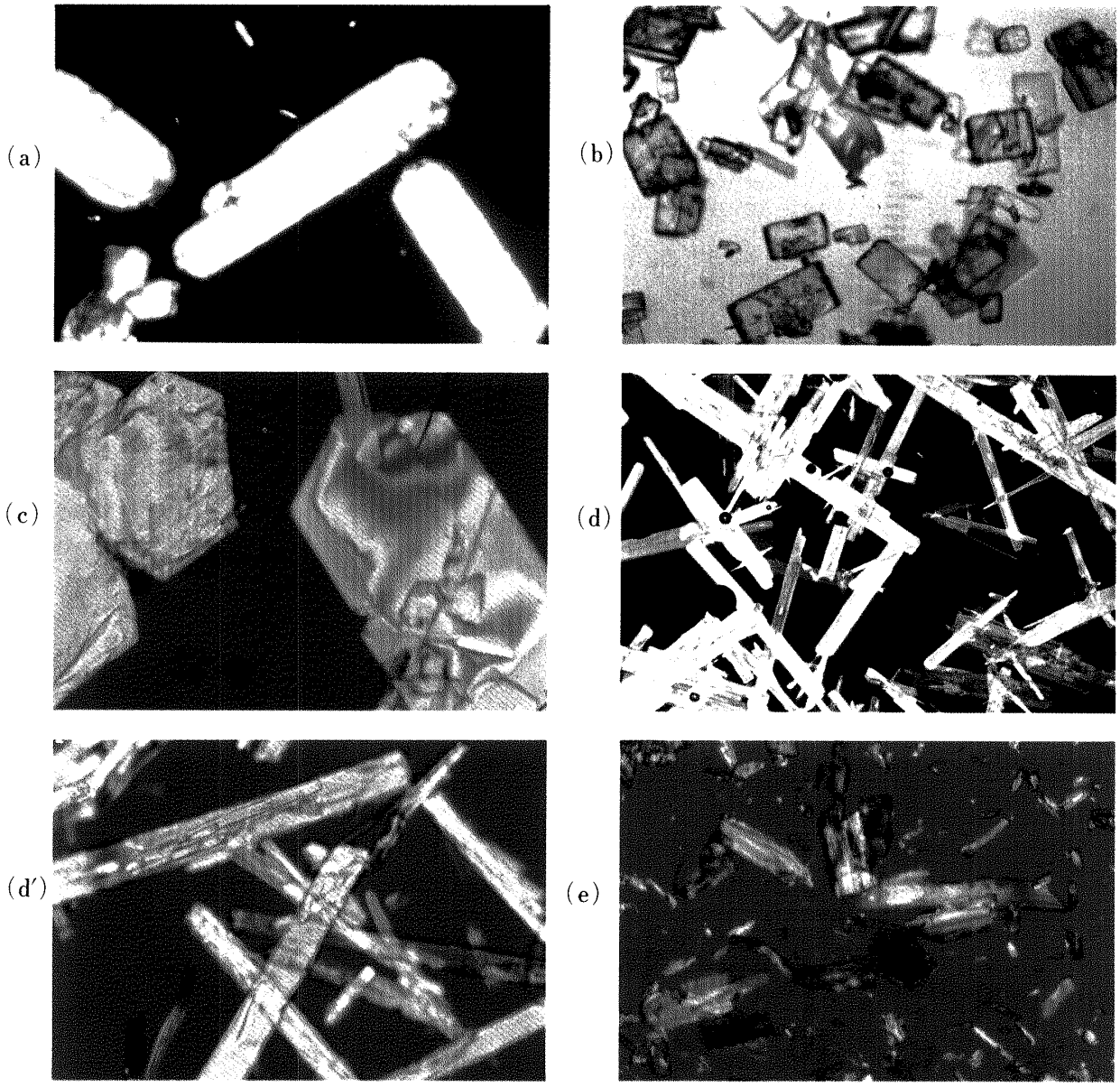

Fig. 2. Polarizing Photomicrographs of Various Habits of Aspirin Crystals

(a) Commercial product ×40 (crossed nicols), (b) from ethanol ×40 (polarizer only), (c) from water ×40 (crossed nicols+gypsum plate), (d) from dioxane ×40 (crossed nicols), (d′) from dioxane ×200 (+gypsum plate), (e) powdered commercial product ×40 (*ibid.*).

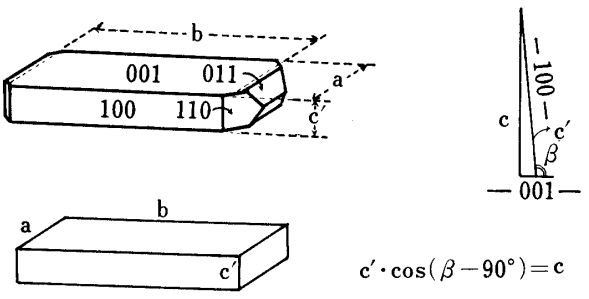

Fig. 3. Habit Parameters of Aspirin Crystals

ation (R) by means of the following equation: $c=R/(n_2-n_1)$, where n_1 and n_2 are the refractive indexes as shown in Table I, and R is the relative retardation, whose value was estimated from the observed interference color under crossed nicols. c is related to c′, the length of an edge of the face (100) along the c-axis, by the following equation: $c=c'\cdot\cos(\beta-90°)$, where the value of β, the monoclinic axial angle of aspirin, is 95°30′. Therefore, practically speaking, c is equal to c′.

Then the surface area (S) as well as the specific surface area (S') of average-size crystals of the particular habit were calculated from the habit parameters, a, b and c by means of the following equation: $S=2(ab+bc+ca)$; $S'=S/abcD$, where D is the density of aspirin, 1.4. Accordingly the habit parameters of various habits of aspirin crystals and the surface areas as well as the specific surface areas calcualted for the crystals of the particular habit are shown in Table II.

Table II. Habit Parameters, Surface Areas and Specific Surface Areas of an Average-size Crystals of Various Habits of Aspirin

No.	Crystal	Habit parameters in mm			Surface area in mm^2	Specific surface area in mm^2/mg
		a	b	c		
1	From water	0.290	0.58	0.0041	0.3435	355.77
2	From dioxane	0.064	1.10	0.0410	0.2362	58.46
3	From water+EG[a)]	0.710	1.40	0.020	2.0724	74.46
4	From ethanol	0.110	0.21	0.015	0.0558	115.05
5	From *n*-hexane	0.013	0.25	0.012	0.0128	234.61
6	From chloroform	0.072	1.20	0.053	0.3076	110.73
7	Market product	0.500	1.20	0.310	2.2540	8.65

a) Ethylene glycol.

II. Dissolution Behavior of Various Crystal Habits of Aspirin

The Dissolution behavior was investigated in an artificial gastric juice of J. P. IX at 37°C with the following aspirin crystals: (1) thin crystals from water (Table II, No. 1), (2) needles from dioxane (Table II, No. 2), (3) elongated prisms recrystallized from a mixed solvent of water and ethylene glycol (Table II, No. 3), (4) commercial product (Table II, No. 7). The results are shown in Fig. 4. As is well known, the dissolution velocity of powdered drugs is given by the following Noyes-Whitney equation:

$$dc/dt = KS(C_s - C),$$

where K is the dissolution constant, S is the total surface area of the powder, C_s is the concentration of a saturated solution of the powder and C is the concentration of the solution. Using both the results shown in Fig. 4 and the specific surface areas shown in Table II the dissolution constant K of aspirin at 37°C was calculated and the results are shown in Table III. As shown in Table III the values of the dissolution constant, K, obtained from the different havits of aspirin crystals was not constant, and it seems that in the case of thin crystals, namely, (001)-predominant crystals, the dissolution constants were smaller than in the case of thicker crystals. To confirm this, various values of K obtained from various crystal habits of aspirin were compared with the habit coefficients calculated from the habit parameters by means of the equation, (ac+bc)/ab, which represents the ratio of the area of the face (001) to the approximate sum of the areas of the remaining faces. As shown in Table III the velocity constant K is

Table III. Correlation of Dissolution Constants with Habit Coefficients in Various Habits of Aspirin Crystals

No.	Crystal	Velocity constant, K (mg/mm^2 min)	Habit coefficient (ac+bc)/ab
1	From water	0.00107(0.00128—0.00086)	0.0209
2	From dioxane	0.00388(0.00426—0.00350)	0.6900
3	From water+EG	0.00267(0.00298—0.00236)	0.0424
7	Market product	0.00842(0.00843—0.00836)	0.8810

approximately proportional to the habit coefficient (ac+bc)/ab. In the case of crystalline powders, the Noyes–Whitney equation must be corrected by adding some coefficient related to the crystal habit.

It was considered therefore that there might be a difference in dissolution velocity among the various types of crystallographic faces. The dissolution velocity of thin crystals, in which (001) was predominant, was found to be smaller than that of thicker crystals in which (001) was less predominant. The difference in dissolution behavior should give rise to a difference in bioavailability. Thus, it is postulated that a difference in dissolution velocity can be observed not only in polymorphs but also in crystal habits of different nature. In some cases, a difference in crystal habits alone may affect the bioavailability behavior, and aspirin appears to be an example of such a case.

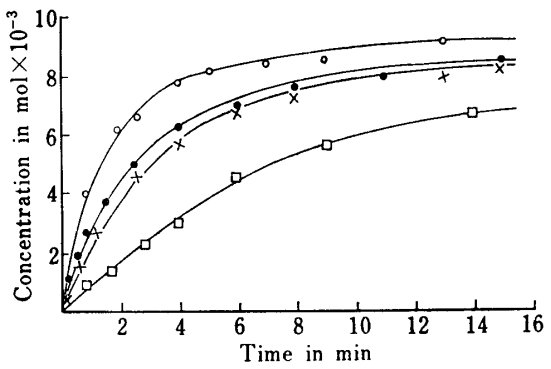

Fig. 4. Dissolution Behavior of Various Habits of Aspirin Ceystals

—○—, from water; —●—, from dioxane; —×—, from water+ethylene glycol; —□—, commercial products.

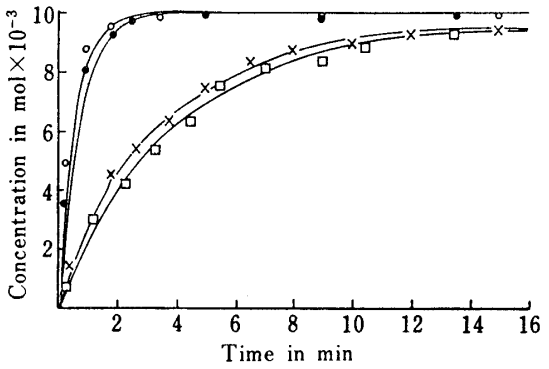

Fig. 5. Dissolution Behavior of Powdered and Sieved Aspirin Crystals

—○—, 200 mesh; —●—, 80—200 mesh; —×—, 48—80 mesh; —□—, 20—48 mesh.

III. Dissolution Behavior of the Powdered Commercial Aspirin

The domestic commercial aspirin (Table II, No. 7) was crushed in an agate mortar and separated into the following groups by sieving: (a) beneath 200 mesh, (b) 80—200 mesh, (c) 48—80 mesh and (d) 20—48 mesh. Then the dissolution behavior of these groups was investigated by using the same method as described in the previous section. The results are shown in Fig. 5. The crystal shapes of these crushed powders are mostly irregular rods elongated along the b-axis. Habit parameters of these crushed powders were estimated as follows: first the largest parameter b was estimated from the size of the sieve used, and then parameters a and c were estimated by multiplying a′/b′ or c′/b′ by the above estimated value of b (a′, b′ and c′ are the parameters of the commercial aspirin). These estimated habit parameters as well as the calculated values of the surface area are shown in Table IV.

Table IV. Estimated Habit Parameters, Dissolution Constants, Habit Coefficients and Specific Surface Areas of Powdered Aspirin Crystals

No.	Crystal	Habit parameters in mm			Velocity constant (mg/mm² min)	Habit coefficient (mm²/mm²)	Specific surface area (mm²/mg)
		a	b	c			
7	Market product	0.500	1.200	0.310	0.00842	0.878	8.6
8	200 mesh	0.030	0.074	0.019	0.01173	0.890	142.4
9	80—200 mesh	0.051	0.124	0.032	0.01695	0.885	84.2
10	48—80 mesh	0.100	0.235	0.060	0.01515	0.855	44.2
11	20—48 mesh	0.235	0.564	0.146	0.01249	0.880	18.4

The velocity constants were also calculated from Fig. 5 by using the specific surface areas listed in Table IV, and these values are also shown in Table IV. It was found from these data that aspirin dissolves more easily after being crushed, probably because of distortion of crystals as shown in Fig. 2(e).

References and Notes

1) *a*) This work was presented at the 28th and 31st General Meetings of the Kinki Branch, Pharmaceutical Society of Japan, Nishinomiya, October 1978, and November 1981, Kobe; *b*) Study of Crystalline Drugs by Means of Polarizing Microscope. IV., Part III: *Chem. Pharm. Bull.*, **28**, 372 (1980).
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