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Interpretation of dissolution rate data from *in vitro* testing of compressed tablets

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To find if theoretically and experimentally a relation existed between the dissolution rate theory of Kitazawa, Johno & others (1975) and that of Wagner (1969), a study was undertaken with uncoated caffeine, aspirin and proxyphylline tablets using two dissolution methods. Although the original treatment for surface area of drug available for dissolution was quite different between the two dissolution theories, the dissolution rate constants obtained were in fair agreement. Hence it might not be always necessary to take into consideration changes in the surface area as a function of dissolution rate, and the $\ln W^{\infty}/(W^{\infty} - W)$ versus time plot devised by Kitazawa & others might be a useful and simple means of obtaining the dissolution rate constant of an active ingredient from a dosage form such as compressed tablet.

The equation of Noyes & Whitney (1897 a, b) has frequently been quoted where the theoretical aspects of the dissolution of a solid have been discussed. In some cases (Levy & Sahli, 1962; Nelson, 1962; Gibaldi & Weintraub, 1968; Tawashi, 1968), an attempt has been made to keep the surface area, S, constant, in which case the dissolution rate, in a sufficient volume of dissolution medium to maintain sink conditions, becomes zero-order. In other cases, as Levy & Hollister (1964) and Wagner (1969) have pointed out, first-order kinetics apply to the analysis of dissolution rate. An equation to calculate the dissolution rate constant of uncoated caffeine tablets having different hardnesses was proposed by Kitazawa, Johno & others (1975) using the rotating basket method of the U.S.P. XVIII and the disintegration test apparatus of the J.P. VIII. They demonstrated that two straight lines were obtained from plots of $\ln C_s/(C_s-C)$ on the vertical axis *vs* time on the horizontal axis following the equation which was obtained by the integration of the Noyes & Whitney equation (1897 a). One was from a time $t = 0$, when the dissolution is started, to a time t_1; at time t_1 the surface area of the drug available for dissolution might be suddenly increased by breakdown of the tablet. The other was from the time t_1 to the completion of dissolution. These results suggested that, although the surface area available for dissolution might be changed continuously and particularly during the course of the dissolution processes, such a change would not play an important role in determining the dissolution rate of the active ingredient from the tablet except when it was discontinuous at the sudden breakdown of the tablet. The findings encouraged us to seek a dissolution rate theory in which surface area is not taken into consideration. The present study was undertaken to elucidate a relation between Wagner's theory (1969) and the dissolution rate theory of Kitazawa & others (1975), using uncoated caffeine and aspirin tablets, which were prepared in our laboratory, and proxyphylline tablets, a commercial uncoated preparation.

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THEORY

Noyes and Whitney equation

Noyes & Whitney (1897a) reported dissolution rates using benzoic acid and lead chloride in a rotating cylinder method. In their studies the surface area of solute available for dissolution remained essentially constant. They showed that the dissolution rate equation up to a saturation was as follows:

$$dC/dt = K (C_s - C) \quad .. \quad (1)$$

where C_s is the equilibrium concentration of solute (= solubility), C is the concentration of the solute at time t, and K is a dissolution rate constant (a first-order rate constant). In subsequent studies (Noyes & Whitney, 1897b; Brunner & Tolloczko, 1900), the surface area of solute available for dissolution, S, was incorporated into the equation to give

$$dC/dt = K_1 S (C_s - C) \quad .. \quad (2)$$

where K_1 is a constant ($K_1 = K/S$). Hixson &

Crowell (1931) multiplied both sides of (2) by the volume of the dissolution medium, V, to give

$$dW/dt = K_2 S (C_S - C) \quad .. \quad (3)$$

where W is the amount of solute in solution at time t, dW/dt is the appearance rate of solute in the solution at time t, and K_2 is a constant ($K_2 = K_1 V$).

Wagner's theory (1969)

Under sink conditions, that is, $C \ll C_S$, usually $C \leq 0{\cdot}10\ C_S$, (3) reduces to

$$dW/dt = K_2 S C_S \quad .. \quad .. \quad (4)$$

and Wagner discussed the case when there are sink conditions and the surface area varies with time. One may assume that during the first-order phase of dissolution the surface area available for dissolution decreases exponentially with time, i.e.

$$S = S^0 e^{-K_3(t - t_0)} \text{ for } (t \geq t_0) \quad .. \quad (5)$$

where S^0 is the surface area available for dissolution at the time when the apparent first-order dissolution phase commences, at time t_0, and K_3 is a constant. Substitution for S in (4) from (5) yields

$$dW/dt = K_2 C_S S^0 e^{-K_3(t - t_0)} \text{ for } (t \geq t_0) \quad .. \quad (6)$$

and integration gives

$$W = W_{t_0} + (K_2/K_3) C_S S^0 \{1 - e^{-K_3(t - t_0)}\} \quad \text{for } (t \geq t_0) \quad .. \quad .. \quad (7)$$

where W_{t_0} is the amount dissolved in the medium at time t_0. Then if $(K_2/K_3) C_S S^0 = M$, (7) may be written

$$W = W_{t_0} + M \{1 - e^{-K_3(t - t_0)}\} \quad \text{for } (t \geq t_0) \quad (8)$$

At infinite time ($t \rightarrow \infty$), (8) becomes

$$W^\infty = W_{t_0} + M \quad .. \quad .. \quad (9)$$

where W^∞ is the amount dissolved at time t_∞, that is, the amount that will dissolve. Therefore, since $W^\infty - W$ is the amount not yet dissolved from the dosage form, subtracting (8) from (9) gives (10).

$$W^\infty - W = M e^{-K_3(t - t_0)} \text{ for } (t \geq t_0) \quad .. \quad (10)$$

Taking logarithms of both sides of (10) gives (11):

$$\log (W^\infty - W) = \log M - \frac{K_3}{2{\cdot}303} (t - t_0) \quad \text{for } (t \geq t_0) \quad .. \quad .. \quad .. \quad (11)$$

Adding $\log 100/W^\infty$ to both sides of (11) gives (12):

$$\log \left\{\frac{100\ (W^\infty - W)}{W^\infty}\right\} = A - \frac{K_3}{2{\cdot}303} t \quad \text{for } (t \geq t_0) \quad .. \quad .. \quad .. \quad (12)$$

where $\log \left\{\frac{100\ (W^\infty - W)}{W^\infty}\right\}$ is the percentage of the solute not dissolved and

$$A = \log \frac{100\ M}{W^\infty} + \frac{K_3}{2{\cdot}303} t_0.$$

Equation (12) suggests that plots of $\log \left\{\frac{100\ (W^\infty - W)}{W^\infty}\right\}$ vs time t might be expected to yield a straight line with slope $- K_3/2{\cdot}303$.

Theory of Kitazawa & others (1975)

Kitazawa & others (1975) reported that the surface area of active ingredient available for dissolution from a compressed uncoated tablet might be regarded as constant, providing that a sufficient volume of dissolution medium to maintain sink conditions was used in accordance with Levy and others' concepts (Levy & Sahli, 1962; Nelson, 1962; Gibaldi & Weintraub, 1968; Tawashi, 1968). To obtain the dissolution rate constant of uncoated caffeine tablets, they applied equation (1), which indicates that the rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution. Therefore, C_S in equation (1) is the equilibrium solubility of solute as mentioned above. However, if the dissolution rate is studied under sink conditions, the concentration when all of the active ingredients are completely dissolved, C^∞, is not always the equilibrium solubility. Accordingly, equation (1) was rewritten by Kitazawa & others (1975) as

$$dC/dt = K' (C^\infty - C) \quad .. \quad (13)$$

where K′ is a constant, C is the concentration at time t, and the values of C^∞ and C were obtained using the equation of Wurster & Taylor (1965).

Integration of equation (13) gives

$$\ln C^\infty/(C^\infty - C) = K' t \quad .. \quad (14)$$

By multiplying the denominator and the numerator of the left side in equation (14) by the volume of dissolution medium, V, which was maintained constant during the experiment, we have

$$\ln C^\infty V/(C^\infty V - C V) = \ln W^\infty/(W^\infty - W) \quad (15)$$

where W^∞ is the amount dissolved at infinite time and W is the amount dissolved at time t. From (14) and (15), (16) was derived:

$$\ln W^\infty/(W^\infty - W) = K' t \quad .. \quad (16)$$

Equation (16) suggests that a plot of $\ln W^\infty/(W^\infty - W)$ versus time t might be expected to yield a straight line with slope K′ which is the dissolution rate constant.

The dissolution rate constant of uncoated caffeine tablets was determined by using equation (16) in our previous paper (Kitazawa & others, 1975). Two straight regression lines were obtained from the plots in all cases and the time at which the two lines intersected was called t_1, the slope of the first being K_1' and that of the second K_2' ($K_1' < K_2'$). As a good correlation between t_1 and the disintegration time was obtained, it was apparent that t_1 was the time at which the tablet was broken down, the change in the dissolution rate constant from K_1' to K_2' at time t_1 being based on an explosive increase in surface area of the drug available for dissolution. Therefore, since the dissolution rate constant is K_1' at $0 \leq t \leq t_1$ and K_2' at $t_1 \leq t \leq t_s$, the limited integration equation of equation (13), bearing in mind equations (14)–(16) is

$$\int_{W=0}^{W \to W^\infty} 1/(W^\infty - W)\, dW = \int_{t=0}^{t=t_1} K_1'\, dt + \int_{t=t_1}^{t \to t_s} K_2'\, dt \quad (K_1' < K_2') \quad (17)$$

where t_s is the infinite time, that is, the time required for 100% of the drug to dissolve.

At $0 \leq t \leq t_1$, equation (16) gives

$$\ln W^\infty/(W^\infty - W) = K_1' t \quad .. \quad (18)$$

By multiplying both sides of (18) by $-1/2{\cdot}303$, we get

$$\log (W^\infty - W)/W^\infty = - \frac{K_1'}{2{\cdot}303} t \quad (19)$$

and converting to percentages gives equation (20):

$$\log \left\{ \frac{100\,(W^\infty - W)}{W^\infty} \right\} = \log 100 - \frac{K_1'}{2{\cdot}303} t = B - \frac{K_1'}{2{\cdot}303} t \quad .. \quad .. \quad .. \quad (20)$$

where $B = \log 100 = 2$.

For $t_1 \leq t \leq t_s$, (16) gives

$$\ln W^\infty/(W^\infty - W) = K_2' t \quad .. \quad (21)$$

In equation (21), because the left hand side is $\ln W^\infty/(W^\infty - W_{t_1})$ at time t_1, the integration constant is $\{\ln W^\infty/(W^\infty - W_{t_1}) - K_2' t_1\}$. Hence (21) gives

$$\ln W^\infty/(W^\infty - W) = K_2' t + \{\ln W^\infty/(W^\infty - W_{t_1}) - K_2' t_1\} \quad .. \quad (22)$$

By multiplying both sides of (22) by $-1/2{\cdot}303$, we get

$$\log (W^\infty - W)/(W^\infty = - \frac{K_2'}{2{\cdot}303} t + \log (W^\infty - W_{t_1})/W^\infty - \frac{K_2'}{2{\cdot}303} t_1 \quad .. \quad (23)$$

and, introducing log 100 as before,

$$\log \left\{ \frac{100\,(W^\infty - W)}{W^\infty} \right\} = - \frac{K_2'}{2{\cdot}303} t + \frac{K_2'}{2{\cdot}303} t_1 + \log \left\{ \frac{100\,(W^\infty - W_{t_1})}{W^\infty} \right\} = D - \frac{K_2'}{2{\cdot}303} t \quad .. \quad .. \quad .. \quad (24)$$

where $D = \frac{K_2'}{2{\cdot}303} t_1 + \log \left\{ \frac{100\,(W^\infty - W_{t_1})}{W^\infty} \right\}$.

Equation (20) and (24) corresponded to (12) of Wagner's theory. From these derivations, it seems reasonable to assume that the dissolution theory of compressed dosage form derived by Kitazawa & others coincides with that of Wagner.

MATERIALS AND METHODS

Materials. All materials were obtained from commercial sources and complied with the Japanese Pharmacopoeia VIII (J.P.) requirements.

Preparation of uncoated tablets. The components of the uncoated tablets used are listed in Table 1. Aspirin and caffeine tablets were prepared in this laboratory and proxyphylline tablets were obtained from Yoshitomi Pharmaceutical Ind., Ltd., Osaka, Japan.

Lactose containing 3 and 6% w/w of hydroxypropylcellulose was prepared by dissolving the binder in ethanol and moistening the lactose powder with it. Caffeine and the lactose (3%) were used as 20/40 mesh granules, aspirin and the lactose (6%) were used as less than 60 mesh powder, and other ingredients were used at less than 100 mesh. Dry blending of these components was with an Erweka

mixer model KB 15S and the mixture was then compressed into a tablet 10 mm in diameter using an Erweka model EK-0 tablet machine.

Table 1. *Components of tablets.*

Caffeine tablet	
Caffeine	25 g
Lactose containing 3% HPC	450 g
Potato starch	15 g
Talc	8 g
Magnesium stearate	2 g
Total	500 g
Weight of a tablet	0·3 g**
Proxyphylline tablet*	
Proxyphylline	200 g
Lactose and starch	284 g
Talc and magnesium stearate	16 g
Total	500 g
Weight of a tablet	0·25 g**
Aspirin tablet	
Aspirin	250 g
Lactose containing 6% HPC	225 g
Potato starch	15 g
Talc	8 g
Magnesium stearate	2 g
Total	500 g
Weight of a tablet	0·5 g**

* A commercial uncoated tablet produced by Yoshitomi Pharmaceutical Ind., Ltd., (commercial name: Monophyllin; Lot No. YMM125). Binder, detailed component, and it's ratio of this preparation were unknown. Caffeine and aspirin tablets were prepared in our laboratory.

** The tablet weights were all within normal limits.

Hardness. The hardness of the tablets was determined using a Monsanto Hardness Tester. Each value was an average of six tablets.

Disintegration time. The J.P. apparatus (Toyama Sangyo model T-2S disintegration test unit) and procedure with disks, which is essentially similar to that described in the U.S.P. XVIII, were used to determine the disintegration time of the tablets in the first fluid in the J.P. (aqueous solution containing 2·0 g of sodium chloride and 24·0 ml of 10% v/v hydrochloric acid in 1000 ml, pH 1·2) at 37°. The disintegration time of aspirin tablets was measured without disks because the tablets stuck to the disks. The disintegration time reported is the time at which all particles passed through the 10 mesh plate in the lower end of the disintegration apparatus. The stirring frequency was 32 strokes min^{-1}, amplitude 55 mm and at least six replicate determinations were made.

Dissolution procedures. The dissolution rate of solute from the tablets was determined by two methods. One was the rotating basket method of the U.S.P. (U.S.P. method) using the Toyama Sangyo model TR-3S and the other was the modified method using the J.P. disintegration test apparatus (J.P. method). An aliquot of 1000 ml of the first fluid in the J.P. was used as the dissolution medium. In the J.P. method, one tablet was placed in one of the six

Table 2. *Hardness, disintegration time, and dissolution characteristics of various uncoated tablets.* All results using J.P. method of dissolution except *c* where U.S.P. method was used.

		Plot of Kitazawa & others†			Wagner's plot‡				
		slope			slope		slope		
Hardness*	DT**	K_1§	K_f§	t_i[a]	K_1§	DRC§[b]	K_f§	DRC§[b]	t_i[a]
Caffeine	(with disk)								
3·8	396	4·21	6·74	395	−1·83	4·21	−2·93	6·75	395
10·7	1033	1·86	5·78	665	−0·81	1·87	−2·51	5·78	665
Proxyphylline	(with disk)								
8·4	387	7·06	19·18	191	−3·07	7·07	−8·33	19·18	192
		3·72[c]	12·22	204	−1·61	3·71	−5·31	12·23	203
Aspirin	(without disk)								
2·8	47	4·65	1·73	656	−2·02	4·65	−0·75	1·73	655
10·7	181	3·46	1·71	912	−1·50	3·45	−0·74	1·70	913

* The values are the average of six determinations using Monsanto Hardness Tester. Values kg.
** DT—Disintegration time values are the average of six determinations with the J.P.VIII procedure. Values s.
† Slope = dissolution rate constant.
‡ Slope × (−2·303) = dissolution rate constant.
§ Values ($\times 10^{-3}$, s^{-1}).
[a] Values s.
[b] DRC: dissolution rate constant.

tubes of the basket, and an appropriate volume of the medium was sampled at measured times, through a pipette plugged with cotton. The same quantity of the medium was added immediately after each sampling to keep the volume of the dissolution medium constant.

Measurement of true density. The true density of the aspirin and caffeine used in the present study was measured with a Beckman air comparison pycnometer model 930 (Beckman-Toshiba Ltd.).

Analytical procedures. Aspirin was hydrolysed to salicylic acid and determined colorimetrically as salicylate with ferric nitrate reagent (Kitazawa, Sakai & Murasaki, 1974). Caffeine and proxyphylline were assayed spectrophotometrically at 270 and 273 nm, respectively.

RESULTS AND DISCUSSION

The dissolution tests were conducted with uncoated caffeine tablets having hardnesses of 3·8 and 10·7 kg by the J.P. method with disks and the results which were calculated and plotted following both of the theories of Wagner (1969) and Kitazawa & others (1975) are in Fig. 1. Two straight regression lines were obtained from these plots in all cases and the slope of the first being K_1 and that of the second K_f. From the slopes of these straight lines, the dissolution rate constants at each stage of the dissolution were calculated following the respective theories and are shown in Table 2. The time at which the two lines intersected was called t_1 and the results calculated were also listed in Table 2.

In spite of the fact that the dissolution equation of Wagner takes into consideration that the surface area available for dissolution varies with time during the first-order phase of dissolution, while the equation of Kitazawa & others was derived having no regard for the surface area, the initial dissolution rate constant, K_1, and the second dissolution rate constant, K_f, from both equations coincided. From these results, it is reasonable to assume that the effect of surface area on the dissolution rates at each stage of dissolution might be negligible.

The dissolution rate of the tablet having a hardness of 10·7 kg was less than that of the tablet of lesser hardness (3·8 kg). The time t_1 was in good agreement with disintegration time with the low hardness tablet but t_1 was less than the disintegration time with the 10·7 kg hardness tablet. These results were similar to those obtained by Kitazawa & others

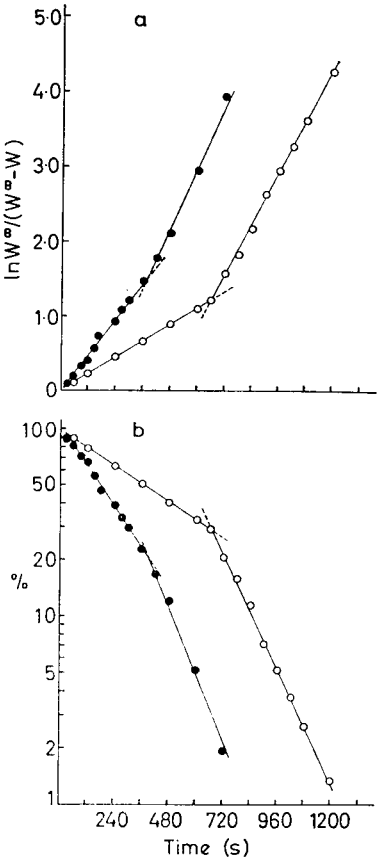

FIG. 1. Plots of $\ln W^\infty/(W^\infty - W)$ versus time following the theory of Kitazawa & others (a); and first-order kinetic plots following Wagner's theory (b) to obtain the dissolution rate constant of uncoated caffeine tablets by the J.P. method with disks. –●– Tablet having hardness of 3·8 kg. –○–Tablet having hardness of 10·7 kg. b—Ordinate—% not dissolved (log scale).

(1975). Furthermore, comparison of these data with results of the present study shows that increase in particle size of the tablet components resulted in an increase in the disintegration time and the decrease in the dissolution rate.

The findings with the caffeine tablets were repeated with the proxyphylline tablets and aspirin tablets. The measurements of dissolution of proxyphylline from tablets were made using the J.P. method with disks and the U.S.P. method. The results were calculated and plotted according to the equations of Kitazawa & others (1975) and of Wagner (1969). As depicted in Fig. 2, the dissolution patterns obtained by both methods were essentially similar to those of the caffeine tablets. Values of the dissolution rate

constants and time t_l of the proxyphylline tablets calculated were listed in Table 2.

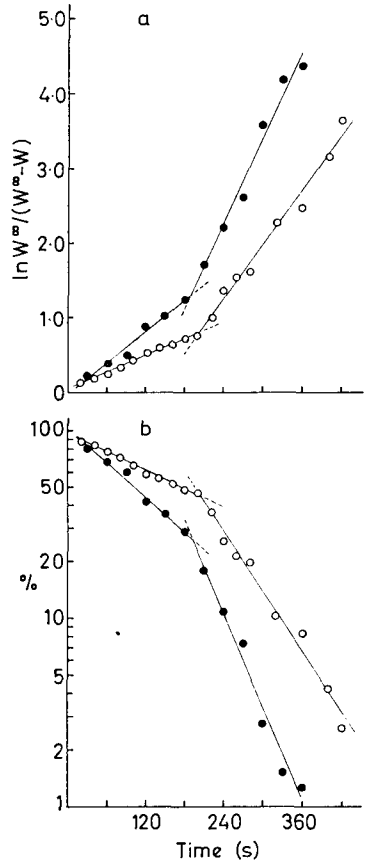

FIG. 2. Plots of ln $W^\infty/(W^\infty - W)$ versus time following the theory of Kitazawa & others (a); and first-order kinetic plots following Wagner's theory (b) to obtain the dissolution rate constant of commercial uncoated proxyphylline tablets by both the J.P. with disks and the U.S.P. methods. -●- J.P. method with disks. -○- U.S.P. method (rate of rotating basket, 150 rpm). b—Ordinate—% not dissolved (log scale).

From these observations, it seems to be reasonable to infer that the dissolution equation of Kitazawa & others could apply over a wide range of dissolution studies using various compressed tablets.

Both the first and the second of the dissolution rate constants obtained by the J.P. method were greater than those of the U.S.P. method and the time t_l was extended in the U.S.P. method. Such findings have been previously reported (Wagner & Pernarowski, 1971; Saito, Suzuki & others, 1974; Kitazawa & others, 1975). The differences were due to the effectively greater degree of agitation in the J.P. method relative to the U.S.P. method.

The dissolution rate measurements of aspirin tablets having hardness of 2·8 and 10·7 kg were made with the J.P. method without disks. The data which were calculated and plotted as before are shown in Fig. 3. From these data the dissolution rate constants and a time t_l, at which the two regression lines intersected are derived and are in Table 2.

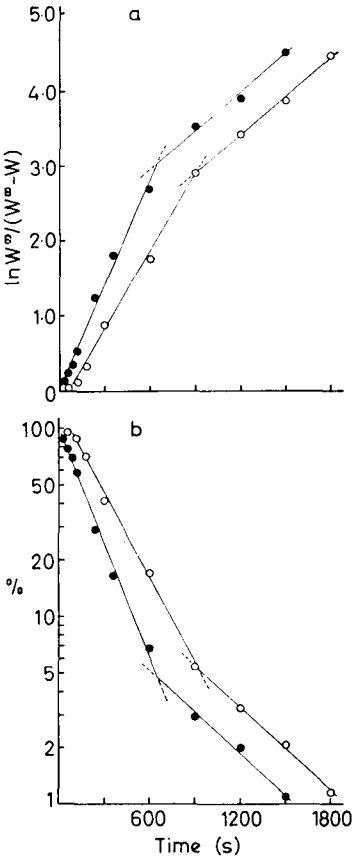

FIG. 3. Plots of ln $W^\infty/(W^\infty - W)$ versus time following the theory of Kitazawa & others (a); and first-order kinetic plots following Wagner's theory (b) to obtain the dissolution rate constant of uncoated aspirin tablets by the J.P. method without disks. -●- Tablet having hardness of 2·8 kg. -○- Tablet having hardness of 10·7 kg. b—Ordinate—% not dissolved (log scale).

Since the disintegration times of the aspirin preparations were comparatively short, the effect of the explosive increase in the surface area by breakdown of the tablets as found with the caffeine and proxyphylline preparations at approximate time of disintegration was not seen. However, as depicted in Fig. 3, the regression lines for both hardnesses had intersections that could have different meanings

from those obtained with caffeine and proxyphylline tablets. The final slopes of both regression lines were apparently more gentle than those of the initial stage of dissolution, suggesting that the rate of dissolution from small particles of the drug was decreased for some reason. A similar decrease in the rate of dissolution during the dissolution processes of aspirin was observed by Wood (1966).

Observations of the course of dissolution revealed that the small particles had sunk to the bottom of the container and would not move. The true densities of the aspirin and caffeine were 1·40 and 1·23 g cm^{-3}, respectively, and with caffeine, the small particles moved freely in the beaker but the degree of agitation of the disintegration apparatus was not enough for the aspirin. This is supported by the fact that dissolution rates of both hardnesses almost coincided after the intersections. Moreover, the insufficient agitation observed with the J.P. method also occurred with the U.S.P. method. The decomposition of the aspirin in the tablets was negligible.

Although the dissolution characteristics of the aspirin tablets differed from those of the other two preparations, the data from both of the equations coincided as shown in Table 2 adding further evidence that the equation of Kitazawa & others has an application over a wide range of dissolution studies.

REFERENCES

BRUNNER, E. & TOLLOCZKO, S. (1900). *Z. phys. Chem.*, **35**, 283–290.

GIBALDI, M. & WEINTRAUB, H. (1968). *J. pharm. Sci.*, **57**, 832–835.

HIXSON, A. & CROWELL, J. (1931). *Ind. Engng Chem.*, **23**, 923–931.

KITAZAWA, S., JOHNO, I., ITO, Y., TERAMURA, S. & OKADA, J. (1975). *J. Pharm. Pharmac.*, **27**, 765–770.

KITAZAWA, S., SAKAI, K. & MURASAKI, H. (1974). *Yakugaku Zasshi*, **94**, 1353–1357.

LEVY, G. & HOLLISTER, L. E. (1964). *J. pharm. Sci.*, **53**, 1446–1452.

LEVY, G. & SAHLI, B. A. (1962). *Ibid.*, **51**, 58–62.

NELSON, E. (1962). *Chem. Pharm. Bull. (Tokyo)*, **10**, 1099–1101.

NOYES, A. A. & WHITNEY, W. R. (1897a). *J. Am. chem. Soc.*, **19**, 930–934.

NOYES, A. A. & WHITNEY, W. R. (1897b). *Z. phys. Chem.*, **23**, 689.

SAITO, T., SUZUKI, S., NANBU, N. & NAGAI, T. (1974). *Yakuzaigaku*, **34**, 143–151.

TAWASHI, R. (1968). *Science, N. Y.*, **160**, 76.

WAGNER, J. G. (1969). *J. pharm. Sci.*, **58**, 1253–1257.

WAGNER, J. G. & PERNAROWSKI, M. (1971). *Biopharmaceutics and Relevant Pharmacokinetics*, 1st edn. p. 110. Hamilton, Illinois: Drug Intelligence Pub.

WOOD, J. H. (1966). In Vitro *Evaluation of the Release from Dosage Forms*, presented at the Eino Nelson Memorial Symposium on Biopharmaceutics, Industrial Pharmacy Section, 113th Annual Meeting of the American Pharmaceutical Association, Dallas, Texas.

WURSTER, D. E. & TAYLOR, JNR, P. W. (1965). *J. pharm. Sci.*, **54**, 670–676.