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Dissolution Kinetics of Soluble Nondisintegrating Disks

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Abstract □ An equation describing the isotropical dissolution of soluble nondisintegrating disks was developed. It was equivalent to the cube root law only if the height and diameter of the disk were equal. The dissolution kinetics of sodium chloride disks were examined, using a beaker equipped with a centrifugal stirrer as the dissolution chamber. The fit of the experimental data to the cube root law had a coefficient of variation of about 4–5%. It was demonstrated statistically that a fit to a square root of mass versus time relation was significantly better. With increasing porosity, the dissolution process proceeded faster than predicted on the basis of the diffusion-convection model. An explanation is proposed by assuming an increased effective dissolution surface.

Keyphrases □ Dissolution kinetics—soluble nondisintegrating disks, equation developed, related to cube root law □ Kinetics, dissolution—soluble nondisintegrating disks, equation developed, related to cube root law

Dissolution kinetics have been studied mainly by applying film theory. Recently, the subject was reviewed for monodisperse particles (1) and polydisperse particle systems (2). Larger bodies such as tablets, which have received little attention so far, have had a constant surface exposed to the dissolution fluid when studied (3). Completely exposed 1-cm sodium chloride cubes were studied (4), as were benzoic acid spheres (5).

The present article discusses the validity of the cube root law for completely exposed water-soluble bodies; the role of tablet porosity was investigated.

THEORETICAL

In the derivation of the cube root law (6), the changing surface during dissolution is expressed in terms of mass change. This approach is possible only for symmetrical bodies; disks do not lend themselves to treatment requiring a fixed ratio between surface and mass. Such treatment requires the inversion of the third-order expression: $\text{mass} = 2\pi\rho r^3 + a\pi\rho r^2$, in which ρ is the tablet density, r is the radius, and a is a constant equal to height (H) minus $2r$.

The root $r = f(M)$ is such that no procedure for the integration of dM/dt is available. Therefore, another approach was followed based on the zero-order decrease rate of linear dimensions of isotropically dissolving particles. In this way, an equation was derived (7) that describes

the dissolution kinetics of small spheres and one arrives at the cube root law.

If a flat cylindrical disk is assumed, the following expressions for isotropical dissolution ensue:

$$\text{mass } M = \pi\rho r_t^2 H_t \quad (\text{Eq. 1})$$

$$dr/dt = b \quad (\text{Eq. 2})$$

$$dH/dt = 2b \quad (\text{Eq. 3})$$

$$r_t = r_0 - bt \quad (\text{Eq. 4})$$

$$H_t = H_0 - 2bt \quad (\text{Eq. 5})$$

where subscripts 0 and t stand for time zero and t , respectively, and b is a constant. Therefore:

$$dM/dt = \pi\rho d(r_t^2 H_t)/dt \quad (\text{Eq. 6a})$$

$$dM/dt = \pi\rho r_t^2 dH/dt + \pi\rho H_t dr_t/dt \quad (\text{Eq. 6b})$$

$$dM/dt = \pi\rho r_t^2 dH/dt + 2\pi\rho H_t r_t dr/dt \quad (\text{Eq. 6c})$$

Substitution of Eqs. 2–5 in Eq. 6c gives:

$$dM/dt = 2\pi\rho b(r_0 - bt)^2 + 2\pi\rho b(H_0 - 2bt)(r_0 - bt) \quad (\text{Eq. 7})$$

which can be rewritten as:

$$dM/dt = C_1 + C_2 t + C_3 t^2 \quad (\text{Eq. 8})$$

with $C_1 = 2\pi\rho b r_0(H_0 + r_0)$, $C_2 = -2\pi\rho b^2(H_0 + 4r_0)$, and $C_3 = 6\pi\rho b^3$. Integration of Eq. 8 results in:

$$M_t = C_1 t + 0.5 C_2 t^2 + 0.33 C_3 t^3 + M_0 \quad (\text{Eq. 9a})$$

or:

$$M_t/M_0 = 1 + C_4 t + C_5 t^2 + C_6 t^3 \quad (\text{Eq. 9b})$$

Equation 9b describes the dissolution of flat nondisintegrating disks; it is equivalent to the Hixson-Crowell cube root law if a cube root of Eq. 9b can be found. Thus, if its coefficients are related as in $(x + y)^3$, then $(C_4)^3 = 27C_6$ and $(C_4)^2 = -3C_5$. Writing $C_4 = C_1/M_0$ and then substituting C_1 (Eq. 8) and M_0 (Eq. 1) give:

$$C_4 = \frac{2(bH_0 + br_0)}{r_0^2 H_0} \quad (\text{Eq. 10})$$

Similarly, C_5 and C_6 can be elaborated. This approach shows that the

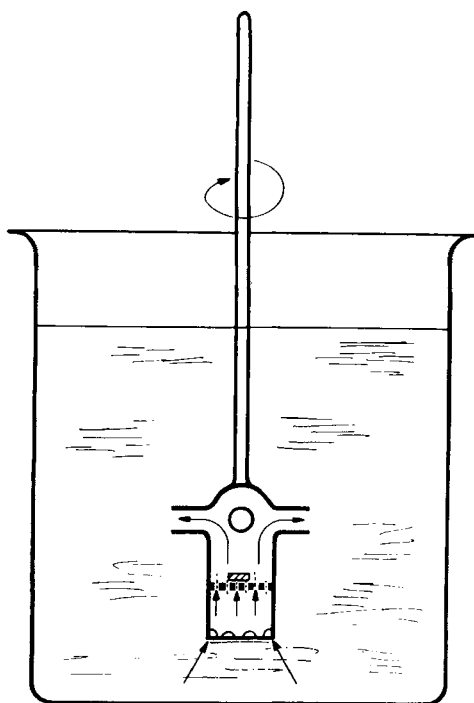


Figure 1—Centrifugal stirrer dissolution assembly.

cube root law applies to the dissolution of nondisintegrating flat disks only if height equals diameter.

The zero-order rate decrease, $b = DC_s/h\rho$, follows directly from the Noyes-Whitney equation, being a function of the experimental conditions (diffusion layer thickness h), the compound involved (diffusion coefficient D and solubility C_s), and the tablet structure (density ρ).

EXPERIMENTAL

Sodium chloride particles (200–500 μm) were compressed into two series of flat cylindrical disks of 7.0-mm diameter and of constant volume, constant height of 7.00 ± 0.05 mm (I), or constant weight of 505–520 mg (II). By varying the weight in Series I and the compaction pressure in II, different porosities were obtained. The porosity was calculated as the percent void space from the densities of sodium chloride and the tablet.

Dissolution experiments were followed conductometrically (Fig. 1). They were carried out in water at 25° in a 250-ml beaker equipped with a centrifugal stirrer; this beaker also served as the dissolution chamber. It combines the versatility of a beaker method with the flow conditions of a column method and is similar to the rotating compartmentalized disk described by Simmons *et al.* (8).

RESULTS AND DISCUSSION

Dissolution Equipment—The centrifugal stirrer assembly was tested for reproducibility of t_{30} , t_{60} , and t_{90} with tablets of Series I at 65 and 135 rpm. The reproducibility of t_{60} is given in Table I as the coefficient of variation of five runs. The reproducibility of t_{30} and t_{90} was comparable to that observed for t_{60} . For example, at 65 rpm, it varied from 0 to 13.7% (t_{30}) and from 2.2 to 5.8% (t_{90}). At 135 rpm, these values were 4.2–11.9% and 4.0–9.9%. Similar results were obtained with Series II.

Comparison of these figures with literature data and experiences with the USP, Levy, and column methods shows that this method performs well as to reproducibility and versatility.

Dissolution Model—The derivation of Eq. 9b assumes isotropical dissolution under sink conditions. This assumption was checked by photographing the dissolution process of a 500-mg disk of 7.0-mm height and diameter at various times during dissolution. The porosity of this disk was 14%. The shape of the disk was retained, and no disintegration was observed.

Since the height to diameter ratio was virtually constant throughout the study, isotropical dissolution was assumed; visually, disintegration was absent in all tests performed. A group of identical disks was dissolved

Table I—Reproducibility of Dissolution Rate of Sodium Chloride Disks in a Centrifugal Stirrer Assembly ($n = 5$)

Weight, mg	Porosity, %	65 rpm		135 rpm	
		Average t_{60} , min	CV, %	Average t_{60} , min	CV, %
562	3.4	3.43	5.3	2.23	5.7
549	5.6	3.34	2.8	2.20	5.4
527	9.4	3.15	0.1	2.05	3.6
508	12.7	3.02	2.9	1.96	4.1
461	20.7	2.52	2.7	1.32	8.9
419	28.0	1.80	3.6	0.70	10.1

at different stirring speeds to check whether their dissolution rate was diffusion controlled. The data were transformed (see *Dissolution Kinetics*) according to $1 - (M_t/M_0)^{0.5} = t/T$, and the rate $DC_s/h\rho$ was calculated, giving a value for the diffusion layer thickness. This parameter was plotted versus the reciprocal of the stirring rate^{0.5} (Fig. 2). According to Levich's equation, this should give a linear relation under diffusion-controlled dissolution:

$$h = 0.643D^{0.33}\nu^{0.17}W^{-0.5} \quad (\text{Eq. 11})$$

where $D_{\text{NaCl}} = 1.484 \times 10^{-5}$ cm²/sec in water at 25° , ν is the kinematic viscosity of water = 0.0092 cm²/sec at 25° , and W is the stirring rate (second⁻¹). From independent estimates of D and ν , the slope of the curve would be 0.0072 cm sec^{-0.5}; the experimental data have a slope of 0.0049 cm sec^{-0.5}, implying that the dissolution was faster than predicted. This finding is consistent with the fact that for a highly water-soluble substance, like sodium chloride, not only a solute gradient but also an appreciable solvent, *i.e.*, water, gradient exists, resulting in an additional bulk solution flow and a faster dissolution process than through diffusion alone (9). The graph, being linear, supports the assumption of a diffusion-controlled process.

Dissolution Kinetics—The validity of the theoretical prediction (Eq. 9b) for the dissolution of nondisintegrating, completely exposed, sodium chloride disks was investigated. The best fit obtainable is not given by Eq. 9b but by a polynomial of the $(n - 1)$ th degree for n data points. To permit evaluation of the fit, the data were transformed to a linear relation of the form $1 - (M_t/M_0)^p = t/T$ for $p = 1, 0.5$, and 0.33 . The $p = 0.33$ stands for the cube root law, which should hold if height and diameter are equal; $p = 1$ and 0.5 are not based on a physical model and were chosen to permit statistical evaluation of the fit.

Therefore, M_t/M_0 values of 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.15, 0.1, and 0.05, representing t_0, t_{10} , etc., up to and including t_{95} , were used. Experimental values for t_0, t_{10} , etc., were then used to calculate the linear regression line by the least-squares method. Five dissolution runs were averaged. The deviation of the data points from the regression line, calculated as the standard deviation, served as a criterion for the quality of the fit. The fits were compared with an F test at a 95% confidence level (Tables II and III).

The fits are given in the tables for different portions of the dissolution curves, *i.e.*, t_0-t_{50} , t_0-t_{80} , and t_0-t_{95} , to note possible trends in the model. The best of every three fits ($p = 1, 0.5$, and 0.33) is underlined. Up to t_{50} , no discrimination was observed (all three were underlined), while $p =$

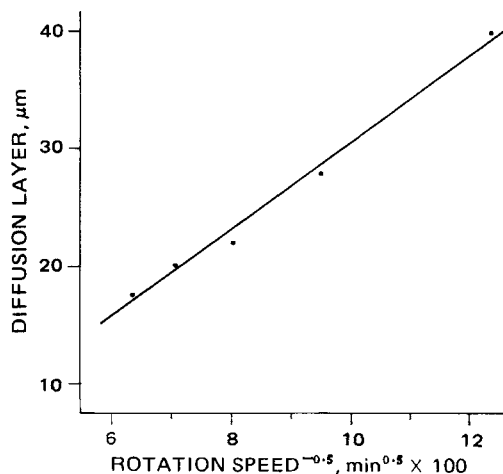


Figure 2—Diffusion layer thickness versus stirring rate for sodium chloride disks using a centrifugal stirrer assembly.

Table II—Standard Deviation of the Fit ^a of Dissolution Kinetics (Averaged over Five Runs at 65 rpm) of Sodium Chloride Disks (Height and Diameter 7.0 mm)

Weight, mg	Porosity, %	Average t_{50} , min	t_0-t_{50}			t_0-t_{80}			t_0-t_{95}		
			$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$
562	3.4	2.77	<u>0.035</u>	<u>0.040</u>	<u>0.052</u>	0.204	<u>0.061</u>	<u>0.082</u>	0.400	<u>0.241</u>	<u>0.163</u>
549	5.6	2.71	<u>0.078</u>	<u>0.057</u>	<u>0.056</u>	0.156	<u>0.049</u>	0.097	0.394	<u>0.053</u>	0.136
527	9.4	2.52	<u>0.022</u>	<u>0.032</u>	<u>0.044</u>	0.180	<u>0.040</u>	<u>0.066</u>	0.436	<u>0.073</u>	<u>0.088</u>
508	12.7	2.44	<u>0.026</u>	<u>0.037</u>	<u>0.046</u>	0.162	<u>0.046</u>	<u>0.077</u>	0.401	<u>0.068</u>	<u>0.099</u>
461	20.7	1.97	<u>0.029</u>	<u>0.022</u>	<u>0.026</u>	0.151	<u>0.023</u>	0.042	0.333	<u>0.041</u>	0.079
419	28.0	1.43	<u>0.029</u>	<u>0.035</u>	<u>0.038</u>	0.122	<u>0.032</u>	<u>0.029</u>	0.248	<u>0.038</u>	0.056

^a Best fits are underlined ($\alpha = 0.05$).

Table III—Standard Deviation of the Fit ^a of Dissolution Kinetics (Averaged over Five Runs at 135 rpm) of Sodium Chloride Disks (Height and Diameter 7.0 mm)

Weight, mg	Porosity, %	Average t_{50} , min	t_0-t_{50}			t_0-t_{80}			t_0-t_{95}		
			$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$
562	3.4	1.78	<u>0.086</u>	<u>0.080</u>	<u>0.082</u>	<u>0.112</u>	<u>0.074</u>	<u>0.100</u>	0.180	<u>0.063</u>	0.123
549	5.6	1.75	<u>0.027</u>	<u>0.006</u>	<u>0.017</u>	0.104	<u>0.019</u>	0.059	0.218	<u>0.032</u>	<u>0.036</u>
527	9.4	1.64	<u>0.022</u>	<u>0.005</u>	<u>0.008</u>	0.101	<u>0.014</u>	0.051	0.222	<u>0.017</u>	0.103
508	12.7	1.56	<u>0.023</u>	<u>0.014</u>	<u>0.021</u>	0.107	<u>0.014</u>	0.041	0.246	<u>0.043</u>	0.075
461	20.7	1.04	<u>0.027</u>	<u>0.009</u>	<u>0.006</u>	0.094	<u>0.020</u>	<u>0.011</u>	0.363	<u>0.052</u>	<u>0.020</u>
419	28.0	0.56	<u>0.013</u>	<u>0.006</u>	<u>0.006</u>	0.035	<u>0.007</u>	0.018	0.088	<u>0.021</u>	<u>0.028</u>

^a Best fits are underlined ($\alpha = 0.05$).

0.5 provided the best result, at t_{80} and t_{95} (e.g., for a 461-mg tablet at 65 rpm). Generally, $p = 0.5$ gave the best fits, but $p = 0.33$ was still usually acceptable, with a coefficient of variation (relative to t_{50}) of about 4–5%. Nevertheless, the derived expression (Eq. 9b) is not supported by the experiments where $p = 0.5$ has to be preferred. Only a comparative statistical evaluation revealed this finding.

The stirrer speed influence for $p = 0.5$ showed a tendency for a better fit up to t_{50} for 135 rpm and up to t_{80} and t_{95} for 65 rpm. Both rates can be used in this type of experiment.

Again for $p = 0.5$, it was checked whether the fit changed during dissolution. At 65 rpm, the fit was always better up to t_{50} and t_{80} compared with t_{95} . At 135 rpm, the best fit was found up to t_{50} . The best fit was still given by $p = 0.5$ in most cases. Especially toward the end of the process, deviations became larger, suggesting more deviation from the conditions under which the model applies.

Little can be said about the influence of porosity on the fit, except that it seems to improve somewhat at higher porosities.

Predicted versus Experimental Dissolution Rate—The data for the disks of equal height and diameter were further investigated to compare the experimentally determined dissolution rate with the rate predicted from the diffusion model, i.e., $b = DC_s/h\rho$. Values for D (1.484×10^{-5} cm²/sec) and C_s (1 g in 2.8 ml) were taken from the literature. Values for h were taken from Fig. 1, and ρ was calculated for the tablet involved, yielding the predicted rate. The experimental rate coefficient was estimated from the t_{50} at which 3.50 mm of the original 7.00-mm tablet height had dissolved. Table IV shows the results.

The usual diffusion-convection models, including Nerst and Levich theory, predict a linear relation with the reciprocal of density. Parrott *et al.* (5) found such a relation for benzoic acid spheres, showing that an equal weight dissolves per unit of surface area in a unit of time. However, their rate value, $DC_s/h\rho$, was much smaller than predicted.

The present results do not confirm these findings; the rate is not equal to the predicted one, although it is substantially closer than in their case. The higher experimental rate may be explained by the presence of a solvent gradient as well as a solute gradient in the dissolution of very

soluble substances, as pointed out by Desai *et al.* (9). This, however, would not explain the failure of the relation between rate and the reciprocal of density. This relation holds reasonably well down to a density of 1.89. Tablets of higher porosity, however, deviate substantially.

To explain this phenomenon, disintegration was disregarded, being visually absent throughout; t_{50} can thus be regarded as practically not influenced by this process. Similarly, the diffusion layer is unlikely to vary between different porosity disks since stirring conditions and disk size are equal. This leaves the influence of the porosity itself, which should then be translated into pore dimensions. Since all disks of varying porosity (Tables II and III) had the same dimensions, the porosity was varied by introducing different numbers of particles. Therefore, high porosity disks contain fewer particles and have larger voids than do low porosity disks.

Without an exact knowledge of the pore size distribution, it is a matter of speculation whether the pores are just smaller or whether particle breaking, owing to higher compression forces necessary to produce low porosity disks, also results in a certain number of larger pores. It seems justified to assume smaller pores in low porosity tablets and larger pores in high porosity tablets. The consequence for the dissolution rate could be as follows. Pores smaller than the diffusion layer fill up rapidly with a saturated solution. The effective dissolution surface then equals the outside dimensions of the tablet, and t_{50} is directly proportional to $(1 - \text{porosity})$.

When larger pores are present, discharge of dissolved material may be faster than saturation of pores, leaving these pores undersaturated. Assuming the same diffusion layer thickness as before would, at least partly, increase the effective diffusion pathlength and thus increase the dissolution time less than expected from the relation with $(1 - \text{porosity})$. In the present experiments, the reverse is true, indicating that other factors are also effective here. A possible explanation might be that the diffusion layer surface becomes larger than the outer surface of the disk by curving inside the pores when they are large enough. A definite conclusion could be reached with a better knowledge of the pore dimensions and the particular hydrodynamics involved.

Diffusion Kinetics for Height Not Equal to Diameter—Experiments were also performed with disks of varying porosity that did not meet the requirements under which the cube root law applies (Tables V and VI). These results indicate that, at both rotation speeds, the dissolution is described fairly well by a square root or cube root expression. Coefficients of variation, relative to t_{50} , were usually smaller than 5%. There seemed to be a preference for a fit based on a $p = 0.5$ transformation, but it was less general than before. In the height range studied, 6.2–8.8 mm, the deviation from the condition $H = 2r$ seemed to have no great consequence. The fits were quite comparable with the ones for the tablets meeting this condition. The dissolution rate again increased with porosity somewhat faster than predicted, i.e., 0.252 cm⁴/g min at the low porosity range and 0.722 cm⁴/g min in the high porosity range.

The difference from the rates given cannot be explained as yet. On the basis of these findings, earlier results (10) on dissolution of 1% potassium sulfate from sucrose lozenges (13 mm, 640 mg, height 3.40 mm, porosity

Table IV—Comparison of Predicted (PR) and Experimental (EXP) Dissolution Rate Constants (Centimeters per Second $\times 10^3$) for Sodium Chloride Disks of Equal Height and Diameter Dissolved at 65 and 135 rpm

ρ^a	65 rpm			135 rpm		
	PR	EXP	EXP ρ	PR	EXP	EXP ρ
2.09	0.633	1.05	2.10	1.02	1.64	3.42
2.04	0.648	1.08	2.19	1.04	1.66	3.38
1.96	0.676	1.16	2.26	1.08	1.78	3.49
1.89	0.701	1.20	2.25	1.12	1.87	3.53
1.71	0.771	1.48	2.53	1.24	2.80	4.80
1.57	0.843	2.04	3.20	1.35	5.21	8.17

^a ρ is tablet density (grams per cubic centimeter).

Table V—Standard Deviation of the Fit ^a of Dissolution Kinetics (Averaged over Five Runs at 65 rpm) of 500-mg Sodium Chloride Disks of 7.0-mm Diameter and Variable Height

Height, mm	Porosity, %	Average t_{50} , min	t_0-t_{50}			t_0-t_{80}			t_0-t_{95}		
			$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$
6.50	7.9	2.58	<u>0.035</u>	<u>0.040</u>	<u>0.052</u>	0.155	<u>0.036</u>	<u>0.083</u>	0.407	<u>0.056</u>	0.113
6.97	14.1	2.38	<u>0.078</u>	<u>0.057</u>	<u>0.056</u>	0.182	<u>0.047</u>	<u>0.065</u>	0.359	<u>0.040</u>	0.134
7.43	19.4	2.17	<u>0.022</u>	<u>0.032</u>	<u>0.044</u>	0.192	<u>0.083</u>	<u>0.080</u>	0.332	<u>0.080</u>	<u>0.142</u>
7.92	24.4	1.86	<u>0.026</u>	<u>0.037</u>	<u>0.046</u>	0.133	<u>0.031</u>	<u>0.050</u>	0.308	<u>0.051</u>	<u>0.079</u>
8.38	28.5	1.42	<u>0.029</u>	<u>0.022</u>	<u>0.028</u>	0.124	<u>0.031</u>	<u>0.023</u>	0.345	<u>0.124</u>	<u>0.049</u>
8.79	31.9	0.90	<u>0.029</u>	<u>0.035</u>	<u>0.038</u>	0.089	<u>0.038</u>	<u>0.031</u>	0.204	0.063	<u>0.027</u>

^a Best fits are underlined ($\alpha = 0.05$).

Table VI—Standard Deviation of the Fit ^a of Dissolution Kinetics (Averaged over Five Runs at 135 rpm) of 500-mg Sodium Chloride Disks of 7.0-mm Diameter and Variable Height

Height, mm	Porosity, %	Average t_{50} , min	t_0-t_{50}			t_0-t_{80}			t_0-t_{95}		
			$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$	$p = 1$	$p = 0.5$	$p = 0.33$
6.21	3.5	1.85	0.028	<u>0.009</u>	0.020	0.147	<u>0.026</u>	<u>0.033</u>	0.261	<u>0.038</u>	<u>0.059</u>
6.50	7.9	1.75	0.024	<u>0.011</u>	0.021	0.108	<u>0.019</u>	0.052	0.269	<u>0.031</u>	0.079
6.97	14.1	1.95	<u>0.022</u>	0.036	0.047	0.141	<u>0.036</u>	<u>0.053</u>	0.379	0.096	<u>0.049</u>
7.43	19.4	1.33	0.039	0.014	<u>0.006</u>	0.111	<u>0.018</u>	<u>0.022</u>	0.225	<u>0.026</u>	0.061
7.92	24.4	0.75	0.028	<u>0.014</u>	<u>0.010</u>	0.082	0.025	<u>0.011</u>	0.177	0.053	<u>0.017</u>
8.38	28.5	0.52	0.018	<u>0.009</u>	<u>0.006</u>	<u>0.068</u>	<u>0.048</u>	<u>0.045</u>	0.134	<u>0.060</u>	<u>0.043</u>
8.79	31.9	0.34	<u>0.008</u>	<u>0.008</u>	<u>0.009</u>	0.033	<u>0.011</u>	<u>0.007</u>	0.128	0.066	<u>0.029</u>

^a Best fits are underlined ($\alpha = 0.05$).

~12%) were reinvestigated. The dissolution was carried out using a column method with a relatively small dissolution compartment. Similar to our findings on sodium chloride disks, the results could be fitted to either a square or a cube root expression, with a slight preference for the square root. This finding suggests a wider occurrence of the square root fit.

CONCLUSIONS

1. Theoretically, dissolution of disks (flat tablets) may be described by the cube root law only if height equals diameter.
2. Experimentally, the dissolution of sodium chloride disks of equal height and diameter is described adequately by the cube root law ($CV = \sim 4-5\%$). Statistically, a square root expression is better, however.
3. Disk porosity influence on dissolution rate deviates from expectations on the basis of diffusion-convection models. The rate is higher than predicted at low porosities. This result might be explained by assuming an increased effective surface area owing to distortion of the stagnant diffusion layer.
4. Dissolution kinetics of disks with unequal height and diameter are satisfactorily fitted by a square root or a cube root expression, the former sometimes being preferred.

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