USP Dissolution III: Semilogarithmic Dissolution Patterns of Tablets in Rotating-Basket Assemblies

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Abstract □ The dissolution of a rapidly soluble, finely subdivided substance in a directly compressed tablet and in a wet granulated tablet was treated experimentally and compared with previous theoretical models. The dissolution curves were sigmoid with a semilogarithmic tail when concentration was plotted *versus* time. As predicted, the slope of the semilogarithmic plots were related to the disintegration decay constant for tablet erosion in the basket.

Keyphrases □ Dissolution—rapidly soluble, finely subdivided substance in directly compressed and wet granulated tablets, compared with previous theoretical models □ Tablets—directly compressed and wet granulated, containing rapidly soluble, finely subdivided substance, dissolution compared with previous theoretical models □ Dosage forms—tablets, directly compressed and wet granulated, containing rapidly soluble, finely subdivided substance, dissolution compared with previous theoretical models

Extensive research has been published recently regarding dissolution rate methodology. Several methods of data treatment exist, but the general plotting modes for tablets have been (*a*) Hixson–Crowell cube root plots with lag time (1, 2), (*b*) σ^{-}-plots (2, 3), (*c*) log-probit plots as suggested by Wagner (4) and Wood (5), and (*d*) Weibull plots as suggested by Langenbucher (6) and Lippman (7). Frequently, dissolution data will fit one of these equations, but there are reported cases (8) where none applies. Whatever the fit may be, little work has been done to explain why dissolution rate profiles in particular situations follow certain patterns.

Part of the dissolution process in the USP dissolution apparatus (or other basket apparatus) takes (or can take) place outside of the basket and part takes place in the basket; the two are not equivalent (9–11). Disintegration also plays a part in dissolution (12, 13). The manner in which this process affects the dissolution of a coarse powder in a nonswellable tablet base has been treated theoretically (14). Since many tablet matrixes exhibit some swelling and since most drug substances are finely subdivided, this special case is treated, experimentally and theoretically, in this report.

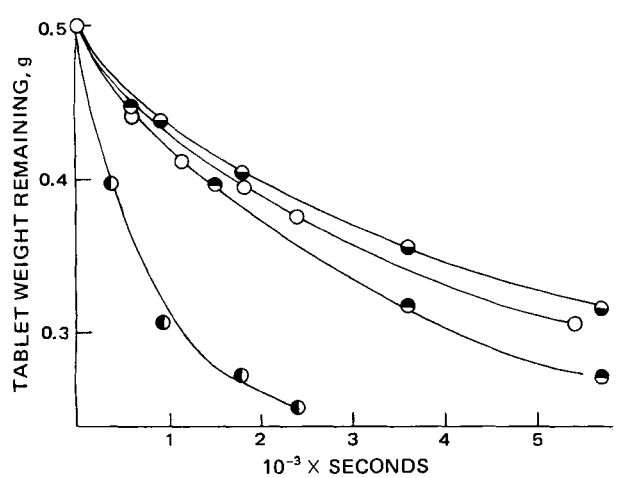

Figure 1—*Weight* versus *time curves of directly compressed tablets. Key:* ◒, *no starch (I);* ○, *10 mg of starch (II);* ◓, *30 mg of starch (III); and* ◐, *50 mg of starch (IV).*

EXPERIMENTAL

Experiments were performed in a USP dissolution rate apparatus operating at 100 rpm at 25°. To test the dissolution of a directly compressed dosage form with varying disintegration times, Formulas I–IV were prepared (Table I). Sufficient powder to make 100 tablets was mixed in a mortar and pestle, and 500-mg portions were weighed and compressed at 5000 lb of force in a hydraulic press. The tablets were 0.582 ± 0.03 cm thick at the crown and 0.25 cm at the edge; the diameter was 1.117 cm. Dissolution was checked in 0.1 *N* HCl at 25°. A volume of 900 ml of liquid was used to dissolve drug from three tablets.

In one set of experiments, the total amount of tablet weight remaining in the basket was determined as a function of time. One tablet was used for each time point. In another set of experiments, the amount of dissolved drug was determined as a function of time by withdrawing samples

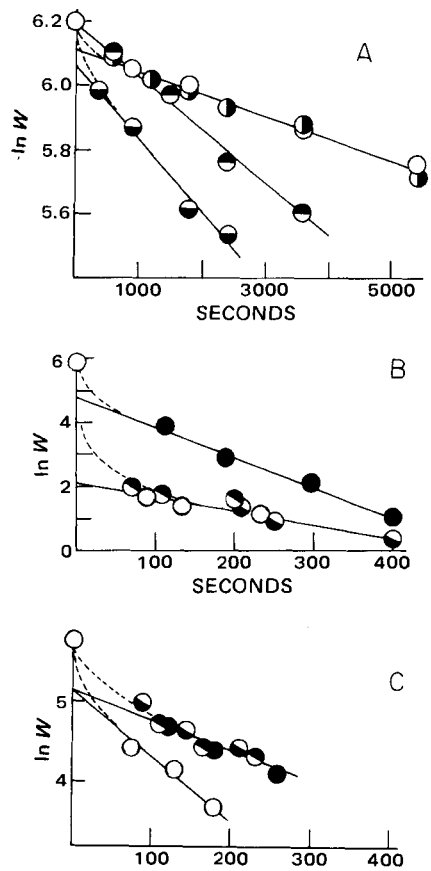

Figure 2—*Plots of ln* W versus t. *A: data from Fig. 1. Key:* ◑, *no starch (I);* ○, *10 mg of starch (II);* ◓, *30 mg of starch (III); and* ◒, *50 mg of starch (IV). B and C: wet granulated tablets (20–30 and 60–80 mesh, respectively). Key:* ○, *no stearic acid (V);* ◑, *1.5 mg of stearic acid (VI);* ◐, *3 mg of stearic acid (VII); and* ●, *9 mg of stearic acid (VIII).*

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Table I—Formulas and Dissolution Parameters of Yellow Tablets

	Amount, mg/Tablet or g/Batch								
	I	II	III	IV	Per Batch	V	VI	VII	VIII
Lactose USP	473.5	463.5	443	423.55	1515	260.31	260.31	260.31	260.31
FD&C Yellow No. 5	1.5	1.5	1.5	1.5	6	1.03	1.03	1.03	1.03
Starch USP (powder)	0	10	30	50	180	31.93	31.93	31.93	
Magnesium stearate	25	25	25	25					
Starch USP (for paste)					45	7.73	7.73	7.73	7.73
Stearic acid						0	1.5	3	9
Total	500	500	500	500	1746	300	301.5	303	309
Disintegration time (D, sec)	2350	1400	750	122	(20–30)	27	63	59	76
					(60–80)	25	28	30	36
SE	47	38	26	5	(20–30)	2	2	3	4
					(60–80)	2	2	2	3

at various times and assaying spectrophotometrically at 420 nm for dye content.

To test the dissolution of wet granulated tablets (with varying USP disintegration test disintegration times), Formulas V–VIII were prepared (Table I). These powders were blended in a planetary mixer, and the starch for paste was dispersed in 100 ml of cold water. The suspension was added to 350 ml of boiling water and formed a gel, which was allowed to cool to 55° and was then added to the blended powders. The wet granules were wet screened through a No. 6 mesh hand screen, dried at 60°, and then classified by sieving. The 20–30- and 60–80-mesh fractions were used. Stearic acid, as a dissolution liquid in chloroform, was added to the dried granules in a small coating pan. The solvent was then removed by hot air.

Tablets of 300 mg, made separately with the 20–30- and 60–80-mesh granules of each of the four formulas, were subjected to dissolution and weight decay studies as described.

RESULTS AND DISCUSSION

A simple, generalized model for the dissolution of a drug in a directly compressed tablet was proposed previously (14). In this model, monodisperse particles of a drug (or model) substance that is coarser than the basket screen are dislodged from a tablet matrix, which, in turn, simply decreases in size with time. This model is realistic in many cases, and some of the data presented here approach this view. Frequently, however, the tablet matrix swells and partially disintegrates prior to erosion (or further, but slower, disintegration), and some of the experimental data generated here follow this pattern. One purpose of this study was to determine whether the predicted correlation between the erosion constant, q (seconds^{-1}), and the semilogarithmic dissolution rate constant, K (seconds^{-1}), which is predicted for the simpler model, also holds for the more complex situation.

If the tablet first swells and flakes off granules rapidly and then disintegrates further in a slower fashion, and if these processes are exponential decay functions, then the weight *versus* time curves of the tablets should be biexponential, *i.e.*, of the nature:

$$W = Q \exp(-qt) + \Gamma \exp(-\alpha t) \qquad \text{(Eq. 1)}$$

where W is the mass of the tablet remaining, Γ and α are attributable to the first rapid disintegration, and Q and q are attributable to the final slower disintegration (erosion) of the tablets in the basket.

Figure 1 shows weight *versus* time plots of the directly compressed tablets, and Fig. 2 shows the data for all tablets tested by semilogarithmic plotting. The parameter values (Q and q) are shown in Table II for all tablets. The goodness of fit is implied by the high correlation coefficients. The value of Γ is obtained as the difference between the original weight and the value of Q. The value for Γ is very small in several cases (*e.g.*, Formulas I, III, and IV); in these instances, the model proposed earlier (14) would hold well. Since this model predicts a correlation between q and K when q is small, it is of interest to see whether this is also the case when q is large and when the weight decay curve is biexponential rather than monoexponential.

For the wet granulated 20–30-mesh tablets, the data relating to the formulas containing stearic acid are clustered together in one group (although there are differences between the three formulations), and they are quite different from the data from the formulation containing no

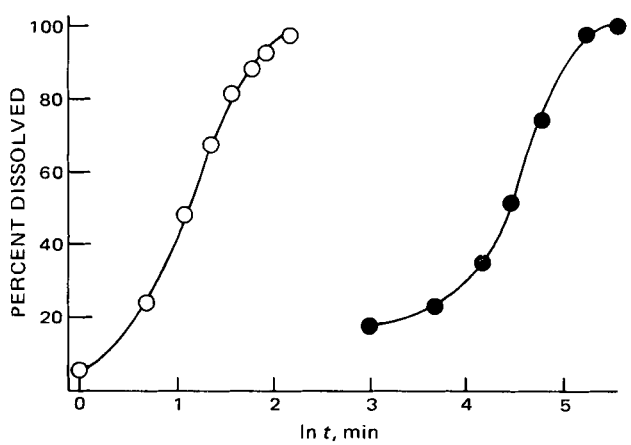

Figure 3—*Plots of* C versus *ln* t *for Formula I* (○) *(no starch) and Formula VIII* (●) *(20–30 mesh, 3% stearic acid).*

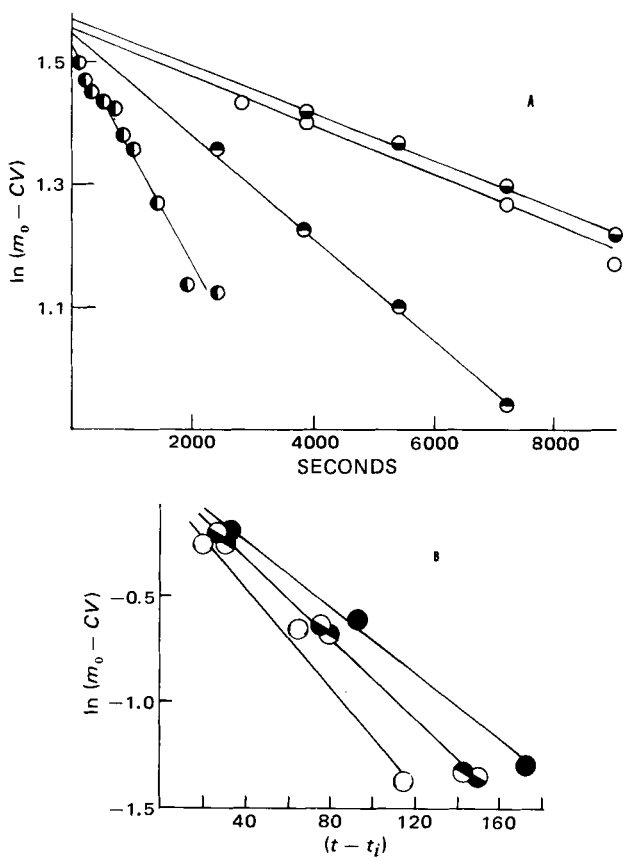

Figure 4—*Plots of ln* ($m_0 - \dot{C}V$) *as a function of time;* m_0 *and* CV *are in milligrams. A: Formulas I–IV. Key:* ◒, *no starch (I);* ○, *10 mg of starch (II);* ◓, *30 mg of starch (III); and* ◑, *50 mg of starch (IV). B: Formulas V–VIII. Key:* ○, *no stearic acid;* ◐, *0.5% stearic acid;* ◑, *1% stearic acid; and* ●, *3% stearic acid.*

Table II—Parameter Values for the Formulas Tested

Formula	Lubricant Level, mg/Tablet	ln W *versus* Time				ln($m_0 - CV$) *versus* Time		
		CR^a	$-q\ 10^3$, sec^{-1}	Q	Γ	CR^a	$K\ 10^3$, sec^{-1}	t_i, sec
I	0	−0.997	0.67	453	47	−0.994	0.038	1630
II	10	−0.998	0.07	459	41	−0.999	0.040	1200
III	30	−0.994	0.17	496	4	−0.950	0.085	599
IV	50	−0.991	0.24	431	69	−0.985	0.170	88
V, 20–30	0	−0.987	7.9	166	134	−0.991	11.8	65
VI, 20–30	1.5	−0.962	3.3	155	145	−0.997	9.4	85
VII, 20–30	3	−0.980	4.7	215	85	−0.998	9.3	62
VIII, 20–30	9	−0.991	4.2	180	120	−0.998	7.9	87
V, 60–80	0	−0.970	12.2	4	296	−0.992	6.3	150
VI, 60–80	1.5	−0.876	2.3	8	292	−0.996	8.3	31
VII, 60–80	3	−0.988	3.4	7	293	−0.973	8.0	65
VIII, 60–80	9	−0.984	9.5	120	180	−0.998	6.1	69

[a] Correlation coefficient.

stearic acid. With tablets made from the 60–80-mesh granules, the formula containing 3% stearic acid is separate from the others, which fall in a clustered group. Apparently, for the larger surface area in the 60–80-mesh granules, more stearic acid is needed to contribute the cohesion necessary to prolong disintegration in the dissolution basket. The argument is not one of monomolecular layers since stearic acid has a close-packed molecular contact area of 20 Å^2 (15). Therefore, it would only take 10^{-5} mole (0.003 mg) to cover a surface area of 10^4 cm^2, the geometric surface area of the 20–30-mesh granules in the 300-mg tablet.

The Γ term is very small in several cases (*e.g.*, Formula III).

The dissolution curves are all typically sigmoid (Fig. 3). The data are presented using ln t (in minutes) as abscissa rather than t, because log-probit plotting is often employed in such situations. In one case (Formula I), the plot is symmetrical about the 50% point (*i.e.*, is log-probit); but in the other case (Formula VIII), it is not.

The tails of all curves are logarithmic time decays (14, 16, 17); *i.e.*, the curves follow:

$$\ln(m_0 - CV) = \ln m_0 - K(t - t_i) \qquad \text{(Eq. 2)}$$

where m_0 is the amount of drug in the tablets originally, C is concentration, V is the volume of dissolving liquid, and t_i is the lag time. This is demonstrated in Fig. 4, and t_i and K values are given in Table II. The goodness of fit is implied by the proximity to unity of the correlation coefficients. Equation 2 obviously holds only for $t > t_i$ (since it otherwise would imply $C = 0$ at $t = t_i$), and t_i will be empirical and may be difficult to reproduce from apparatus to apparatus.

It is difficult to graph q *versus* K because the data fall in two clusters, one with very low q values and one with much higher q values. In Fig. 5, therefore, the correlation of ln K *versus* ln q is shown. The data are grouped as indicated in Fig. 2; the common q value for Formulas VI–VIII is used for the 20–30-mesh fraction, as is the common q value for Formulas V–VII for the 60–80-mesh fraction. The correlation coefficient is 0.985 for the relationship $\ln q = 1.19 \ln K + 1.286$; *i.e.*, q and K correlate but not quite linearly.

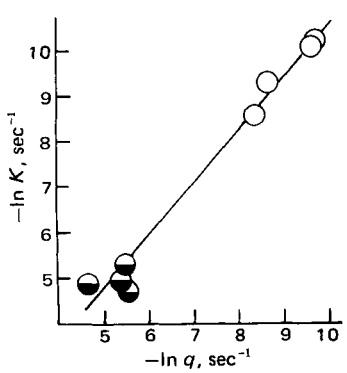

Figure 5—*Correlation between* K *and* q.

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