USP Dissolution Test II: Sigmoid Dissolution Profiles from Directly Compressed Tablets

J. T. CARSTENSEN ˣ, JAMES L. WRIGHT, KENNETH W. BLESSEL *, and JANE SHERIDAN *

Received December 16, 1976, from the *School of Pharmacy, University of Wisconsin, Madison, WI 53706.* Accepted for publication March 25, 1977. *Present address: Hoffmann-La Roche Inc., Nutley, NJ 07110.

Abstract □ The basic steps involved in the dissolution of a directly compressed tablet in a USP basket dissolution apparatus were examined *via* data generation. The proposed model explains why a dissolution curve can be sigmoid shaped and why the portion past the lag time has a log-linear undissolved mass *versus* time correlation.

Keyphrases □ Dissolution—directly compressed tablet in USP basket apparatus, sigmoid-shaped curve explained □ Apparatus, dissolution—USP basket, directly compressed tablet, sigmoid-shaped curve explained

Dissolution curves of dosage forms in the USP dissolution apparatus often are S-shaped. Only a few attempts to explain the basic phenomena leading to an S-shaped curve have been reported (1, 2). An explanation is given here for the dissolution of a drug substance in a directly compressed tablet, where the drug substance is monodisperse with diameter d_0.

THEORETICAL

The situation considered is one where a tablet disintegrates into prime drug particles. Without a loss of generality, it can be considered that the tablet consists of drug particles only and that it is made up of a total of T_0 drug particles of diameter d_0 initially, *i.e.*, that it has a weight of $w = T_0\pi d_0^3\rho/6$. The tablet weight in the basket, after the onset of the dissolution test, decreases exponentially (3); *i.e.*:

$$T = T_0e^{-q\theta} \qquad \text{(Eq. 1)}$$

where θ is the experimentally observed time and q is denoted as an erosion constant.

The dissolution process can be examined in three portions. The first phase (Fig. 1*a*) is where the drug particles dislodged from the tablet have not yet decreased sufficiently in size to pass through the basket, which has an opening of d_1 cm. In the USP apparatus, this opening is $d_1 = 0.042$ cm (40 mesh). The dislodged particles will decrease in size according to the cube root law provided that they are isometric and that sink conditions prevail (4):

$$d = d_0 - F_0t \qquad \text{(Eq. 2)}$$

where:

$$F_0 = 2k_0S/\rho \qquad \text{(Eq. 3)}$$

and k_0 is the intrinsic dissolution rate constant (centimeters per second) in the basket and S is the drug solubility. At a certain time, θ_1, the particles that dislodged first will have decreased in size sufficiently to pass through the basket. Time θ_1 is given by:

$$d_1 = d_0 - F_0\theta_1 \qquad \text{(Eq. 4)}$$

The second phase is at time points beyond θ_1 but prior to the time, θ_2, where the particles that dislodged first will have completely dissolved (Fig. 1*b*). This point in time is arrived at in the following fashion. If k_1 is considered the intrinsic dissolution rate constant in the *vessel*, it will obviously differ from k_0 because of the different hydrodynamic conditions in the vessel. In general (5):

$$k_0 = 1.5k_1 \qquad \text{(Eq. 5)}$$

so that:

$$F_0 = 1.5F_1 \qquad \text{(Eq. 6)}$$

Time θ_2 is then given by:

$$0 = d_1 - F_1(\theta_2 - \theta_1) \qquad \text{(Eq. 7)}$$

and the three phases can be characterized as depicted in Fig. 1. The three phases according to time are given by: first phase, $\theta < \theta_1$; second phase, $\theta_1 < \theta < \theta_2$; and third phase, $\theta_2 < \theta$.

To arrive at an expression for the mass undissolved at time θ, one can consider the first phase. The number of particles formed (eroded off) t sec after the experiment is started, *i.e.*, in a time element $(t|t + dt)$, is given by:

$$-dT = qT_0e^{-qt}\,dt \qquad \text{(Eq. 8)}$$

After θ sec, these particles, which were created at time t, have been exposed to dissolution for a period of time equaling $\tau = (\theta - t)$. Therefore, their diameter (Eq. 2) is given by $d = d_0 - F_0(\theta - t)$, and the undissolved mass (m) of the particles dislodged at time t will at time θ be:

$$m = qT_0e^{-qt}(\rho\pi/6)[d_0 - F_0(\theta - t)]^3\,dt \qquad \text{(Eq. 9)}$$

Integrating this equation from $t = 0$ to $t = \theta$ then gives the total mass of the *particles* that are not dissolved at time θ; the mass of the *tablet* that is not dissolved at time θ is $T_0e^{-q\theta}\rho d_0^3\pi/6$. Therefore, the expression for the mass undissolved at time θ is:

$$m = T_0e^{-q\theta}\rho d_0^3\pi/6 + T_0(\pi\rho/6)\int_0^\theta qe^{-qt}[d_0 - F_0(\theta - t)]^3\,dt \qquad \text{(Eq. 10)}$$

The integral can be evaluated through integration by parts and has the value:

$$-\left[e^{-qt}\left\{(d_0 - F_0(\theta - t))^3 + 3\left(\frac{F_0}{q}\right)(d_0 - F_0(\theta - t))^2 + 6\left(\frac{F_0}{q}\right)^2(d_0 - F_0(\theta - t)) + 6\left(\frac{F_0}{q}\right)^3\right\}\right]\Bigg|_0^\theta$$

$$= \left[\{d_0 - F_0\theta\}^3 + 3\left(\frac{F_0}{q}\right)\{d_0 - F_0\theta\}^2 + 6\left(\frac{F_0}{q}\right)^2\{d_0 - F_0\theta\} + 6\left\{\frac{F_0}{q}\right\}^3\right] - e^{-q\theta}\left[d_0^3 + 3\left(\frac{F_0}{q}\right)d_0^2 + 6\left(\frac{F_0}{q}\right)^2 d_0 + 6\left(\frac{F_0}{q}\right)^3\right] \qquad \text{(Eq. 11)}$$

In general, if τ is the time elapsed from the time a particle has size d_i, then the integral may be written:

$$\int_{\zeta_1}^{\zeta_2} qe^{-qt}(d_i - F_i\tau)^3\,dt = I(i, \tau, \{\zeta_1\ \zeta_2\}) \qquad \text{(Eq. 12)}$$

This nomenclature facilitates the writing of the expressions for the mass undissolved as a function of time in the three phases.

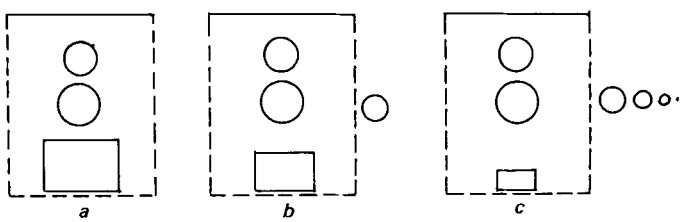

Figure 1—*Schematic of a tablet in a basket dissolution apparatus at various stages. Key:* a, *some disintegration, but dislodged particles have not decreased in size sufficiently to pass through basket mesh;* b, *more disintegration than* a *and the particles first formed have decreased in size sufficiently to pass through the basket but no particles have completely dissolved; and* c, *more disintegration than* b *and the particles formed first have completely dissolved.*

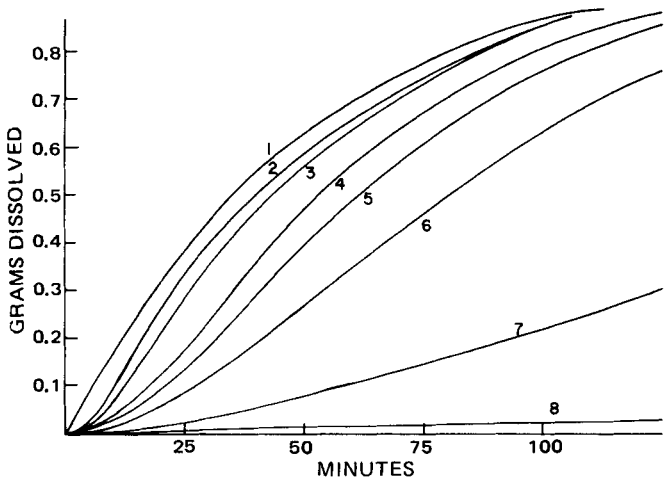

Figure 2—*Dissolution rate curves generated from 1 g of drug in a tablet, with* q = *0.02 min*$^{-1}$. *The* F *values (in centimeters per minute) are: 0.15 (1), 0.045 (2), 0.003 (3), 0.0015 (4), 0.00105 (5), 0.0006 (6), 0.00015 (7), and 0.000015 (8).*

In the first phase:

$$m = T_0 e^{-q\theta} \rho \pi d_0^3/6 + I(0, (\theta - t), \{0, \theta\}) \qquad \text{(Eq. 13)}$$

In the second phase:

$$m = T_0 e^{-q\theta} \rho \pi d_0^3/6 + I(0, (\theta - t), \{\theta - \theta_1, \theta\}) + I(1, (\theta - \theta_1 - t), \{0, \theta - \theta_1\}) \qquad \text{(Eq. 14}a\text{)}$$

In the third phase:

$$m = T_0 e^{-q\theta} \rho \pi d_0^3/6 + I(0, (\theta - t), \{\theta - \theta_1, \theta\}) + I(1, (\theta - \theta_1 - t), \{\theta - \theta_2, \theta - \theta_1\}) \qquad \text{(Eq. 14}b\text{)}$$

The actual expressions for Eqs. 14*a* and 14*b* are given in Eqs. 15*a* and 15*b*, respectively.

The expansion of Eq. 13 is shown in Eq. 11.

In the second phase:

$$m = T_0 e^{-q\theta} \rho \pi d_0^3/6 + T_0 \frac{\rho\pi}{6} \left\{ (d_1 - F_1(\theta - \theta_1))^3 + 3\left(\frac{F_1}{q}\right)(d_1 - F_1(\theta - \theta_1))^2 + 6\left(\frac{F_1}{q}\right)^2 (d_1 - F_1(\theta - \theta_1)) + 6\left(\frac{F_1}{q}\right)^3 - e^{-\theta q}\left[d_0^3 + 3\left(\frac{F_0}{q}\right) d_0^2 + 6\left(\frac{F_0}{q}\right)^2 d_0 + 6\left(\frac{F_0}{q}\right)^3 \right] + e^{-(\theta-\theta_1)q}\left[3\left\{\left(\frac{F_0}{q}\right) - \left(\frac{F_1}{q}\right)\right\} d_1^2 + 6\left\{\left(\frac{F_0}{q}\right)^2 - \left(\frac{F_1}{q}\right)^2\right\} d_1 + 6\left\{\left(\frac{F_0}{q}\right)^3 - \left(\frac{F_1}{q}\right)^3\right\}\right]\right\} \qquad \text{(Eq. 15}a\text{)}$$

In the third phase:

$$m = T_0 e^{-q\theta} \rho \pi d_0^3/6 + T_0 \frac{\rho\pi}{6} \left\{ e^{-(\theta-\theta_2)q}\, 6\left(\frac{F_1}{q}\right)^3 + e^{-(\theta-\theta_1)q}\left\{ 3\left[\left(\frac{F_0}{q}\right) - \left(\frac{F_1}{q}\right)\right] d_1^2 + 6\left[\left(\frac{F_0}{q}\right)^2 - \left(\frac{F_1}{q}\right)^2\right] d_1 + 6\left[\left(\frac{F_0}{q}\right)^3 - \left(\frac{F_1}{q}\right)^3\right]\right\} - e^{-q\theta}\left\{ d_0^3 + 3\left(\frac{F_0}{q}\right) d_0^2 + 6\left(\frac{F_0}{q}\right)^2 d_0 + 6\left(\frac{F_0}{q}\right)^3 \right\}\right\} \qquad \text{(Eq. 15}b\text{)}$$

If q is small and if $F/q \ll 1$, then the leading term at long times predominates, *i.e.*:

$$m \sim (\pi/6) \rho T_0 e^{-q\theta} d_0^3 \qquad \text{(Eq. 16)}$$

or:

$$\ln m = -q\theta + \ln m_0 \qquad \text{(Eq. 17)}$$

If q is large, then the term with the lowest exponent predominates and, at long times:

$$m \sim (\pi/6)\, \rho T_0 6 (F_1/q)^3 e^{-(\theta-\theta_2)q} \qquad \text{(Eq. 18)}$$

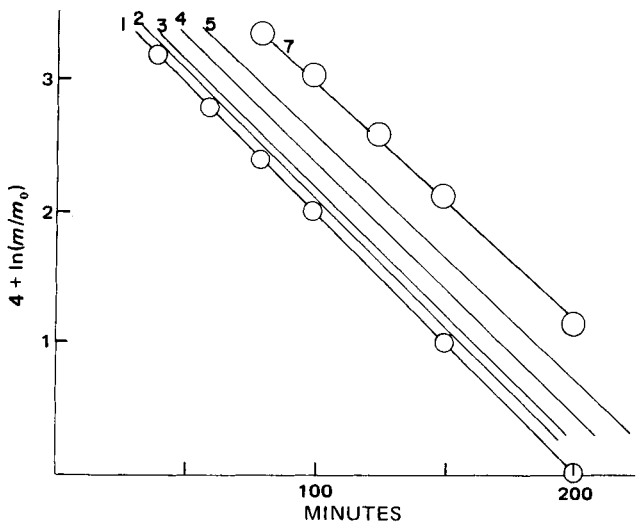

Figure 3—*Data in Fig. 2 treated according to Eq. 19. The curves are not experimental curves; the points in curves 1 and 7 are calculated points included (in these two cases) to demonstrate the goodness of fit.*

or:

$$\ln m = -q\theta + q\theta_2 + \ln m_0 6 (F/q)^3 \qquad \text{(Eq. 19)}$$

In the latter case, the intercept of a plot of the logarithm of the undissolved amount *versus* time will not intercept at ln m_0, although it will be linear at high time values.

Because of the initial lag, the curves will all have skewed S-shapes and adhere to either Weibull or log-normal distributions when the percent dissolved is plotted *versus* time.

DISCUSSION

Several generated curves are shown in Fig. 2. In each case, d_0 = 0.1 cm (1000 μm), d_1 = 0.042 cm (420 μm, 40 mesh), and ρ is $(6/\pi)$. The value of T_0 is 1000 so that the initial weight of drug is $1000(\pi/6)(6/\pi)0.1^3$ = 1.0 g. The factor in front of each integral is then 1000.

It is seen from Fig. 3 that the generated curves adhere to Eq. 19. Seven time points (40, 60, 80, 100, 125, 150, and 200 min) were selected for the generated curves in Fig. 2 to arrive at the curves in Fig. 3; the least-squares fit parameters based on these seven time values are listed in Table I. For q = 0.02 min^{-1}, F values of 0.006–0.15 cm/min give slopes close to the value of q. The length of time for a particle to dissolve completely, θ_2, is related to F by $\theta_2 = 0.081/F$ or:

$$\ln \theta_2 = -\ln F + \ln 0.081 = -\ln F - 2.52 \qquad \text{(Eq. 20)}$$

The intercept to slope ratio (θ') of the lines in Table I are the "lag times" obtained by log-linear plotting (and, hence, is biased by the fact that approximations are made). The values of the lag times are plotted *versus* the values of F on a log–log plot in Fig. 4. The least-squares fit of this plot is:

$$\ln \theta' = -1.02F - 3.809 \qquad \text{(Eq. 21)}$$

As predicted in Eq. 20, the slope is −1, but the intercepts are different. Equation 21 holds for $F > 0.006$ when $q = 0.02$, *i.e.*, for F/q ratios above 0.3. The intercepts do not coincide, which means that the lag time from

Table I—Least-Squares Fit Parameters of Lines in Fig. 3

Curve	F, cm/min	Slope, min^{-1}	Correlation Coefficient ($-R$)	Intercept
1	0.15	−0.0200	1.000	0.0029
2	0.0045	−0.0200	1.000	0.1165
3	0.0030	−0.0200	1.000	0.1769
4	0.0015	−0.0199	1.000	0.3658
5	0.00105	−0.0195	0.9996	0.4923
6	0.0006	−0.0167	0.9952	0.5969
7	0.00015[a]	−0.0158	0.9988	1.2888

[a] All fits are based on the time points indicated in the text above 40 min, except curve 7 for which points above 100 min only were used.

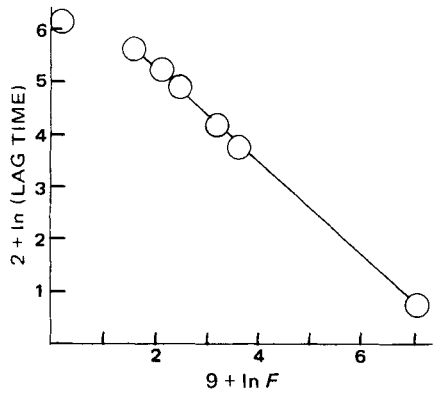

Figure 4—*Logarithm of the lag times of the lines in Fig. 3 (Table I) plotted* versus *the logarithm of the corresponding* F *values.*

log-time plots (θ') are proportional to the appropriate θ_2 values since ln (θ_2/θ') = 1.29, *i.e.*:

$$\theta_2 = 3.63\theta' \qquad \text{(Eq. 22)}$$

Although time is shown in minutes, it could be in any time unit; the important parameter is the F/q ratio. Therefore, the same curves would be generated if all time units are multiplied by ($^1/_{60}$) (to give the data in seconds) or by 15 to give the data in quarter hours, and so on.

In summary, directly compressed tablets can have sigmoid-shaped USP dissolution rate curves in which the tail is log-linear in time if sink conditions are applicable.

REFERENCES

(1) J. H. Wood, presented at the Industrial Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Dallas meeting, Apr. 1966.

(2) J. T. Carstensen, in "Dissolution Technology," L. Leeson and J. T. Carstensen, Eds., Industrial Pharmaceutical Technology Section, Academy of Pharmaceutical Sciences, American Pharmaceutical Association, Washington, D.C., 1974, p. 192.

(3) J. T. Carstensen, J. Wright, K. Blessel, and J. Sheridan, *J. Pharm. Sci.*, in press.

(4) J. T. Carstensen, "Pharmaceutics of Solids and Solid Dosage Forms," Wiley, New York, N.Y., 1977, p. 77.

(5) J. T. Carstensen, T. Lai, and V. K. Prasad, *J. Pharm. Sci.*, **66**, 607 (1977).

ACKNOWLEDGMENTS

Presented at the APhA Academy of Pharmaceutical Sciences, Orlando meeting, November 1976 ["Abstracts," vol. 6, p. 114, paper 79].

Evaluation of Acceptance Criteria for Particulate Limits for Small-Volume Parenteral Products

KIYOSHI TSUJI ˣ **and A. R. LEWIS**

Received December 17, 1976, from *Control Analytical Research and Development and Mathematical Services, The Upjohn Company, Kalamazoo, MI 49001.* Accepted for publication March 31, 1977.

Abstract □ The precision of and correlation between the USP membrane filtration–microscopic method and the instrumental method for sizing and quantifying particulate matter in small-volume parenteral products were determined using simulated products. The total variance for the instrumental counts was lower than the USP method for all products in the 10–25-μm particle range and for most products in the ≥25–50-μm range. A linear relationship between the instrumental counts and the USP counts was demonstrated for the 10–25-μm particle range. However, the instrumental reading was higher than the USP method for counts of 10 or more particles/ml. The instrumental and the USP methods failed to correlate on particulate sizes greater than 25 μm. The content of particulate matter in over 100 small-volume parenteral products was sized and quantified by the USP and the instrumental methods. From the instrumental data, a statistical treatment for the analysis of particulate data is presented as an objective method of evaluating acceptance criteria on particulate matter in small-volume parenteral products.

Keyphrases □ *Particle* content determinations—small-volume parenterals, USP membrane filtration–microscopic and instrumental methods compared □ Parenterals, small volume—particle content determinations, USP membrane filtration–microscopic and instrumental methods compared □ Dosage forms—various small-volume parenterals, particle content determinations, USP membrane filtration–microscopic and instrumental methods compared

Interest in particulate matter in parenteral products was dramatically heightened by Garvan and Gunner (1, 2), who became concerned over the large number of visible particles in intravenous solutions manufactured in Australia. They presented evidence of the harmful effects of such contaminants by infusing intravenous solutions into rabbits; granulomas were produced in the lung, each containing fragments of cellulose particles. They identified the source of most particles as originating from locally produced rubber closures; other particulates were identified as cellulose fibers. They also examined numerous brands of intravenous solutions manufactured in Australia, England, Europe, the Philippines, and the United States and found particles in most products.

In 1966, Vessey and Kendall (3) published a method of determining particulate matter in large-volume parenteral solutions using an automated counter. They proposed an arbitrary limit for particulate matter in these solutions. This proposal was modified and adopted by the British Pharmacopoeia in 1973 (4); the limits are less than 1000 particles/ml equal to or larger than 2 μm and less than 100 particles/ml equal to or larger than 5 μm. Recently, Bikhazi *et al.* (5) extrapolated the BP regulation and proposed that the average counts per 1 ml of parenteral preparation should contain not more than 700 particles equal to or greater than 1 μm, 200 equal to or greater than 2 μm, 100 equal to or greater than 3 μm, and 40 equal to or greater than 5 μm.

"The First Supplement to the USP XIX and NF XIV" (6) established the limit for particulate matter in large-volume parenteral products as not more than 50 parti-