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Establishment of Sink Conditions in Dissolution Rate Determinations

Theoretical Considerations and Application to Nondisintegrating Dosage Forms

By MILO GIBALDI and STUART FELDMAN

The importance of approximating perfect sink conditions for the determination of dissolution rates which may be correlated with *in vivo* results is pointed out. A theoretical treatment of zero and first-order dissolution under perfect sink and nonsink conditions is presented. It is shown that unless sink conditions are maintained, *in vitro* results will bear little relationship to *in vivo* observations. The use of an organic solvent phase which can function as a reservoir for dissolved drug and thereby maintain sink conditions in the aqueous dissolution fluid is demonstrated for a model nondisintegrating tablet exhibiting zero-order drug release. The use of an organic solvent reservoir for the determination of first-order dissolution rates is also discussed.

One of the most important as well as most difficult approaches in the biopharmaceutic evaluation of a drug is the quantitative correlation of absorption and *in vitro* dissolution kinetics. Levy *et al.* (1) have recently reported the development of a single *in vitro* dissolution rate test which correlates quantitatively with the gastrointestinal absorption, in man, of aspirin from three markedly different types of dosage forms. The basic method, however, is limited to the study of drugs which are relatively water soluble.

Dissolution rate-limited absorption implies that there is no build-up of drug concentration in the gastrointestinal fluids, *i.e.*, the fluids function as a perfect sink. Unless this condition is embodied in the design of the *in vitro* test (*i.e.*, drug concentration in the dissolution fluids does not exceed 10 to 20% of solubility), *in vitro* results will bear little relationship to *in vivo* observations (2).

As noted recently by Levy (2), those drugs which represent the greatest dissolution problem are also those which are least soluble and give the greatest difficulty with respect to maintenance of perfect sink conditions. Frequently, it is necessary to use exceedingly large volumes of solvent for this purpose and to adopt very sensitive analytical procedures. At times, it may be very difficult to follow the dissolution of more than a small fraction of the drug contained in the dosage form. Under these conditions one must assume a uniform pattern of release rate. Wood (3), however, has pointed out that in practice there are many cases in which one point in time or a rate constant does not characterize the dissolution process and a full dissolution curve (based on the total drug content of the dosage form) is required for *in vitro* to *in vivo* correlation.

A definite need exists for the development of methodology to maintain sink conditions during dissolution rate determinations of poorly soluble drugs. Levy (2) has suggested two possibilities: the use of an upper organic phase which can act as a reservoir for the dissolved drug or the addition of adsorbents to the aqueous medium. The ability of adsorbents to maintain "sink" conditions had been demonstrated previously by Wurster and Polli (4). Both approaches involve the same principle, *i.e.*, removal of dissolved drug from the dissolution medium and prevention of accumulation. The removal of drug from the dissolution fluid is analogous to removal of drug from the gastrointestinal fluids by the absorption process in dissolution rate-limited absorption.

The present report concerns the theory and application of the use of an upper organic solvent

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phase for the maintenance of perfect sink conditions during dissolution rate determinations of nondisintegrating solids in aqueous systems.

EXPERIMENTAL

Model Dosage Form—Nondisintegrating flat-faced tablets of pure drug were prepared by compressing 300 mg. of benzoic acid or 600 mg. of salicylic acid by means of a Carver model B hydraulic press equipped with a 0.5-in. diameter punch and die. The compression pressure was 10,000 p.s.i.

Dissolution Assembly—The assembly consisted of a 500-ml. three-neck round-bottom flask immersed in a constant-temperature bath adjusted to 37° ± 0.1°. A 3-in. Teflon stirring blade and shaft attached to a stirring motor was inserted in the center neck. The motor was controlled by a Servodyne constant torque unit which also served to provide a direct read-out of speed of rotation.

Dissolution Procedure in 0.1 N HCl—One hundred and fifty milliliters of 0.1 *N* HCl was placed in the flask and permitted to equilibrate to 37°. The stirring blade was immersed in the dissolution medium to a depth of 20 mm. and accurately centered by means of a guide. The stirrer was rotated at a speed of 25, 50, or 100 r.p.m. and the benzoic acid or salicylic acid tablet was placed in the medium by dropping it through the side neck, along the side of the flask. The tablet remained at the bottom of the flask throughout each determination.

One-milliliter samples of the solution were taken at appropriate intervals, diluted, and assayed spectrophotometrically using a Beckman model DB-G spectrophotometer. A volume of 0.1 *N* HCl (maintained at 37°) equal to the sample volume was added immediately after each sampling. Absorbances were measured at 226 and 302 mμ for benzoic acid and salicylic acid, respectively. By appropriate calculations (5), the total amount of drug in solution as a function of time was determined.

The dissolution of benzoic acid was followed under conditions approximating a perfect sink, *i.e.*, benzoic acid concentration in the dissolution fluid never exceeded 12% of solubility. The dissolution of salicylic acid was followed well beyond sink conditions. At the end of the determination the salicylic acid concentration in the dissolution medium approximated 80% of solubility.

Dissolution Procedure in 0.1 N HCl with Upper Organic Solvent Phase—After addition of the 150 ml. of 0.1 *N* HCl and positioning of the stirrer, the tablet was dropped into the aqueous phase but remained unstirred while 150 ml. of organic solvent was slowly added to the flask. Stirring was initiated after addition of the organic solvent. Dissolution of benzoic acid was studied in 0.1 *N* HCl layered with a 1:1 mixture of cyclohexane and 1-octanol, while dissolution of salicylic acid was studied in 0.1 *N* HCl layered with a 1:1 mixture of cyclohexane and 2-octanol.

The selection of the upper organic solvent phase is dictated solely by a consideration of the partition coefficient of the drug between the aqueous dissolution medium and the organic sink. The total dose of drug to be studied must represent less than 20% of its solubility in the selected volume of organic solvent.

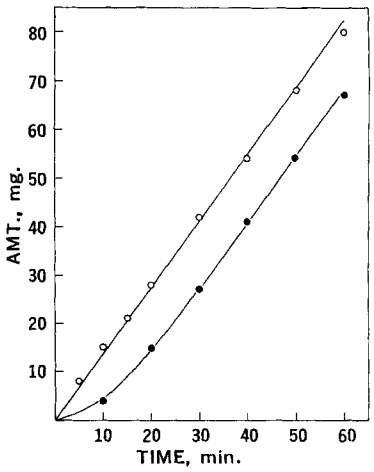

Fig. 1—Rate of appearance of benzoic acid from constant surface tablets in 0.1 N *HCl* (○) *and in cyclohexane–1-octanol layer above a 0.1* N *HCl phase* (●).

At various intervals after initiation of stirring, 1-ml. samples of the organic phase were taken, diluted with methanol, and assayed spectrophotometrically. The volume of the organic phase was maintained constant by replenishing with solvent after each sampling. By appropriate calculations, the total amount of drug appearing in the organic solvent phase as a function of time was determined.

Determination of Rate of Partitioning—The rate of partitioning of benzoic acid from water to 1:1 cyclohexane–1-octanol was determined in the dissolution assembly at 37° and 25 r.p.m. At time zero the aqueous phase contained 0.3 mg./ml. benzoic acid in 0.1 *N* HCl. The organic solvent phase was sampled at various intervals after addition and the quantity of benzoic acid present at each interval was determined.

RESULTS AND DISCUSSION

The dissolution of benzoic acid in 0.1 *N* HCl followed apparent zero-order kinetics over the time period studied. The appearance of benzoic acid as a function of time at 50 r.p.m. is illustrated in Fig. 1. The apparent zero-order dissolution rate constants determined at 25, 50, and 100 r.p.m. are listed in Table I. A plot of log dissolution rate *versus* log stirring rate is shown in Fig. 2. According to the equations developed by Cooper and Kingery (6), which relate the diffusion controlled dissolution rate from the surface of a rotating disk to the velocity of rotation (stirring rate), a plot of the logarithm of dissolution rate (expressed here in mg./min./total surface area) *versus* the logarithm of stirring rate (expressed in r.p.m.) should yield a straight line with a slope of 0.5. As indicated in Fig. 2, the slope of the line fitted to the benzoic acid data (0.494) is quite close to the theoretical value. Thus, the described relationship between dissolution rate and stirring rate holds for the methodology used in the present study.

The rate of appearance of benzoic acid in the cyclohexane–octanol phase during the dissolution process also followed zero-order kinetics, after an initial lag period. A representative plot is included.

TABLE I—KINETIC DATA FOR THE DISSOLUTION OF BENZOIC ACID FROM CONSTANT SURFACE TABLETS IN 0.1 *N* HCl LAYERED WITH CYCLOHEXANE–1-OCTANOL

Stirring Rate, r.p.m.	k_0,[a] mg./min.	k_0[b], mg./min.	B[c], mg.	k_p,[d] min.$^{-1}$
25	1.00	0.87	12.2	0.071 (0.067)[e]
50	1.36	1.35	12.1	0.111
100	2.00	2.00	5.2	0.385

[a] Zero-order dissolution rate constant of drug in 0.1 *N* HCl, for exposed surface area of 9.0 cm.^{2}. [b] Zero-order rate constant for appearance of drug in organic solvent phase. [c] Calculated steady-state amount of drug in 0.1 *N* HCl layered with solvent. [d] Calculated first-order partition rate constant (× interfacial area) of drug from 0.1 *N* HCl to cyclohexane–1-octanol. [e] Experimentally determined partition rate constant (× interfacial area).

in Fig. 1. The zero-order rate constants for appearance of drug in the organic phase at the various stirring speeds studied are listed in Table I. There is excellent agreement between the zero-order dissolution rate constants and the zero-order appearance rate constants at both 50 and 100 r.p.m. At 25 r.p.m. the rate of appearance of drug in the organic phase adhered to zero-order kinetics but the rate constant was somewhat lower than the dissolution rate constant found in 0.1 *N* HCl at 25 r.p.m. The reason for this phenomenon appears to be related to the effective stirring rate, *i.e.*, although the paddle rotated at 25 r.p.m., the flow of aqueous fluids about the tablet was dampened by the physical presence of the organic layer. An estimate of the effective stirring rate in the two-phase system at a paddle speed of 25 r.p.m. was obtained by extrapolating the data shown in Fig. 2 (assuming that appearance rate corresponded to dissolution rate). The experimental appearance rate was found to correspond to an effective stirring rate of 20 r.p.m. The dampening effect appeared to be totally absent at 50 and 100 r.p.m.

The rate of appearance of drug in the organic phase may be related to the dissolution rate in the aqueous phase by means of the following kinetic model:

$$A \xrightarrow{k_0} B \xrightarrow{k_p} C \qquad \text{(Eq. 1)}$$

where A is the amount of drug in the tablet, B is the amount of drug in the aqueous phase, C is amount of drug in the organic layer, k_0 is the zero-order dissolution rate constant, and k_p is the first-order rate constant for partitioning of drug from the aqueous phase to the organic solvent phase. The rates of change of B and C may be expressed by the following differential equations:

$$dB/dt = k_0 - k_pB \qquad \text{(Eq. 2)}$$

and

$$dC/dt = k_pB \qquad \text{(Eq. 3)}$$

Integrating Eqs. 2 and 3 yields, respectively:

$$B = \frac{k_0}{k_p}(1 - e^{-k_pt}) \qquad \text{(Eq. 4)}$$

and

$$C = k_0t - \frac{k_0}{k_p}(1 - e^{-k_pt}) \qquad \text{(Eq. 5)}$$

At some finite time t, $e^{-k_pt} \rightarrow 0$ and Eqs. 4 and 5 reduce to Eqs. 6 and 7:

$$B = \frac{k_0}{k_p} = \text{constant} \qquad \text{(Eq. 6)}$$

and

$$C = k_0t - \frac{k_0}{k_p} \qquad \text{(Eq. 7)}$$

The more rapid the rate of partitioning, the shorter the time period required for the attainment of true steady-state kinetics, *i.e.*, B = constant, $dB/dt = 0$. After attainment of steady-state, a plot of C *versus* time should yield a straight line with a slope of k_0.

The experimental data permitted calculation of k_p by means of Eq. 7 and B at the steady state by means of Eq. 6. These calculated values are listed in Table I. The k_p value of 0.071 calculated from the data at 25 r.p.m. was in agreement with the experimentally determined value of 0.067.

The data in Table I indicate a positive correlation between k_p and stirring rate. The reason for this relationship is that the k_p values are actually a product of the first-order rate constant for diffusion across the interface and the interfacial area between the water and solvent phases. As stirring rate is increased, the turbulence at the interface increases causing a degree of mixing and "emulsification" in the interfacial region. This increase in the "thickness" of the interface results in a marked increase in the mean interfacial area. It is likely that the increased interfacial area is primarily responsible for the increased values of k_p.

The steady-state values listed in the table represent only 0.8 to 1.8% of the solubility of benzoic acid in 0.1 *N* HCl. This is an excellent indication of the efficiency of the organic solvent in maintaining near-perfect sink conditions in the aqueous phase.

The salicylic acid studies were designed to

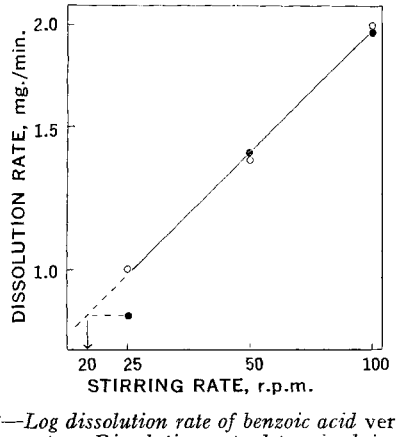

Fig. 2—Log dissolution rate of benzoic acid versus *log stirring rate. Dissolution rate determined in 0.1* N *HCl* (○) *and in 0.1* N *HCl layered with cyclohexane–1-octanol* (●).

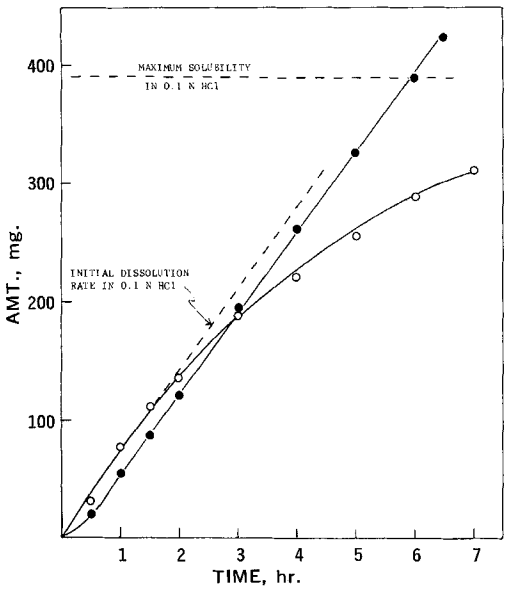

Fig. 3—Rate of appearance of salicylic acid from constant surface tablets in 0.1 N HCl (○) under nonsink conditions and in cyclohexane–2-octanol layer above a 0.1 N HCl phase (●) where perfect sink conditions are approximated. The broken horizontal line indicates the total solubility of drug in 150 ml. of 0.1 N HCl.

illustrate the different dissolution kinetics which result from lack of sink conditions and to demonstrate the resolution of these differences by means of an organic solvent reservoir. The model dosage form of salicylic acid was anticipated to retain a constant surface area during the release of a significant amount of drug. Hence, the gastric absorption of a large percentage of a dose of salicylate from this constant surface dosage form would be expected to follow zero-order kinetics. For any meaningful *in vivo–in vitro* correlation the dissolution rate method should at least demonstrate the same order of kinetics as the absorption process. The data in Fig. 3 show that this is clearly not the case when dissolution is followed under nonsink conditions.

The appearance of salicylic acid in 0.1 *N* HCl at 50 r.p.m. followed apparent zero-order kinetics up to about 25% of solubility. When the salicylate levels exceeded 30% of solubility, marked deviations from zero-order kinetics were noted and in fact, dissolution appeared to be first order. The apparent zero-order rate constant calculable from the initial dissolution data was 1.15 mg./min./total surface area.

When the dissolution of salicylic acid was followed in 0.1 *N* HCl layered with an organic solvent reservoir a totally different kinetic picture emerged. (See Fig. 3.) After an initial lag phase (required to establish steady state conditions), the rate of appearance of drug in the cyclohexane–octanol phase followed apparent zero-order kinetics. By means of the organic reservoir it was possible to demonstrate that the release rate from the model dosage form of a quantity of drug *in excess* of its total solubility in 0.1 *N* HCl adhered to apparent zero-order kinetics. In the absence of the reservoir it appeared that the release rate of a quantity of drug equal to only 25% of its solubility followed zero-order kinetics.

The zero-order rate constant for appearance of salicylic acid in the organic phase after attainment of steady state, *i.e.*, the apparent zero-order dissolution rate constant, was calculated to be 1.14 mg./min. This value is in agreement with the apparent initial zero-order rate constant of 1.15 mg./min. determined under nonsink conditions. The amount of drug in the aqueous phase after attainment of steady state was calculated by means of Eqs. 6 and 7 and found to be 17.1 mg. Thus, the maximum accumulation of drug in the aqueous phase in the presence of the organic reservoir represented less than 5% of solubility.

The reason for the different dissolution kinetics under nonsink conditions is readily explained by the Noyes-Whitney equation (7). The following example is illustrative. The dissolution of a quantity of drug A_0, in a dosage form designed to provide zero-order release, is followed in a quantity of solvent which is just sufficient to dissolve the total amount of drug in the dosage form, *i.e.*, $X_s = A_0$, where X_s is the total solubility of the drug in the given volume of solvent. Under these conditions, the rate of loss of drug from the dosage form may be expressed as:

$$-dA/dt = k(X_s - X) \qquad \text{(Eq. 8)}$$

where X is the amount of drug in solution at time t. Assuming dissolution rate-limited absorption *in vivo*, or sink conditions *in vitro*, Eq. 8 reduces to a zero-order equation, *i.e.*,

$$-dA/dt = k\,(X_s) = \text{constant} \qquad \text{(Eq. 9)}$$

and

$$A = A_0 - (k \cdot X_s)t \qquad \text{(Eq. 10)}$$

However, under the nonsink conditions in this particular example, Eq. 8 may be expressed as:

$$-dA/dt = k[A_0 - (A_0 - A)] \qquad \text{(Eq. 11)}$$

or

$$-dA/dt = kA \qquad \text{(Eq. 12)}$$

and

$$A = A_0 e^{-kt} \qquad \text{(Eq. 13)}$$

Therefore, a drug which may be absorbed, or dissolve, under sink conditions in a zero-order fashion may demonstrate first-order dissolution kinetics under nonsink conditions.

APPLICATION TO FIRST-ORDER DISSOLUTION

A drug which dissolves from a given dosage form in an apparent first-order fashion (1, 2) will also show marked differences in *in vitro* dissolution kinetics depending on the conditions employed for dissolution rate determination. Using an example similar to the one cited above, one may illustrate these phenomena. The dissolution of a quantity of drug A_0 contained in a dosage form from which first-order release occurs is followed in a quantity of solvent which is just sufficient to dissolve the total amount of drug, *i.e.*, $X_s = A_0$, where X_s is the total solubility of the drug in the given volume of solvent.

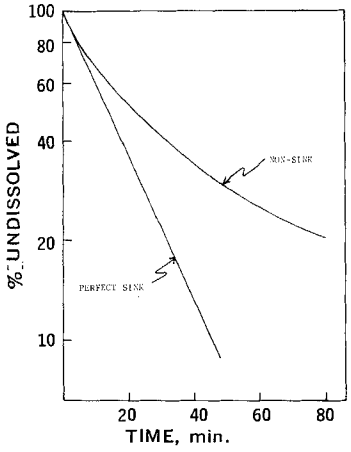

Fig. 4—Plot of per cent drug undissolved from hypothetic dosage form releasing drug in a first-order fashion under perfect sink and nonsink conditions.

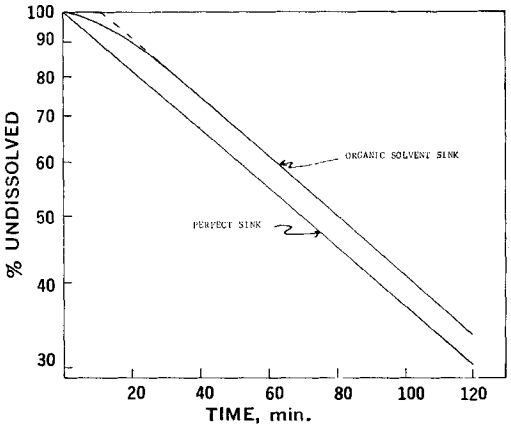

Fig. 5—Plot of per cent drug undissolved from hypothetic dosage form releasing drug in a first-order fashion under perfect sink conditions and under conditions where a perfect sink is approximated by the presence of an organic solvent reservoir.

Under these conditions the rate of loss of drug from the dosage form may be expressed as:[1]

$$-dA/dt = k(X_s - X)A \qquad \text{(Eq. 14)}$$

where X is the amount of drug in solution at time t. Assuming dissolution rate-limited absorption *in vivo* or sink conditions *in vitro*, Eq. 8 reduces to a first-order equation, *i.e.*,

$$-dA/dt = (k\,X_s)A = k'A \qquad \text{(Eq. 15)}$$

and

$$A = A_0 e^{-k't} \qquad \text{(Eq. 16)}$$

However, under the nonsink conditions cited in this example, Eq. 14 may be expressed as:

$$-dA/dt = k[A_0 - (A_0 - A)]A$$

or

$$-dA/dt = kA^2 \qquad \text{(Eq. 17)}$$

Therefore,

$$A = \frac{A_0}{1 + (kA_0)t} = \frac{A_0}{1 + k't} \qquad \text{(Eq. 18)}$$

which represents an integrated form of a *second-order* rate equation.

Figure 4 is a hypothetic plot of first-order loss of drug from a dosage form under perfect sink and nonsink conditions. The marked difference in results clearly reinforces the hypothesis that unless sink conditions are maintained in dissolution rate determinations, *in vitro* results may bear little relationship to *in vivo* observations. The difference between the two plots diminishes as $A_0/X_s \to 0$.

An organic solvent reservoir which functions to maintain approximate sink conditions is also applicable to the determination of first-order dissolution rates. The rate of appearance of drug in the organic phase may be related to the first-order dissolution rate in the aqueous phase by means of the following kinetic model:

$$A \xrightarrow{k'} B \xrightarrow{k_p} C \qquad \text{(Eq. 19)}$$

which is analogous to the model presented in Eq. 1 for zero-order dissolution. If the choice of organic solvent and other experimental conditions are such that $k_p/k' \geqslant 10$, then within a short period of time after initiation of dissolution the appearance of drug in the organic solvent phase may be approximated by the following equation:

$$\ln (A_0 - C) \cong \ln A_0 - k't = \ln A \qquad \text{(Eq. 20)}$$

A hypothetic plot of per cent drug undissolved from a dosage form releasing drug in a first-order fashion (calculated by determining the amount of drug in an organic solvent reservoir phase and subtracting this value from A_0) is illustrated in Fig. 5. This curve is shown in contrast to a curve for the same dissolution process occurring under theoretically perfect sink conditions. The hypothetic conditions were selected such that $k' = 0.01$ min.$^{-1}$ and $k_p = 0.1$ min.$^{-1}$. After an initial lag phase, the curve determined with the use of an organic solvent reservoir parallels exactly the theoretic line. The larger the value of k'/k_p, the shorter will be the lag time before Eq. 20 becomes valid.

Present studies in these laboratories are concerned with the development of methodology for the determination of dissolution rates of poorly water-soluble drugs from disintegrating tablets and capsule dosage forms by means of an organic solvent reservoir for maintenance of sink conditions.

[1] Equation 14 represents a modification of the Noyes-Whitney equation. Since dissolution is apparent first order, it follows that $S \cong k'A$ where S is the surface area.

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