Influence of Shape Factors on Kinetics of Drug Release from Matrix Tablets I: Theoretical

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Abstract □ An expression having a basic cubic form was derived to describe the *in vitro* release of drugs from slow-release tablets formulated with a homogeneous insoluble matrix. While the rate of drug release varies with tablet shape, rate constants that are independent of shape are included in the expression. By comparison with previously published work, it was shown that the rate constants may be described in terms of the physicochemical properties of the tablet constituents and the degree of compression. Therefore, it should be possible to evaluate the rate constants for model formulations and then, using the pertinent release expression, to predict the rate of drug release from tablets having identical compositions but varying widely in shape and size.

Keyphrases □ Tablets, slow release—*in vitro* release from homogeneous insoluble matrix, theory and equations relating release and tablet shape □ Drug release from matrix tablets—relationship between release and tablet shape, theory, equations □ Timed-release tablets—*in vitro* slow release from homogeneous insoluble matrix, effect of tablet shape, theory, equations

The advantages of timed-release medication were noted by Lazarus and Cooper (1), who stated: "The primary advantage of increasing the duration of action of a drug is to prolong its therapeutic effect, particularly where continuous action at an adequate level is essential for mitigation of the disease process itself." Attempts to meet such an aim have been numerous, giving rise to many timed-release dosage forms.

A technique often used in the manufacture of timed-release tablets is to formulate a core of material that slowly releases drug and surround it with a layer containing the same drug in a formulation designed for rapid release (2, 3). In this way, the desired therapeutic blood level of the drug should be rapidly achieved and then maintained over a suitable time. However, in some instances, the outer rapidly releasing layer is not utilized and such dosage forms become, in effect, slow-release tablets. The therapeutic efficacy of slow-release tablets has been investigated for hyoscyamine (4), alprenolol (5, 6), prednisolone (7), potassium chloride (8, 9), norepinephrine chloride (10), and lithium (11).

The purposes of this paper are to propose kinetic expressions for the rate of drug release from slow-release tablets and to relate release to tablet shape. The expressions should be equally valid when applied to the slow-release core of timed-release tablets.

REVIEW OF KINETIC TREATMENT

The release of solutes from nondisintegrating solids has been described by many kinetic theories, some of which apply specifically to slow-release matrix tablets. If it is assumed that the surface area of the solid (tablet) changes negligibly during dissolution (in effect remaining essentially equal to its initial value) and that sink conditions are operative, integration of an equation similar to that used by Nernst and Brunner (12) between time t and zero time will yield:

$$W_0 - W_t = Kt \qquad \text{(Eq. 1)}$$

where W_0 is the initial weight of solute (drug) in the solid (tablet), W_t is the weight of solute (drug) remaining in the solid (tablet) at time t, and K is a proportionality constant having the dimensions of weight per unit time. Dividing through by W_0 and simplifying yield:

$$f_t = K_0 t \qquad \text{(Eq. 2)}$$

where f_t is the fraction of solute (drug) dissolved (released) at time t, and K_0 is the zero-order release rate constant having the dimension of reciprocal time[1]. Thus, a plot of the fraction of drug released against time will be linear if sink conditions are operative and if the exposed surface area is maintained constant. Various workers (13–15) reported data that fit such a plot, either when the exposed surface area was experimentally maintained constant or assumed to be so.

Hixson and Crowell (16, 17), recognizing that the surface area of a regular particle is proportional to the two-thirds power of its volume, derived their classic "cube root law," which may be written as:

$$W_0^{1/3} - W_t^{1/3} = K_s t \qquad \text{(Eq. 4)}$$

where K_s is a constant incorporating the surface-volume proportionality and has the dimensions of the cube root of weight per unit time. This relationship applies to tablets where dissolution takes place normal to the exposed surface, and, if the tablet dimensions decrease in proportion to one another, the exact initial geometric shape of the tablet is maintained at all times. Dividing through by $W_0^{1/3}$, simplifying (see Eq. 3), and rearranging yield:

$$(1 - f_t)^{1/3} = 1 - K_\beta t \qquad \text{(Eq. 5)}$$

where K_β is the release rate constant having the dimension of reciprocal time. Thus, a plot of the cube root of the fraction of drug unreleased against time will be linear if sink conditions are operative and if the tablet dimensions decrease in proportion. Various workers (18–21) reported data that fit such a plot.

Wagner (22–24), assuming that the exposed surface area of a tablet decreased exponentially with time, suggested that drug release from most slow-release tablets could be described adequately by apparent first-order kinetics. In the symbolism of this report:

$$W_t = W_0 e^{-K_1 t} \qquad \text{(Eq. 6)}$$

where K_1 is the apparent first-order rate constant having the dimension of reciprocal time. Dividing through by W_0, simplifying (see Eq. 3), and taking logarithms yield:

$$\ln (1 - f_t) = -K_1 t \qquad \text{(Eq. 7)}$$

Thus, a plot of the logarithm of the fraction of drug unreleased

[1] One of the implied simplifying expressions:

$$f_t = 1 - \frac{W_t}{W_0} \qquad \text{(Eq. 3)}$$

will also be used in later derivations and so is stated explicitly at this juncture.

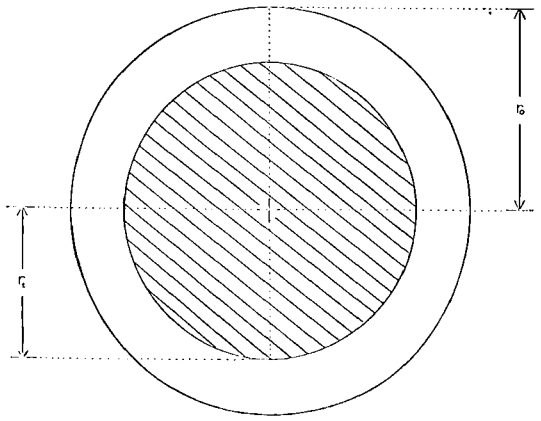

Figure 1—*Bisection of a spherical matrix tablet at time = t. Hatched area is unreleased portion; clear area is ghost portion.*

against time will be linear if sink conditions are operative. Many workers reported data that fit such a plot, and a few examples (13, 25–28) are illustrative of this commonly used plot.

In 1963, Higuchi (29) derived a kinetic theory for a spherical, slow-release pellet having a homogeneous matrix. The system discussed is illustrated in Fig. 1, which shows the situation at time t. Because of the insolubility of the matrix, the pellet still exhibits its initial radius of r_0, but leaching of the drug actually takes place at the release boundary that has a radius of r_t. Between the two radii, there is an already leached region of the sphere, the "ghost" portion, containing the matrix substance only; within the radius r_t, there remains the unreleased portion containing both drug and matrix. If it is assumed that the weight of drug in diffusive passage across the ghost portion is negligible compared to that remaining in the unreleased portion, the weight of drug remaining in the pellet is proportional to the volume (and, hence, the cube of the radius) of the unreleased portion. This assumption, which parallels that of Hixson and Crowell (16, 17), may be expressed for a regular solid as follows (see also Eq. 3):

$$\frac{W_t}{W_0} = \frac{V_t}{V_0} = \left[\frac{r_t}{r_0}\right]^3 = 1 - f_t \qquad \text{(Eq. 8)}$$

where V_t is the volume of the unreleased portion at time t, and V_0 is the initial volume of the unreleased portion and equals the volume of the pellet. By assuming further that the solubility of the drug in the dissolution fluid, C_s, is much less than the weight of drug present per initial tablet volume, A, Higuchi was able to show, in the symbolism of this report:

$$1 - 3\left[\frac{r_t}{r_0}\right]^2 + 2\left[\frac{r_t}{r_0}\right]^3 = Bt \qquad \text{(Eq. 9)}$$

where B is a release rate constant having the dimension of reciprocal time.

Substituting from Eq. 8 and rearranging give:

$$2(1 - f_t) - 3(1 - f_t)^{2/3} = Bt - 1 \qquad \text{(Eq. 10)}$$

This nonlinear equation, which applies only to spherical, slow-release pellets, is conveniently plotted using the fraction of drug released as the ordinate and the square root of time as the abscissa. Higuchi noted that data reported by Simoons (30) fit such a plot when sink conditions are operative.

Another kinetic theory was derived by Higuchi (29). By virtue of its mode of derivation, this theory, which is for tablets having a granular matrix, is limited to release of drug from planar surfaces of constant area; experimentally the area is the initial surface area, S_0. In the symbolism of this report, the equation is:

$$\frac{W_0 - W_t}{S_0} = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 11)}$$

where D is the diffusion coefficient of the drug in the dissolution fluid, ϵ is the porosity of the matrix (ghost portion), and τ is the tortuosity factor of the matrix. After rearranging and dividing through by W_0, the expression may be simplified (see Eq. 3) to give:

$$f_t = K_H t^{1/2} \qquad \text{(Eq. 12)}$$

where K_H may be termed the Higuchi release rate constant having the dimension of the reciprocal of the square root of time[2]. Thus, a plot of the fraction of drug released against the square root of time will be linear if sink conditions are operative. Many workers reported data that fit such a plot, some (31–40) by experimentally maintaining a constant planar surface area and others (27, 28, 41) by assuming it to be so.

THEORETICAL

Boundary Retreat Distance—Because the following derivations apply to slow-release tablets formulated with a homogeneous insoluble matrix, a ghost portion, similar to that illustrated in Fig. 1 will be present once drug release has commenced.

As drug release proceeds, the release boundary, where the actual dissolution of solid drug occurs, retreats further from the tablet edge (Fig. 2). The length of the boundary retreat distance, X_t, increases with time in a manner analogous to that shown by Higuchi (42) for the release of drugs from ointments:

$$X_t = K_b t^{1/2} \qquad \text{(Eq. 14)}$$

where K_b is the boundary retreat rate constant having the dimensions of length per unit square root of time. It may be expected that the magnitude of this constant will be dependent on the physical properties of the drug and tablet excipients and on the compaction pressure used in manufacturing the tablet; however, the constant is independent of both the shape and dimensions of the tablet.

Tablet Shapes and Boundary Retreat Distance—Two shapes predominate among commercially available tablets. The first is cylindrical; the second is biconvex, which may be visualized as a cylinder with a spherical segment added above and below.

If dissolution takes place normal to the release boundary (16, 17, 29), the boundary retreat distance, X_t, will be equal in all directions. The situation is shown in Fig. 3 for a cylindrical tablet and in Fig. 4 for a biconvex tablet. For the former, both the initial tablet radius, r_0, and half the initial tablet height, h_0, are reduced at time t to:

$$r_t = r_0 - X_t \qquad \text{(Eq. 15)}$$

and:

$$h_t = h_0 - X_t \qquad \text{(Eq. 16)}$$

where r_t and h_t are the parameters at time t. For the biconvex tablet, a geometric analysis reveals the following parameter reductions at time t:

$$r_t = r_0 - X_t \qquad \text{(Eq. 15)}$$

$$R_t = R_0 - X_t \qquad \text{(Eq. 17)}$$

where R_t and R_0 are the radii of the spherical segment:

$$HE_t = HE_0 - Y_t \qquad \text{(Eq. 18)}$$

where HE_t and HE_0 are half the heights of the tablet edge and Y_t is the dependent boundary retreat distance, and:

$$HD_t = HD_0 - (X_t - Y_t) \qquad \text{(Eq. 19)}$$

[2] The implied simplifying expression:

$$K_H = \frac{S_0}{W_0}\sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 13)}$$

will be useful in the further theoretical development and is stated explicitly at this juncture.

where HD_t and HD_0 are the heights of the spherical segment.

Release Rate Constant—To simplify further derivations for both tablet shapes, it is convenient to divide the boundary retreat distance (Eq. 14) by the initial tablet radius to give:

$$\frac{X_t}{r_0} = \left(\frac{K_b}{r_0}\right)t^{1/2} \quad \text{(Eq. 20)}$$

If:

$$\frac{K_b}{r_0} = K_r \quad \text{(Eq. 21)}$$

then:

$$\frac{X_t}{r_0} = K_r t^{1/2} \quad \text{(Eq. 22)}$$

where K_r is the release rate constant having only the dimension of the reciprocal of the square root of time. While its magnitude is independent of tablet shape, it is dependent on the tablet radius.

Kinetic Expression for Cylindrical Tablet—*Step 1*—The tablet parameters at time t are restated in terms of the initial tablet radius, r_0, and the boundary retreat distance, X_t. If:

$$q = \frac{r_0}{h_0} \quad \text{(Eq. 23)}$$

where q is a ratio factor, then Eq. 16 modifies to:

$$h_t = \frac{r_0}{q} - X_t \quad \text{(Eq. 24)}$$

The tablet radius at time t needs no restatement (Eq. 15).

Step 2—The volume of the cylindrical unreleased portion at time t is given by (43):

$$V_t = 2\pi r_t^2 h_t \quad \text{(Eq. 25)}$$

Substituting from Eqs. 15 and 24 gives:

$$V_t = 2\pi(r_0 - X_t)^2(r_0/q - X_t) \quad \text{(Eq. 26)}$$

Expanding gives:

$$V_t = 2\pi\left[\frac{r_0^3}{q} - r_0^2 X_t\left(1 + \frac{2}{q}\right) + r_0 X_t^2\left(2 + \frac{1}{q}\right) - X_t^3\right] \quad \text{(Eq. 27)}$$

Rearranging gives:

$$V_t = \frac{2\pi r_0^3}{q}\left[1 - (q+2)\frac{X_t}{r_0} + (2q+1)\frac{X_t^2}{r_0^2} - \frac{qX_t^3}{r_0^3}\right] \quad \text{(Eq. 28)}$$

But from Eq. 23 and a knowledge of mensuration (43):

$$\frac{2\pi r_0^3}{q} = 2\pi r_0^2 h_0 = V_0 \quad \text{(Eq. 29)}$$

Substituting into Eq. 28 and rearranging yield:

$$1 - \frac{V_t}{V_0} = (q+2)\frac{X_t}{r_0} - (2q+1)\frac{X_t^2}{r_0^2} + \frac{qX_t^3}{r_0^3} \quad \text{(Eq. 30)}$$

This expression shows the fractional loss in volume of the unreleased portion at time t.

Step 3—Substituting from Eq. 22 gives:

$$1 - \frac{V_t}{V_0} = (q+2)K_r t^{1/2} - (2q+1)(K_r t^{1/2})^2 + q(K_r t^{1/2})^3 \quad \text{(Eq. 31)}$$

If the drug is homogeneously distributed throughout the matrix tablet (29), and if the weight of drug in diffusive passage across the ghost portion is negligible compared to that remaining in the unreleased portion (29), then by substitution from Eq. 8:

$$f_t = (q+2)K_r t^{1/2} - (2q+1)(K_r t^{1/2})^2 + q(K_r t^{1/2})^3 \quad \text{(Eq. 32)}$$

This is the final kinetic expression, having a cubic form, that relates the fraction of drug released to time for a cylindrical tablet. While in theory the value of q may be infinitely variable, elegant tablets are manufactured with $q > 1$.

Kinetic Expression for Biconvex Tablet—This derivation is more complex but proceeds *via* the same steps as the cylindrical tablet derivation.

Step 1—The ratio of Y_t to X_t varies with the time of dissolution. The value of Y_t may be expressed by:

$$Y_t = \frac{Z_t}{K_r}(X_t) \quad \text{(Eq. 33)}$$

where Z_t is a simplifying factor that varies with time. The derivation of Eq. 33 is shown in the *Appendix*. If:

$$p = \frac{r_0}{HD_0} \quad \text{(Eq. 34)}$$

where p is a ratio factor, then Eq. 19 modifies to:

$$HD_t = \frac{r_0}{p} - (X_t - Y_t) \quad \text{(Eq. 35)}$$

Substituting from Eq. 33 gives:

$$HD_t = \frac{r_0}{p} - X_t(1 - Z_t/K_r) \quad \text{(Eq. 36)}$$

Consideration of Fig. 4 shows that:

$$HE_t = h_t - HD_t \quad \text{(Eq. 37)}$$

Substituting from Eqs. 24 and 36 and rearranging give:

$$HE_t = r_0(1/q - 1/p) - \frac{Z_t}{K_r}(X_t) \quad \text{(Eq. 38)}$$

Step 2—The volume of the biconvex unreleased portion at time t is given by the sum of the volume of the cylindrical portion and the volume of two spherical segments (43):

$$V_t = \pi\left[\frac{HD_t^3}{3} + r_t^2(HD_t + 2HE_t)\right] \quad \text{(Eq. 39)}$$

Substituting from Eqs. 15, 36, and 38 and expanding yield:

$$V_t = \pi\left[\frac{r_0^3}{3p^3q}\{6p^3 - 3p^2q + q\} - \frac{r_0^2 X_t}{p^2 q}\left\{4p^2 + p^2q - 2pq + q + \left(\frac{Z_t}{K_r}\right)q(p^2-1)\right\} + \frac{r_0 X_t^2}{pq}\left\{2p + 2pq + \left(\frac{Z_t}{K_r}\right)2q(p-1) + \left(\frac{Z_t^2}{K_r^2}\right)q\right\} - \frac{X_t^3}{3}\left\{4 + 3\left(\frac{Z_t^2}{K_r^2}\right) - \frac{Z_t^3}{K_r^3}\right\}\right] \quad \text{(Eq. 40)}$$

It is helpful to use five simplifying constants, C_3–C_7:

$$C_3 = 6p^3 - 3p^2q + q \quad \text{(Eq. 41)}$$

$$C_4 = 4p^2 + p^2q - 2pq + q \quad \text{(Eq. 42)}$$

$$C_5 = 2p + 2pq \quad \text{(Eq. 43)}$$

$$C_6 = q(p^2 - 1) \quad \text{(Eq. 44)}$$

$$C_7 = 2q(p-1) \quad \text{(Eq. 45)}$$

With these constants included:

$$V_t = \pi\left[C_3\frac{r_0^3}{3p^3q} - \frac{r_0^2 X_t}{p^2 q}\left\{C_4 + C_6\left(\frac{Z_t}{K_r}\right)\right\} + \frac{r_0 X_t^2}{pq}\left\{C_5 + C_7\left(\frac{Z_t}{K_r}\right) + q\left(\frac{Z_t^2}{K_r^2}\right)\right\} - \frac{X_t^3}{3}\left\{4 + 3\left(\frac{Z_t^2}{K_r^2}\right) - \frac{Z_t^3}{K_r^3}\right\}\right] \quad \text{(Eq. 46)}$$

Rearranging gives:

$$V_t = \pi r_0^3\left(\frac{C_3}{3p^3q}\right)\left[1 - \frac{3p}{C_3}\left\{C_4 + C_6\left(\frac{Z_t}{K_r}\right)\right\}\frac{X_t}{r_0} + \frac{3p^2}{C_3}\left\{C_5 + C_7\left(\frac{Z_t}{K_r}\right) + q\left(\frac{Z_t^2}{K_r^2}\right)\right\}\frac{X_t^2}{r_0^2} - \frac{p^3 q}{C_3}\left\{4 + 3\left(\frac{Z_t^2}{K_r^2}\right) - \frac{Z_t^3}{K_r^3}\right\}\frac{X_t^3}{r_0^3}\right] \quad \text{(Eq. 47)}$$

But from Eqs. 23, 34, and 41, the zero-time equivalent of Eq. 37, and a knowledge of mensuration (43):

$$\pi r_0^3\left(\frac{C_3}{3p^3q}\right) = \pi\left[\frac{HD_0^3}{3} + r_0^2(HD_0 + 2HE_0)\right] = V_0 \quad \text{(Eq. 48)}$$

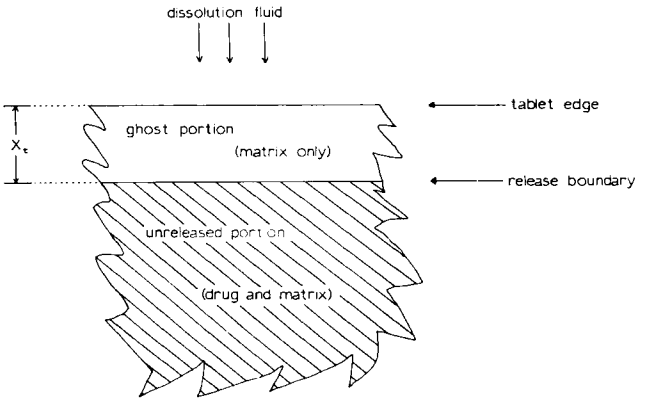

Figure 2—*Vertical bisection of a matrix tablet at time = t, showing the inward retreat of the release boundary.*

Substituting into Eq. 47 and rearranging give:

$$1-\frac{V_t}{V_0}=\frac{3p}{C_3}\left\{C_4+C_6\left(\frac{Z_t}{K_r}\right)\right\}\frac{X_t}{r_0}-\frac{3p^2}{C_3}\left\{C_5+C_7\left(\frac{Z_t}{K_r}\right)+q\left(\frac{Z_t^2}{K_r^2}\right)\right\}\frac{X_t^2}{r_0^2}+\frac{p^3q}{C_3}\left\{4+3\left(\frac{Z_t^2}{K_r^2}\right)-\frac{Z_t^3}{K_r^3}\right\}\frac{X_t^3}{r_0^3} \quad \text{(Eq. 49)}$$

Step 3—Substituting from Eq. 22, with the assumptions made previously (29), gives:

$$f_t=\frac{3p}{C_3}\left\{C_4+C_6\left(\frac{Z_t}{K_r}\right)\right\}K_rt^{1/2}-\frac{3p^2}{C_3}\left\{C_5+C_7\left(\frac{Z_t}{K_r}\right)+q\left(\frac{Z_t^2}{K_r^2}\right)\right\}(K_rt^{1/2})^2+\frac{p^3q}{C_3}\left\{4+3\left(\frac{Z_t^2}{K_r^2}\right)-\frac{Z_t^3}{K_r^3}\right\}(K_rt^{1/2})^3 \quad \text{(Eq. 50)}$$

This is the final kinetic expression, having a basic cubic form, that relates the fraction of drug released to time for a biconvex tablet. While in theory the values of q and p may be infinitely variable, elegant tablets are manufactured with $q > 1$ and $p > 1$.

Special Condition of Derived Biconvex Tablet Expression—A spherical tablet may be considered a limited form of a biconvex tablet in which the two hemispheres are joined base to base. The height of each hemisphere is then half the tablet height, which in turn is equal to the radius of each hemisphere:

$$HD_0 = h_0 = r_0 \quad \text{(Eq. 51)}$$

It thus follows from Eqs. 23 and 34 that:

$$q = p = 1 \quad \text{(Eq. 52)}$$

Furthermore, the values of C_3–C_5 (Eqs. 41–43) become:

$$C_3 = C_4 = C_5 = 4 \quad \text{(Eq. 53)}$$

For a hemisphere, it may be shown (see *Appendix*) that:

$$Z_t = 0 \quad \text{(Eq. 54)}$$

Substituting from Eqs. 52–54 in Eq. 50 yields:

$$f_t = 3K_rt^{1/2} - 3(K_rt^{1/2})^2 + (K_rt^{1/2})^3 \quad \text{(Eq. 55)}$$

This final kinetic expression for a spherical tablet (which is virtually nonexistent commercially) could also have been derived by a route analogous to that used for cylindrical and biconvex tablets.

Summarized Expressions—The three derived expressions (Eqs. 32, 50, and 55) all have a basic cubic form, so they may be summarized:

$$f_t = G_1K_rt^{1/2} - G_2(K_rt^{1/2})^2 + G_3(K_rt^{1/2})^3 \quad \text{(Eq. 56)}$$

where G_1–G_3 may be termed shape factors; their values are shown in Table I. This summarized expression, which contains the radius-dependent release rate constant, K_r, may be modified

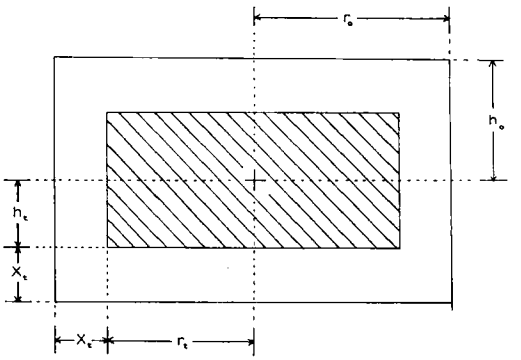

Figure 3—*Vertical bisection of a cylindrical matrix tablet at time = t. Hatched area is unreleased portion; clear area is ghost portion.*

using Eq. 21 to give an expression containing the boundary retreat rate constant, K_b, which is independent of the initial tablet radius as well as of the tablet shape:

$$f_t = \frac{G_1}{r_0}K_bt^{1/2} - \frac{G_2}{r_0^2}(K_bt^{1/2})^2 + \frac{G_3}{r_0^3}(K_bt^{1/2})^3 \quad \text{(Eq. 57)}$$

It should be recognized that, for biconvex tablets, the values of the shape factors would also require modification to replace K_r with K_b.

DISCUSSION

To compare the effect of shape alone on the release of drugs, all parameters other than shape must be standardized. Thus the tablet formulation, the initial tablet weight, the initial tablet radius, the degree of compression (and, hence, the initial tablet volume), and the dissolution test conditions should be the same for different tablet shapes. The parameters of three example tablets, identical in all respects except shape, are shown in Table II together with the times for half and complete release of drug. Their release plots are shown in Fig. 5 using the graphical coordinates analogous to those chosen by Higuchi (29): fraction of drug released and the square root of time. For a series of tablets identical in every respect but shape, a comparison of release plots indicates that the differences in rates of release are related to the shape factors.

Thus, it should be possible to prepare a pilot tablet (of any suitable shape) of a slow-release matrix formulation and determine the boundary retreat rate constant, K_b, of that formulation under the compaction load used. From this knowledge, the release rate constant, K_r, for tablets having the same formulation, but with any desired initial radius, initial volume, and shape, may be calculated providing the compaction load is the same. Furthermore, the rate of drug release from such tablets can be predicted.

Release from One Planar Surface of Cylindrical Tablet—

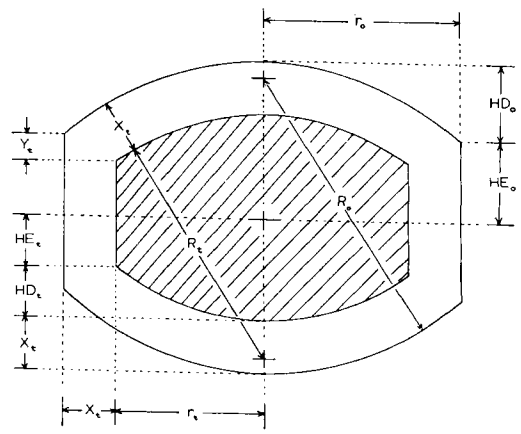

Figure 4—*Vertical bisection of a biconvex matrix tablet at time = t. Hatched area is unreleased portion; clear area is ghost portion.*

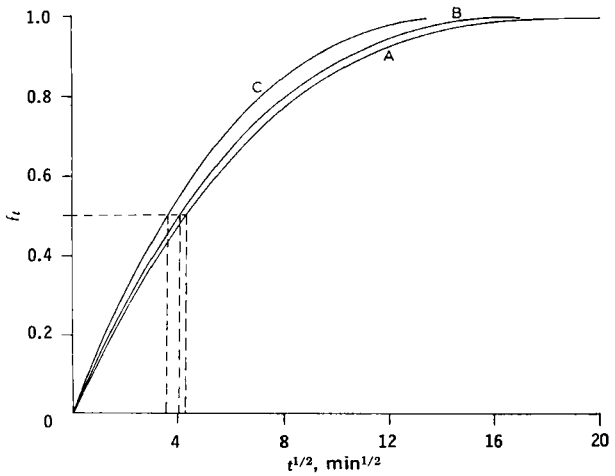

Figure 5—*Theoretical Higuchi plot of the fraction of drug released,* f_t, *with time,* t, *from matrix tablets identical in all respects except shape. Key: A, spherical; B, biconvex; and C, cylindrical. Curves were computed using the parameters listed in Table II and the release equations listed in Table I.*

The release of drugs from many cylindrical, slow-release tablets has been tested by experimentally maintaining a constant surface area (31–40). An impermeable barrier of some kind is maintained, allowing access of the dissolution fluid to one planar surface only; these dissolution conditions are shown in Fig. 6. A kinetic expression may be derived with Step 1 being identical to that for cylindrical tablets having all surfaces exposed to the dissolution fluid (Eqs. 15, 23, and 24).

Step 2—The volume of the cylindrical unreleased portion at time t is given by (43):

$$V_t = \pi r_0^2(2h_0 - X_t) \qquad \text{(Eq. 58)}$$

Substituting from Eq. 23 and manipulating as before give:

$$1 - \frac{V_t}{V_0} = \frac{q}{2}\left(\frac{X_t}{r_0}\right) \qquad \text{(Eq. 59)}$$

Step 3—Substituting from Eq. 22, with the assumptions made previously (29), gives:

$$f_t = \frac{q}{2}(K_r t^{1/2}) \qquad \text{(Eq. 60)}$$

Or, substituting from Eqs. 21 and 23 gives:

$$f_t = \frac{1}{2h_0}(K_b t^{1/2}) \qquad \text{(Eq. 61)}$$

where $2h_0$ is the initial tablet height. These are the final kinetic expressions relating the fraction of drug released to time t for a cylindrical tablet tested when only one planar surface of constant area is exposed to the dissolution fluid. Hence, it is valid to compare Eqs. 60 and 61 with Eq. 12, in which case:

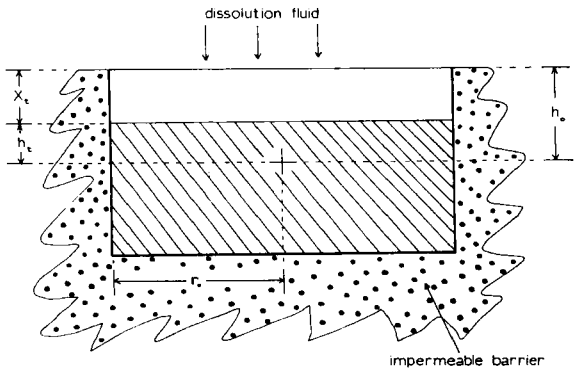

Figure 6—*Vertical bisection of a cylindrical matrix tablet at time* = t *where dissolution takes place from one constant planar surface only. Hatched area is unreleased portion; clear area is ghost portion.*

Table I—Values of Shape Factors in Release Expressions Derived for Three Shapes of Slow-Release Tablets

Shape Factor	Tablet Shape: Spherical	Cylindrical	Biconvex[a]
G_1	3	$q + 2$	$\frac{3p}{C_3}\left\{C_4 + C_6\left(\frac{Z_t}{K_r}\right)\right\}$
G_2	3	$2q + 1$	$\frac{3p^2}{C_3}\left\{C_5 + C_7\left(\frac{Z_t}{K_r}\right) + q\left(\frac{Z_t^2}{K_r^2}\right)\right\}$
G_3	1	q	$\frac{p^3q}{C_3}\left\{4 + 3\left(\frac{Z_t^2}{K_r^2}\right) - \frac{Z_t^3}{K_r^3}\right\}$
	Eq. 55	Eq. 32	Eq. 50

[a] Each value of K_r may be substituted by K_b/r_0 (see Eq. 21).

$$K_r = \frac{2K_H}{q} \qquad \text{(Eq. 62)}$$

and:

$$K_b = 2h_0K_H \qquad \text{(Eq. 63)}$$

Thus the rate constants of this paper may be related to a constant analogous to that derived by Higuchi (29). Furthermore, pilot studies of rate constants, made when only one planar surface of constant area is exposed to the dissolution fluid, may be used to predict the rates of release from tablets of the same formulation with all surfaces exposed, even though they have different shapes, initial radii, and initial volumes; however, the degree of compression must be the same.

Fundamental Parameters of Rate Constants—By definition:

$$W_0 = AV_0 \qquad \text{(Eq. 64)}$$

For a cylindrical tablet with one constant planar surface exposed to the dissolution fluid:

$$W_0 = A\left(\frac{2\pi r_0^3}{q}\right) \qquad \text{(Eq. 65)}$$

and:

$$S_0 = \pi r_0^2 \qquad \text{(Eq. 66)}$$

Substituting Eqs. 65 and 66 into Eq. 13 and simplifying yield:

$$K_H = \frac{q}{2Ar_0}\sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 67)}$$

Substituting into Eq. 62 and simplifying yield:

$$K_r = \frac{1}{Ar_0}\sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 68)}$$

Substituting from Eq. 21 gives:

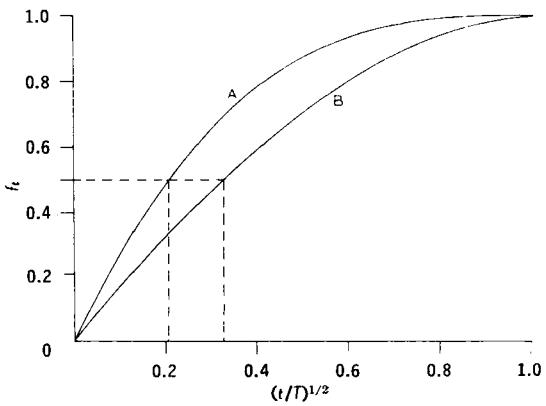

Figure 7—*Comparison of the fraction of drug released,* f_t, *with time,* t, *from spherical matrix tablets. The time is expressed as a fraction of the time for complete release* (T). *Key: A, Eq. 74; and B, Eq. 75.*

Table II—Parameters and Release Times of Drug from Three Slow-Release Tablets Identical in All Respects Except Shape

Tablet Shape	Parameters						Release Times, min	
	K_r, min^{-1}	r_0, mm	V_0, mm^3	q	p	a	Half-Release	Complete Release
Spherical (Eq. 55)	0.05	3.0	113.1	—	—	—	17.02	400.0
Cylindrical (Eq. 32)	0.05	3.0	113.1	1.500	—	—	12.37	177.8
Biconvex (Eq. 50)	0.05	3.0	113.1	1.179	2.618	1.500[a]	15.64	287.9

[a] This value of $a = R_0/r_0$ is common for "extra deep" biconvex tablets (46).

$$K_b = \frac{1}{A}\sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 69)}$$

Hence it is shown that the boundary retreat rate constant, K_b, depends only on the physicochemical properties of the tablet constituents and the degree of compression, whereas the release rate constant, K_r, also depends on the initial tablet radius. While it should be feasible to calculate the values of K_b and K_r from measurements of their fundamental parameters, in practical terms it is probably easier to determine the constants by direct release studies. For both rate constants to be algebraically valid, $2A > \epsilon C_s$ to comply with the assumption that the weight of drug in diffusive passage across the ghost portion is negligible compared to that remaining in the unreleased portion. Higuchi (29) noted that A should be greater than ϵC_s by a factor of three or four.

Time for Complete Release—Consideration of Figs. 3 and 4 reveals that at complete release ($f_t = 1$) for a tablet where $q > 1$:

$$X_t = h_0 \qquad \text{(Eq. 70)}$$

(where $h_0 = HE_0 + HD_0$ for biconvex tablets). Substituting in Eq. 23 gives:

$$q = \frac{r_0}{X_t} \qquad \text{(Eq. 71)}$$

Substituting into Eq. 22 gives:

$$\frac{1}{q} = K_r T^{1/2} \qquad \text{(Eq. 72)}$$

where T is the value of t when $f_t = 1$. Thus:

$$K_r = \frac{1}{qT^{1/2}} \qquad \text{(Eq. 73)}$$

Hence, Eq. 56 may be rewritten:

$$f_t = \frac{G_1}{q}\left\{\frac{t^{1/2}}{T^{1/2}}\right\} - \frac{G_2}{q^2}\left\{\frac{t^{1/2}}{T^{1/2}}\right\}^2 + \frac{G_3}{q^3}\left\{\frac{t^{1/2}}{T^{1/2}}\right\}^3 \qquad \text{(Eq. 74)}$$

For spherical tablets, where $q = 1$, it is therefore possible to prepare a standard plot of fraction released against the fraction of the square root of time for complete release. Such a plot is shown in Fig. 7, and it may be calculated that half-release occurs when $t^{1/2}/T^{1/2} = 0.2063$. In other words, for a spherical matrix tablet, the first 50% of the release occurs in approximately the first 4.5% of the complete release time.

Uniqueness of Release Expressions—To demonstrate that the expressions derived for spherical (Eq. 55), cylindrical (Eq. 32), and biconvex (Eq. 50) tablets are unique, the data used to plot Fig. 5 were also plotted on apparent first-order coordinates (Fig. 8) and Hixon–Crowell coordinates (Fig. 9). As can be seen, the data do not give linear plots.

In Fig. 7 a comparison is made between the release profiles of spherical tablets as predicted by the standard expression (Eq. 74) and as predicted from Higuchi (29); to effect comparison, Eq. 10 has been modified by setting $T = t$ when $f_t = 1$ to give finally:

$$2(1 - f_t) - 3(1 - f_t)^{2/3} = \frac{t}{T} - 1 \qquad \text{(Eq. 75)}$$

The different profiles result from different assumptions concerning the concentration gradient of the drug in passage across the ghost portion. It is possible to obtain the derived expression by use of Fick's first law (44) by assuming the concentration gradient to be uniform; Higuchi, however, considered a nonuniform concentration gradient.

Experimental work to test the derived expressions has been performed and the results are presented in a following paper (45).

APPENDIX

Relationship of Dependent Boundary Retreat Distance, Y_t, to Boundary Retreat Distance, X_t—There are two mensuration formulas (43) for the volume of a spherical segment at time t:

$$VD_t = \frac{\pi}{3}HD_t(3R_t - HD_t) \qquad \text{(Eq. A1)}$$

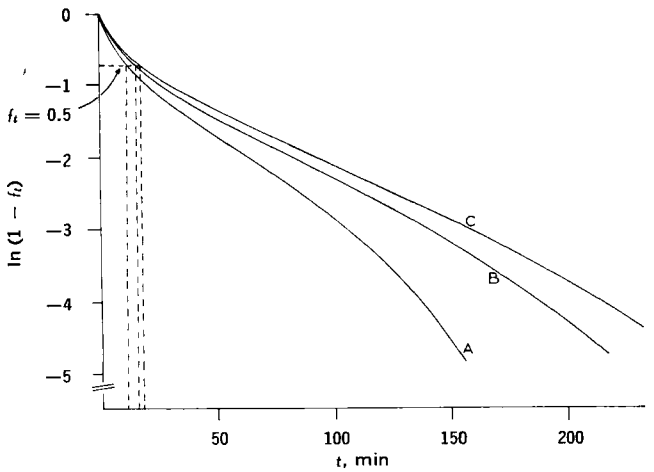

Figure 8—*Theoretical apparent first-order plot of the fraction of drug unreleased, 1 − f_t, with time, t, from matrix tablets identical in all respects except shape. Key: A, spherical; B, biconvex; and C, cylindrical.*

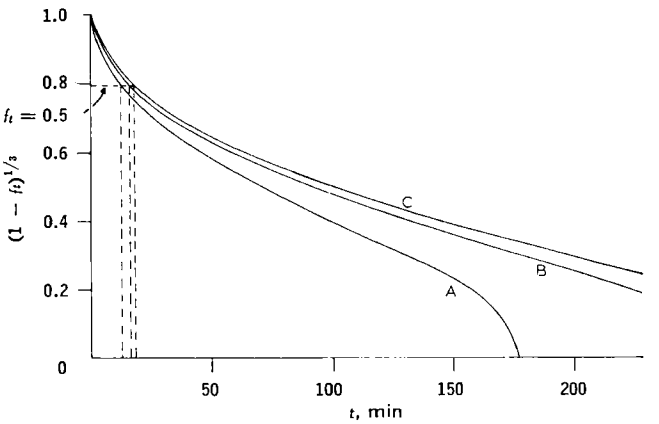

Figure 9—*Theoretical Hixson–Crowell plot of the fraction of drug unreleased, 1 − f_t, with time, t, from matrix tablets identical in all respects except shape. Key: A, spherical; B, biconvex; and C, cylindrical.*

and:

$$VD_t = \frac{\pi}{6} HD_t(HD_t^2 - 3r_t^2) \qquad \text{(Eq. A2)}$$

Equating the two:

$$HD_t^2 - 2R_tHD_t + r_t^2 = 0 \qquad \text{(Eq. A3)}$$

For a biconvex tablet, where $HD_t < R_t$, the real root of the quadratic equation is:

$$HD_t = R_t - [R_t^2 - r_t^2]^{1/2} \qquad \text{(Eq. A4)}$$

Substituting from Eqs. 15 and 17 gives:

$$HD_t = R_0 - X_t - [R_0^2 - r_0^2 - 2R_0X_t - 2r_0X_t]^{1/2} \qquad \text{(Eq. A5)}$$

If:

$$a = \frac{R_0}{r_0} \qquad \text{(Eq. A6)}$$

where a is a ratio factor, then Eq. A5 modifies to:

$$HD_t = ar_0 - X_t - [r_0^2(a^2 - 1) - X_tr_02(a - 1)]^{1/2} \qquad \text{(Eq. A7)}$$

At zero time (when $X_t = 0$), Eq. A7 becomes:

$$HD_0 = ar_0 - [r_0^2(a^2 - 1)]^{1/2} \qquad \text{(Eq. A8)}$$

Substituting from Eqs. A7 and A8 into Eq. 19 and simplifying yield:

$$Y_t = [r_0^2(a^2 - 1)]^{1/2} - [r_0^2(a^2 - 1) - X_tr_02(a - 1)]^{1/2} \qquad \text{(Eq. A9)}$$

Rearranging gives:

$$Y_t = r_0(a^2 - 1)^{1/2} - r_0\left[(a^2 - 1) - \frac{X_t}{r_0}2(a - 1)\right]^{1/2} \qquad \text{(Eq. A10)}$$

Let C_1 and C_2 be two simplifying constants:

$$C_1 = a^2 - 1 \qquad \text{(Eq. A11)}$$

$$C_2 = 2(a - 1) \qquad \text{(Eq. A12)}$$

Simplifying Eq. A10 gives:

$$Y_t = r_0[(C_1)^{1/2} - (C_1 - \left(\frac{X_t}{r_0}\right)C_2)^{1/2}] \qquad \text{(Eq. A13)}$$

Substituting from Eq. 22 for r_0 gives:

$$Y_t = \frac{X_t}{K_rt^{1/2}}[(C_1)^{1/2} - (C_1 - K_rt^{1/2}C_2)^{1/2}] \qquad \text{(Eq. A14)}$$

If:

$$Z_t = \frac{1}{t^{1/2}}\ [(C_1)^{1/2} - (C_1 - K_rt^{1/2}C_2)^{1/2}] \qquad \text{(Eq. A15)}$$

where Z_t is a simplifying factor that varies with time, then Eq. A15 modifies to:

$$Y_t = \frac{Z_t}{K_r}(X_t) \qquad \text{(Eq. A16 or 33)}$$

For a hemisphere, $a = 1$. Hence:

$$C_1 = 0 \qquad \text{(Eq. A17)}$$

$$C_2 = 0 \qquad \text{(Eq. A18)}$$

It follows that:

$$Z_t = 0 \qquad \text{(Eq. A19)}$$

Linear Representation of Spherical Tablet Release Expression—The release expression for a spherical tablet (Eq. 55) is identical to:

$$(1 - f_t)^{1/3} = 1 - K_rt^{1/2} \qquad \text{(Eq. A20)}$$

Equation A20 is analogous to Eq. 5, the Hixson–Crowell "cube root law" (16, 17). Hence, estimates of the release rate constant, K_r, and the boundary retreat rate constant, K_b, may be found from a linear plot as illustrated in Fig. 10.

Such a linear representation is not possible for the release of drug from cylindrical or biconvex tablets because the dimensions of the unreleased portions do not decrease in proportion to one another as drug release proceeds. In addition, the linear representation of nonlinear release (dissolution) data can give rise to slope inaccuracies at high f_t values[3].

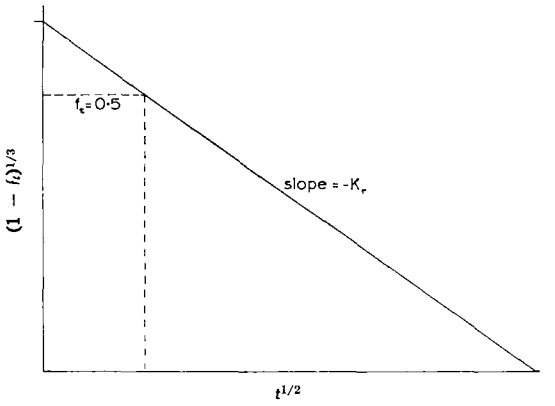

Figure 10—*Fraction of drug unreleased, 1 − f_t, with time, t, from a spherical matrix tablet, showing an analogy with Hixson–Crowell kinetics. See Eq. A20.*

REFERENCES

(1) J. Lazarus and J. Cooper, *J. Pharm. Sci.*, **50**, 715(1961).

(2) E. Stempel, *Drug Cosmet. Ind.*, **98**, 36(1966).

(3) R. F. Shangraw, *Hosp. Pharm.*, **2**, 19(1967).

(4) A. Brändström and J. Sjögren, *Acta Pharm. Suecica*, **4**, 157(1967).

(5) G. Johnsson, J. Sjögren, and L. Sölvell, *Eur. J. Clin. Pharmacol.*, **3**, 74(1971).

(6) R. Johansson, C. G. Regärdh, and J. Sjögren, *Acta Pharm. Suecica*, **8**, 59(1971).

(7) P. F. D'Arcy, J. P. Griffin, J. S. Jenkins, W. F. Kirk, and A. W. C. Peacock, *J. Pharm. Sci.*, **60**, 1028(1971).

(8) J. Weiss, *Acta Pharm. Suecica*, **8**, 661(1971).

(9) D. Ben-Ishay and K. Engelman, *Clin. Pharmacol. Ther.*, **14**, 250(1973).

(10) N. O. Lindberg and C. G. A. Persson, *Acta Pharm. Suecica*, **9**, 237(1972).

(11) U. Otto, L. Paalzow, and G. Suren, *ibid.*, **9**, 595(1972).

(12) W. Nernst and E. Brunner, *J. Amer. Chem. Soc.*, **47**, 52(1904).

(13) M. Gibaldi and S. Feldman, *J. Pharm. Sci.*, **56**, 1238(1967).

(14) H. Weintraub and M. Gibaldi, *ibid.*, **59**, 1792(1970).

(15) A. G. Mitchell and D. J. Saville, *J. Pharm. Pharmacol.*, **21**, 28(1969).

(16) A. W. Hixson and J. H. Crowell, *Ind. Eng. Chem.*, **23**, 923(1931).

(17) *Ibid.*, **23**, 1002(1931).

(18) E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 269(1955).

(19) W. I. Higuchi, E. L. Parrott, D. E. Wurster, and T. Higuchi, *ibid.*, **47**, 376(1958).

(20) D. E. Wurster and J. A. Seitz, *ibid.*, **49**, 335(1960).

(21) F. Langenbucher, *J. Pharm. Sci.*, **58**, 1265(1969).

(22) J. G. Wagner, *ibid.*, **58**, 1253(1969).

(23) J. G. Wagner, *Drug Stand.*, **27**, 178(1959).

(24) *Ibid.*, **28**, 30(1960).

(25) L. C. Shroeter, J. E. Tingstad, E. L. Knoechel, and J. G. Wagner, *J. Pharm. Sci.*, **51**, 865(1962).

(26) J. Lazarus, M. Pagliery, and L. Lachman, *ibid.*, **53**, 798(1964).

(27) J. B. Schwartz, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **57**, 274(1968).

(28) D. C. Baun and G. C. Walker, *Pharm. Acta Helv.*, **46**, 94(1971).

(29) T. Higuchi, *J. Pharm. Sci.*, **52**, 1145(1963).

(30) J. R. A. Simoons, "Formulation and Experimental Evalu-

[3] J. Cobby, M. Mayersohn, and B. Farlinger, to be published.

ation of Oral Sustained Release Medication Based on the Principle of Delayed Diffusion," Drukkerij Wed. G. Van Soest N. V., Amsterdam, The Netherlands, 1962.
(31) S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **54**, 1459(1965).
(32) S. J. Desai, P. Singh, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **55**, 1224(1966).
(33) *Ibid.*, **55**, 1230(1966).
(34) *Ibid.*, **55**, 1235(1966).
(35) P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **56**, 1542(1967).
(36) *Ibid.*, **56**, 1548(1967).
(37) *Ibid.*, **57**, 217(1968).
(38) H. Lapidus and N. G. Lordi, *J. Pharm. Sci.*, **55**, 840(1966).
(39) *Ibid.*, **57**, 1292(1968).
(40) B. Farhadieh, S. Borodkin, and J. D. Buddenhagen, *J. Pharm. Sci.*, **60**, 209(1971).
(41) J. B. Schwartz, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **57**, 278(1968).
(42) T. Higuchi, *ibid.*, **50**, 874(1961).
(43) "Handbook of Chemistry and Physics," 49th ed., The Chemical Rubber Co., Cleveland, Ohio, 1968, pp. A-256–A-259.
(44) A. Fick, *Ann. Phys.*, **170**, 59(1855).
(45) J. Cobby, M. Mayersohn, and G. C. Walker, *J. Pharm. Sci.*, **63**, 732(1974).
(46) Concavity Chart, Stokes Compacting Equipment, Rexdale, Ontario, Canada.

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Influence of Shape Factors on Kinetics of Drug Release from Matrix Tablets II: Experimental

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Abstract □ Tablets were prepared from two slow-release formulations, both containing stearyl alcohol as a homogeneous insoluble matrix. The release of salicylic acid and of ephedrine was measured *in vitro*. It was found that the release profiles could be described by a nonlinear expression for both cylindrical and biconvex tablets. Even though the rate of drug release varied noticeably with tablet shape, regression analysis of the release data indicated that the rate constants included in the expression did not vary significantly ($p = 0.05$) with shape for tablets of the same overall composition.

Keyphrases □ Tablets, slow release—release of salicylic acid and ephedrine from homogeneous insoluble matrix (stearyl alcohol), experimental relationship between release and tablet shape □ Drug release from matrix tablets—experimental relationship between release and tablet shape, salicylic acid and ephedrine from stearyl alcohol □ Timed-release tablets—slow release of salicylic acid and ephedrine from homogeneous insoluble matrix (stearyl alcohol), effect of tablet shape

In a previous report (1), an expression, having a cubic form, was presented describing the dissolution kinetics of a drug from a slow-release matrix tablet:

$$f_t = G_1K_rt^{1/2} - G_2(K_rt^{1/2})^2 + G_3(K_rt^{1/2})^3 \qquad \text{(Eq. 1)}$$

where f_t is the fraction of drug released to time t, K_r is the release rate constant having the dimension of the reciprocal of the square root of time, and G_1–G_3 are shape factors. The values of G_1–G_3 are dependent on the shape of the tablet under study; values for three tablet shapes—spherical, cylindrical, and biconvex—are shown in Table I. For the first two shapes, the shape factors are constants and may be obtained from measurements of the initial dimensions of the tablet. However, for a biconvex tablet, the values of the shape factors vary with time and may be obtained partially from the initial dimensions of the tablet and partially in the course of the kinetic considerations of the release process.

A plot of the fraction of drug released, f_t, against the square root of time, $t^{1/2}$, will give a nonlinear curve, the exact profile depending on the tablet shape. One purpose of this study was to determine if the proposed equation describes experimental release data for cylindrical and biconvex tablets. Values for the release rate constants, K_r, may then be obtained for both tablet shapes by nonlinear regression analysis of the curves.

The value of the release rate constant varies inversely with the initial tablet radius, r_0, as shown previously (1):

$$K_r = \frac{K_b}{r_0} \qquad \text{(Eq. 2)}$$

where K_b is a proportionality constant, termed the boundary retreat rate constant, having the dimensions of length per unit square root of time. The boundary retreat rate constant is a measure of the rate at which dissolution fluid is able to penetrate into the insoluble tablet matrix to effect drug dissolution and release; it may be expressed (1) in terms of the same fundamental parameters described by