Effect of Geometry on the Dissolution of Pharmaceutical Tablets and Other Solids: Surface Detachment Kinetics Controlling

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During the past decade there has been increasing concern for developing rational approaches to the design of pharmaceuticals. A major innovation which arose from the recognition that time-invariant medication levels in the body are physiologically desirable was the development of a variety of sustained-release dosage forms (for example, oral, subcutaneous). A primary objective in designing such dosage forms is to ensure near constancy of the medication rate. With medications consisting of active ingredient dispersed in an inert carrier matrix, the continual decline of active component concentration in the matrix lowers the medication rate over the course of time (*1*). With solid tablets, the surface concentration of active medication can be maintained, but surface area tends to decrease with time. This also gives a progressively lower medication rate. The tendency for most dosage forms, even sustained-release ones, is thus to exhibit a continual fall-off in body concentration with the passage of time.

The present paper is part of an effort to elucidate design principles which will permit better formulations to be achieved. We wish to consider in this initial study solid dosage forms consisting of an active ingredient plus other materials such as inerts and binders. In particular we wish to investigate the effect of pellet geometry on the dissolution behavior of such solids. We will assume that the solids are homogeneous and nonporous, and incorporate enough of the proper binders to ensure that they dissolve slowly, rather than disintegrate.

DISSOLUTION MODEL

The theory of how a nonporous solid dissolves in a fluid is not well developed. The picture usually presented is, as discussed by Gallily and Friedlander (*3*) and by Rosner (*6*), one involving two main steps: detachment of an atom, molecule, or ion from the solid surface, followed by diffusion of this species through an adjacent stagnant layer out into the bulk of the fluid. While the diffusion step is a familiar one, little seems to be known about the chemical or physical nature of the detachment process. It is common practice to use the film model (*6*)

$$(dw/dt) = \left[\frac{k\mathcal{D}}{k\delta + \mathcal{D}}\right] S(C_0 - C_b) \qquad (1)$$

to describe dissolution.

Depending on the relative magnitudes of k and $(\mathcal{D}/\delta)$, the dissolution process can be controlled by detachment kinetics, diffusion, or by both. For solids having a very slow dissolution rate, surface detachment tends to control. This view is confirmed by Ullah and Cadwallader (*7*) who state "In drugs of low solubility, the dissolution process is controlled by the interfacial rate." Regardless of the route of drug administration, when sufficiently low solubility pertains Equation (1) may be written

$$(dw/dt) = kS\Delta C \qquad (2)$$

Because dissolution is slow we may safely ignore the movement of the solid-fluid interface and perform our analysis on a pseudo steady state basis. Additional assumptions which are reasonable include isothermal conditions, and that the particle is large enough so that, over nearly all of its lifetime, any effects on C_0 due to radius of curvature may be neglected. Certainly it may be argued that there are many objects, such as cylinders, which have corners of small radius of curvature, and that at these locations local C_0 values will be different from those which pertain to flat areas. We will assume that the effects of anomalous corner behavior on the basic geometric and overall dissolution rate phenomena are insignificant by comparison to the contributions of the flat portions. Whether this assumption is valid will require further analysis and experimental study.

Equation (2) indicates that the amount of surface area will proportionately affect the dissolution rate. Thus, to bring about a constant rate of medication one must attempt to keep the surface area of the dissolving solid as nearly constant as practical. We wish now to consider the dissolution behavior of various-shaped solids.

SOLID SPHERE DISSOLVING UNDER SURFACE DETACHMENT CONTROL

Since the simplest geometrical shape to analyze is the sphere, we shall begin with it. As shown above, when surface detachment kinetics control, the rate of mass dissolution from the solid is given by $(dw/dt) = kS\Delta C$. Hence, for a sphere

$$-\rho_s \frac{d\left(\frac{4}{3}\pi R^3\right)}{dt} = k(4\pi R^2)\Delta C$$

This has the solution $R = R_0 - Kt$, where $K = k\Delta C/\rho_s$ and R_0 is the sphere radius at time zero. Defining dimensionless time as $\tau = Kt/R_0$ [note $\tau = 1$ corresponds to the sphere "lifetime"], we may write the solution as $R/R_0 = (1 - \tau)$. Recalling that the rate of dissolution will be proportional to the surface area, we conclude that f the ratio of the instantaneous dissolution rate to the initial dissolution rate is

$$f = (1 - \tau)^2$$

This relation plotted in Figure 1 indicates a rather sharp

dropoff in dissolution rate with time for a sphere; at half the time for complete dissolution, the rate has fallen by 75%.

SOLID CYLINDER DISSOLVING UNDER SURFACE DETACHMENT CONTROL

The cylinder is an interesting geometry in that, depending on the L/D ratio, one may encounter a range from flat disks to slender rods. Analyzing the dissolution behavior of a cylinder of arbitrary L/D ratio turns out as will be seen to be simple. And yet some interesting results will be found.

Considering a cylinder of length L and diameter D, the rate at which the cylinder is reduced in axial volume at any instant is

$$-\pi R^2 \rho_s (dL/dt) = k(2\pi R^2)\,\Delta C \qquad (3)$$

while the rate of mass lost from the cylinder radially is

$$-\rho_s \pi L(dR^2/dt) = k\,(2\pi RL)\,\Delta C \qquad (4)$$

These equations have the solutions $L = L_0 - 2Kt$ and $D = D_0 - 2Kt$. The total area of the cylinder at any time relative to the initial area, and therefore the fractional dissolution rate f is given by

$$f = \frac{(D_0 - 2Kt)^2 + 2(D_0 - 2Kt)(L_0 - 2Kt)}{D_0^2 + 2D_0L_0} \qquad (5)$$

Three interesting cases may be identified with respect to the dissolution behavior of such a cylinder.

Case I. $L_0 = D_0$

When the initial length and diameter of the cylinder are equal then the length and diameter go to zero at the same instant. That is, the cylinder lifetime is $\tau = 1$, where $\tau = 2Kt/L_0 = 2Kt/D_0$. When $L_0/D_0 = 1$, $f = (1 - \tau)^2$. Looking back at the analysis for a sphere we find exactly the same expression. Hence, the behaviors of dissolution rate versus dimensionless time for a sphere and for a cylinder of $L/D = 1$ are identical.

Case II. Long Cylinder ("Rod"), or $L_0/D_0 \to \infty$

When this type of geometry prevails, the cylinder diameter will go to zero sooner than the length. Since the diameter disappearance decides the instant of the whole solid disappearance, the dimensionless time scale should be defined in terms of D_0 rather than L_0. In other words, if we define $\tau_D = 2Kt/D_0$ and $\tau_L = 2Kt/L_0$ then the time t at complete dissolution ($\tau = 1$) based on D_0 will be much earlier than that based on L_0. Physically we must of course choose the earlier of the two lifetimes as our basis.

For this case, when $L_0 >> D_0$ Equation (5) becomes $f \cong (1 - \tau)$ where $\tau = 2Kt/D_0$, that is, the dissolution rate drop-off is linear in τ—a physiologically better situation than when L/D was unity.

Case III. Flat Disk, or $L_0/D_0 \to 0$

When this type of geometry pertains, the cylinder length goes to zero first, so that here the dimensionless time must be defined in terms of L_0 (that is, $\tau = 2Kt/L_0$). Interestingly enough, for $D_0 >> L_0$ Equation (5) reduces to $f \cong 1$. Thus there occurs no significant drop in rate of dissolution with time in this case. One would naturally have expected this since the near constancy of total surface area with time is intuitively obvious. We now have seen that both the $L_0 >> D_0$ and $D_0 >> L_0$ situations are superior to the $L_0 = D_0$ situation—something one might not have guessed.

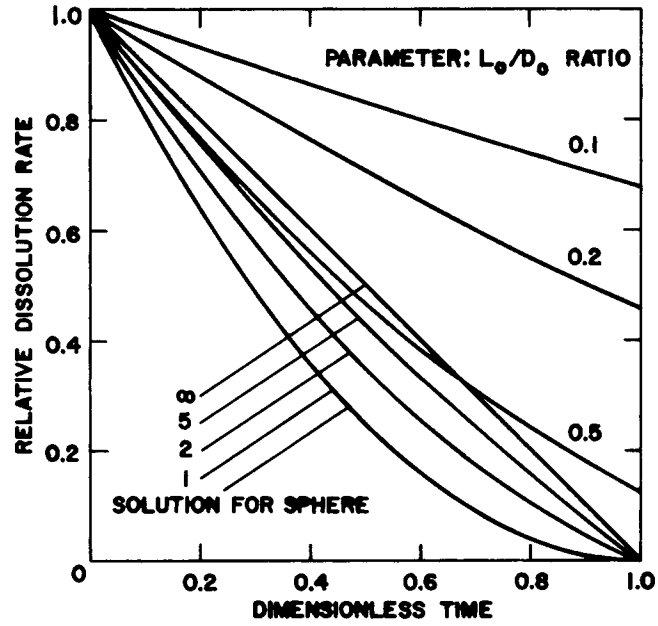

Fig. 1. Dissolution behaviors of cylinders of various length/diameter ratios.

GENERAL FORMULAS FOR CYLINDERS

Equation (5) can be written in general form using τ and defining $A = L_0/D_0$ as

$$f = \frac{(1 - \tau)[1 + 2A - 3\tau]}{(1 + 2A)} \qquad \text{for} \quad A > 1$$

$$f = \frac{(1 - A\tau)[1 + 2A - 3A\tau]}{(1 + 2A)} \qquad \text{for} \quad A < 1$$

When $D_0 < L_0$, one *must* define τ as $2Kt/D_0$. Likewise, for $D_0 > L_0$, τ *must* be written as $2Kt/L_0$. For $D_0 = L_0$ either definition may be used, as they are equivalent.

Figure 1 shows curves of f versus τ for a few selected values of A along with the curve for a dissolving solid sphere. The curve for $L/D \to 0$ in this figure is of course a horizontal line at $f = 1$. It is interesting to note that, for all L/D ratios below unity (that is, disklike cylinders), the relative dissolution rate remains finite right up to the very point of disappearance. Although the disklike cylinder is immeasurably thin just prior to total dissolution, it still has a relatively large surface area. In contrast, for $L/D > 1$ (that is, rodlike cylinders) the vanishing diameter always leads to an approach to zero surface and zero relative rate as $\tau \to 1$.

To make clear the effect of L/D ratio on dissolution behavior of cylinders, we have plotted in Figure 2 the relative dissolution rate at $\tau = 0.5$ versus the L/D parameter. The maximum dissolution rate decrease clearly occurs for $L/D = 1$, for which case the time behavior is identically as poor as that of a solid sphere.

CYLINDERS WITH CONCENTRIC BORES

We have seen that cylinders of near normal shape (L/D not too far from unity) yield dissolution rate curves which exhibit substantial declines. A very simple means of counteracting such drop-off behavior is to manufacture the cylinder with a concentric bore. An inner surface area which grows with time is thus created, and this largely counterbalances the decrease in external area. Indeed, it can be shown that if transfer from the cylinder ends can

be suppressed by the use of special coatings then the changes in the inner and outer areas exactly cancel.

Figure 3 shows the behavior of cylinders of $L_0/D_0 = 1$ (an arbitrary choice for purposes of example) having various sized bores of radius r_0, *with* transfer from the end areas taken fully into account. By comparison with Figure 2, the great benefits of providing an internal bore can be seen. A practical difficulty which might arise in the application of this concept is the greater susceptibility of such a configuration to mechanical fracture, especially as total dissolution is approached.

The curves in Figure 3 contain an anomaly in that the solution for $r_0/R_0 = 0$ does not coincide with the "complete" cylinder solution. Mathematically $r = r_0 + Kt$, and hence even if $r_0 = 0$ one finds that an inner surface of radius $r = Kt$ is predicted. There occurs therefore a discontinuity in the mathematical result depending on whether one assumes no initial central bore or one of infinitesimally small radius. Inasmuch as we would expect our model of surface detachment control to fail for very narrow bores where the diffusion resistance is highly accentuated we must simply ignore this paradox as being physically inapplicable. The theoretical development applies then only for cases where the inner bore is large enough to ensure that diffusion effects on the dissolution process are neglectable.

SPHERES WITH INTERNAL CYLINDRICAL BORES

The very poor (from a physiological standpoint) dissolution behavior of spherical pellets can be markedly improved by providing an internal cylindrical bore through the center of the sphere. For this case it can be easily shown (2) that

$$f = \left[\frac{(R_0 - Kt)^2 - (r + Kt)^2}{(R_0^2 - r_0^2)}\right]^{1/2} = (1 - \tau)^{1/2}$$

where $\tau = 2Kt/(R_0 - r_0)$. The fractional dissolution rate drops off as the square root of the amount of dimensionless time remaining. It is particularly interesting that this dependence on τ does *not* hinge at all on the relative magnitudes of R_0 and r_0, so that the dimensionless time behavior is the same regardless of whether the center bore is initially large or small in diameter.

Figure 4 compares the dissolution behavior of "complete" spheres $[f = (1 - \tau)^2]$ with that of spheres having central bores $[f = (1 - \tau)^{1/2}]$. The large effect of providing a growing inner surface is clear. However, there still occurs a rapid drop-off near $\tau = 1$, which would probably still make such a configuration unacceptable physiologically.

An anomaly similar to that which was found to occur for bored-out cylinders also occurs in the present situation. Its resolution is the same as before and need not be discussed any further here.

SOLID SHAPES OTHER THAN CYLINDERS AND SPHERES

An alternate approach to the problem of providing a near-constant-dissolution-rate tablet can be based on the realization that during dissolution convex surfaces tend to shrink in area, while concave surfaces tend to expand in area. One novel pellet configuration (4) which utilizes this principle is shown in Figure 5. The pellet contains both convexities and concavities, created by angles between the various surfaces. Upon dissolution, a convex surface which is one having an angulation of the surfaces of more

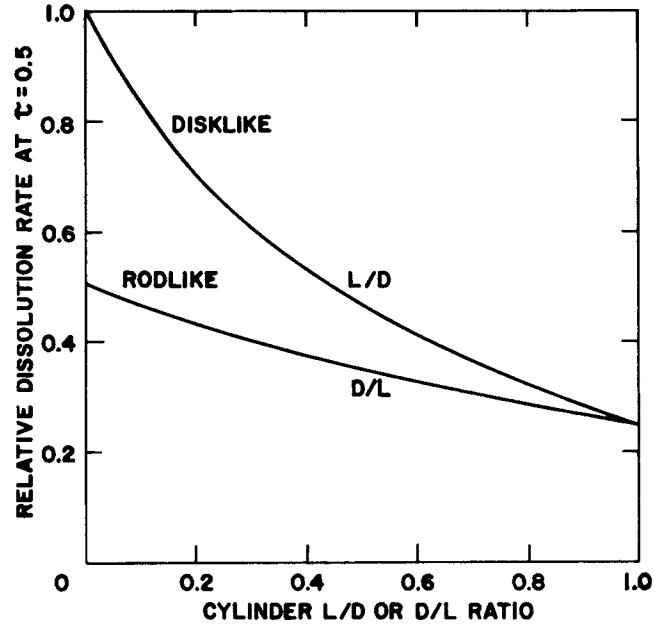

Fig. 2. Effect of cylinder geometry on decrease in dissolution rate.

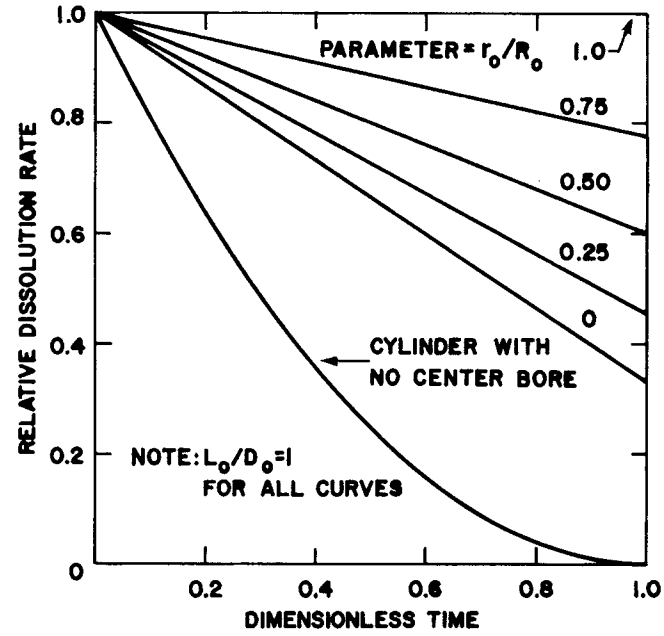

Fig. 3. Comparison of cylinders with and without concentric bores.

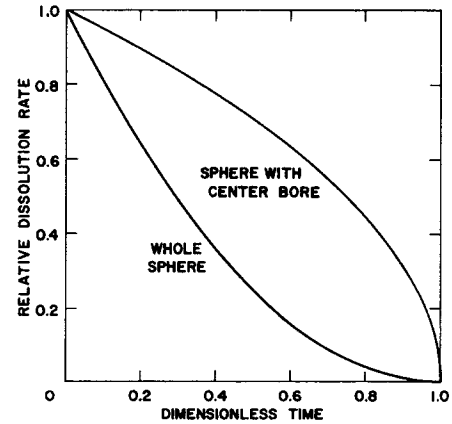

Fig. 4. Dissolution behaviors of spheres with and without center bores.

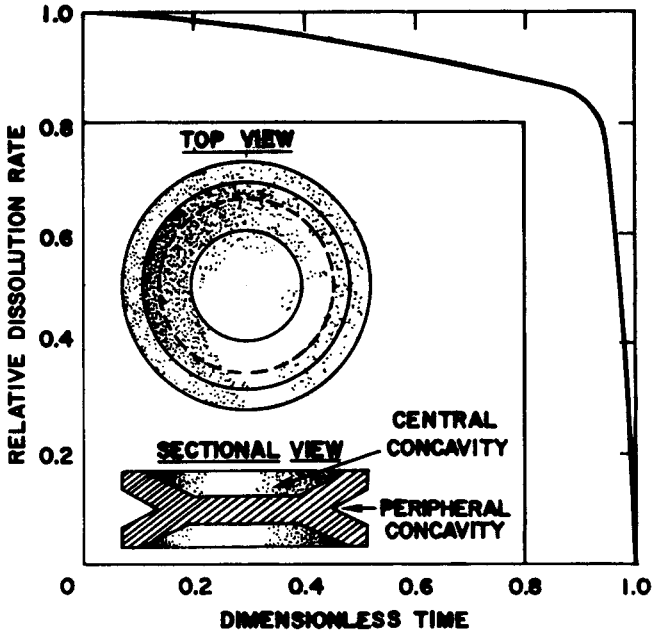

Fig. 5. Dissolution behavior of pellet designed with convex and concave surfaces.

CROSS CLOVER LEAF

Fig. 6. Cross-sectional views of some right-cylindrical pharmaceutical pellet designs.

than 180° becomes smaller in area. In contrast, a concavity which is an area having an angulation of surfaces smaller than 180° increases in area. Surface area tends to be greatly preserved by such means. Figure 5 shows the dissolution rate behavior for a typical tablet of this type.

Other types of convex-concave pellet forms which have been proposed (5) are shown in Figure 6. The "clover leaf" configuration is particularly interesting. It is a general principle of all such right cylindrical forms that an exact balance between concave and convex surface areas cannot be achieved, if there is an absence of internal bores. This is so because any such surface will change with time in proportion to its radius of curvature in subtended radians. It can be shown that for any right cylindrical shape, the total convex surface area *must* cover 2π subtended radians *more* than the concave surface area. Despite this geometric limitation, a greater approach to constancy of dissolution rate can nevertheless be achieved. If the length of the pellet is small, then, regardless of the cross-sectional convolutional nature of the pellet, disk-like behavior (constant rate) will be approached. Alternatively, a portion of the convex surface areas can be coated (for example, with lacquer) to suppress its greater contribution.

An essential consideration in this approach is the juxtaposition of the convex and concave surfaces (8). The arrangement must be designed so that the removal of material from the body surfaces does not erase the basic distribution of convexities and concavities *before* the bulk of the pellet has dissolved. That is, the general *shape* of the pellet must endure until complete dissolution has been achieved.

CONCLUSIONS

The above results disclose the general nature of the effect of geometry on the dissolution of low solubility solids. We have seen that flat disks, cylinders with internal concentric bores, and convex-concave pellets all exhibit dissolution behaviors which are vastly better, physiologically, than spheres and other common shapes (for example, oblate and prolate spheroids).

Some theoretical points which remain to be clarified include: 1. the range of solubility over which the surface detachment control model strictly applies, 2. the importance of corner effects, and 3. the behavior of various simple geometries under combined detachment-diffusion control.

Experimental aspects which we plan to investigate include the general agreement of actual dissolution behavior with the model developed in this paper, corner dissolution and the growth of internal bores, and determination of how far a complex pellet will dissolve before gross fracturing is apt to occur.

While many questions remain, it is nevertheless felt that the developments of the present paper will serve as useful guidelines for the rational design of sustained release pharmaceuticals.

NOTATION

A = cylinder initial length to diameter ratio
C_b = solute concentration in bulk of fluid
C_0 = solute concentration corresponding to saturation
D = diameter of sphere or cylinder
$\mathcal{D}$ = diffusion coefficient
f = relative, or fractional, dissolution rate
k = rate constant for surface detachment
K = constant equal to $k\Delta C/\rho_s$
L = length of cylinder
r = radius of internal bore
R = radius of cylinder or sphere
S = surface area
t = time
V = volume of solid
w = mass of solid

Greek Letters

Δ = used to define $\Delta C = C_0 - C_b$
ρ_s = solid density
τ = dimensionless time
τ_D = dimensionless time based on diameter disappearance
τ_L = dimensionless time based on length disappearance

Subscripts

0 = denotes value at start of dissolution

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