

monomer becomes almost constant as the total concentration of bile acid is raised to and beyond the CMC, the rate of passive diffusion similarly should reach a limiting value at this same point if bile acid monomer were the only species diffusing passively across the bowel wall." In fact, transfer rate actually increased more rapidly with increasing concentrations of sodium taurocholate above the CMC. Micellar taurocholate moves across the intestinal membrane twice as fast as the monomeric form. Based on the authors' findings one need not conclude that micellar transport of taurocholate proceeds at a faster rate than monomer transport or indeed that it occurs at all. It is possible that micellar concentrations of bile salt in contact with the mucosa significantly enhance the permeability of the membrane toward the monomeric species.

The nature of the mechanisms by which bile salts exert their effects on the biologic membrane is not clear at present. Studies in the literature and in this laboratory suggest certain working hypotheses which may be explored. The low level, premicellar, effects of STDC may be associated with depletion of membrane calcium. Webling *et al.* (17) have demonstrated a weak interaction between bile salts and calcium, and the effects of calcium depletion on membrane permeability have been shown by Tidball (18) with ethylenediamine tetraacetic acid (EDTA). Unpublished data from this laboratory indicate that the effects of EDTA on salicylate transfer across the everted intestine are of the same order as those observed with low concentrations of STDC. The ability of bile salts to solubilize phospholipids (19), which are components of the cell membrane, and actually restructure the membrane offers a possible explanation for the high level effect of STDC. These possibilities are being actively explored.

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## Regulation of Dissolution Rate by Pellet Geometry

E. G. RIPPPIE and J. R. JOHNSON

**Abstract** □ The influence of surface configuration on the dissolution behavior of pellets suspended in a turbulent flow field has been investigated. The rate of dissolution of extruded cellulose acetate hydrogen phthalate pellets was found to be a complex function of surface geometry. The study was undertaken to determine the *in vitro* sustained release characteristics of pellets of a form such that their loss of effective surface area during dissolution is minimized. Factors involved in the design of such pellets are discussed and data are presented which indicate the dissolution characteristics of test forms.

**Keyphrases** □ Dissolution rate—pellet geometry effect □ Extrusion process—pellet formation □ Pellet surface area—dissolution effect □ Colorimetric analysis—spectrophotometer

Processes occurring at the solid-liquid or solid-gas interface of multiphase systems can often be rate-controlled effectively by regulating the solid surface area available. This would imply that, by maintaining a constant surface area, the rate of a surface-controlled

process could also be held constant. A number of workers have observed the absorption of subcutaneous pellet implants of certain steroids to be proportional to exposed surface (1-3), and that absorption occurs at a reasonably constant rate if surface area is maintained by repeated implantations. This principle can be applied to processes in which the solid phase is consumed and not replenished by forming the solid into a shape such that loss of mass will not result in a loss of surface area. In the simplest case, the participation of a given element of surface in the overall process is independent of its topography and of its general location with regard to the other elements of surface in the system. Smokeless powders and solid rocket fuels are frequently produced in a form designed to maintain a reasonably constant surface area during combustion and represent an outstanding example of this principle.

In contrast to this mechanism, loss of mass from a surface by dissolution is not, in general, a simple function of surface area alone, but must be considered as

the resultant of a number of rate-controlling processes through which the phenomenon of mass transport is accomplished. Three general cases may be cited wherein the overall process is either diffusion-controlled, controlled by the maximum rate at which solute molecules can leave the solid surface, or controlled by both processes when they occur at comparable rates. It will be shown that the rate of dissolution from various points on the convoluted surface of granules of complex shape varies greatly depending on the rate-limiting processes effective at each given location. Wurster (4) has observed this behavior in the case of cylindrical tablets containing large pores.

Since drug availability and the blood levels which result often are determined by the rate of release from the dosage form (5-10), it is reasonable to expect that drug availability from an oral dosage form can be controlled by regulating the surface area over which dissolution occurs. The present study was undertaken to investigate the sustained release characteristics of relatively small granules or pellets of a shape such that their loss of effective surface area during dissolution was minimized.

### EXPERIMENTAL

**Preparation of Pellets**—The pellets used for this study were formed by extrusion from a thermoplastic mixture which was soluble in alkaline or neutral aqueous media and which had good mechanical strength. Eighty grams of cellulose acetate hydrogen phthalate, 8 ml. of diethyl phthalate, and 2 g. of bromocresol purple were dissolved separately in minimum quantities of acetone, mixed, and the resulting solution poured onto sheets of plate glass. After evaporation of the acetone at room temperature, the film, approximately 0.5 mm. in thickness, was peeled from the glass and allowed to air-dry at room temperature for an additional 24 hr. The material was then cut into strips for insertion into the extrusion press.

The extrusion apparatus shown in Fig. 1 consisted of a 5.08-cm. (2-in.) stainless steel cylinder having a 1.58-cm. ( $5/8$ -in.) bore and closely fitting brass plunger. This cylinder was fitted with a steel nozzle in which various shaped dies could be placed. The extrusion die assembly was mounted vertically in the heavy steel frame of a hydraulic press. The entire die assembly was wrapped in electric heating coils which provided the temperature control necessary for satisfactory extrusion. This temperature was not measured but was

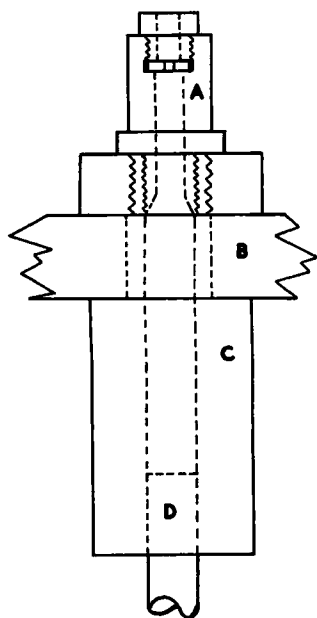


Figure 1—Pellet extrusion apparatus. A, nozzle and die assembly; B, press frame; C, cylinder; D, plunger.

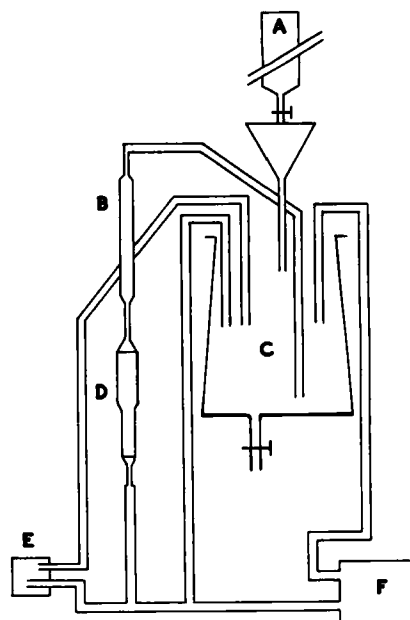


Figure 2—Diagram of dissolution apparatus. A, solvent reservoir; B, rotometer; C, mixing vessel; D, dissolution chamber; E, colorimeter cell; F, pump.

empirically adjusted by means of a powerstat to a level found to give consistently good results.

The plastic film was packed into the stainless steel extrusion cylinder, allowed to reach temperature, and extruded into long rods having various cross sectional forms. The several dies used were designed to make rods of the same cross sectional area and thus of the same weight per unit length. The extruded material was cut into pellets 7 mm. in length weighing approximately 22 mg. each. Forms selected for study were of clover leaf, cross, and circular cross section for reasons which will be discussed later.

**Dissolution Measurements**—The dissolution apparatus consisted of a dissolution chamber, Randolph pump, rotometer, mixing vessel, and an absorbance cell designed to fit a colorimeter<sup>1</sup> (Fig. 2). The pump was connected to the dissolution chamber and a shunt was used to control the solvent flow rate so as to suspend the dissolving solids in the chamber. A rotometer was positioned between the dissolution chamber and the mixing vessel to monitor the solvent flow. Solvent was pumped continuously from the mixing vessel through the colorimeter cell and back to the mixing vessel. The dissolution chamber consisted of a cylindrical glass tube 14 cm. in length with a gradation of diameter from 2 cm. at the bottom to 2.5 cm. at the top. This change in diameter, occurring over a 1-cm. segment midway up the tube, provided a gradation in flow sufficient to suspend the dissolving pellets. Screens at the ends of the chamber prevented the accidental loss of any pellets during a run. The mixing vessel was a 500-ml. conical flask provided with an outlet tube at the bottom.

Eight pellets of a given shape were used for each run. At the beginning of a run, the apparatus was filled with 470 ml. of solvent containing a predetermined concentration of dissolved pellets. The pellets for study were then placed in the dissolution chamber and the pump started. Fresh solvent was added slowly to maintain the colorimeter reading at 76% transmittance as the pellets dissolved. After the addition of 200 ml. of fresh solvent, the time was recorded and 200 ml. of used solvent was withdrawn from the mixing vessel. This process was repeated until approximately 70% of the initial volume of the pellets had dissolved. The apparatus was then stopped and the pellets removed, dried, weighed, and measured. Excellent agreement was obtained between repeated determinations. All runs were repeated a minimum of three times and average values were reported.

The solvent used throughout this work was an aqueous buffer, pH = 6.85 ± 0.02 (0.015 M NaH<sub>2</sub>PO<sub>4</sub>, 0.015 M Na<sub>2</sub>HPO<sub>4</sub>). At this pH, the pellets dissolved in a convenient time period of between

<sup>1</sup> Spectronic 20.

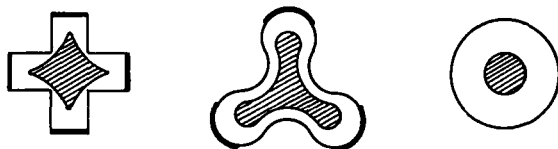


Figure 3—Cross-sectional view of the extruded forms of the pellets. Heavy lines on the outer surfaces of the cross and clover leaf forms indicate areas to which lacquer was applied to improve dissolution behavior. Shaded areas represent the approximate cross-sectional aspect of the uncoated pellets after 70% dissolution.

1 and 2 hr. Pellets were measured with an optical micrometer to provide data which were used to calculate surface area. Density measurements were made with a 10-ml. pycnometer using distilled water. The density values obtained were 1.32 g./cm.<sup>3</sup> for the clover leaf, 1.33 for the cylinder, and 1.34 for the cross. Runs were carried out at a temperature of  $27 \pm 0.5^\circ$ , and incremental rates of dissolution were determined from the times required to consume 200-ml. portions of fresh solvent. The concentration of dissolved pellet at 76% transmittance was found from a Beer's law plot to be 50.6 mg. of pellet/l. of solvent. All absorbance measurements were made at a wavelength of 592 m $\mu$  so as to follow the release of the bromocresol purple present in the pellets as an indicator of dissolution.

### THEORY

**Pellet Design**—The pellets were composed of cellulose acetate hydrogen phthalate and bromocresol purple, both of which are weak acids and are soluble in alkaline aqueous media. Diethyl phthalate was included in the formulation as a plasticizer. Since the dissolution rate was to be followed by observance of the dye concentration, it was necessary that the mass behave as a homogeneous solid and that dissolution occur solely at the pellet surface with no leaching of the individual components. The pellet formulation selected was found to satisfy this requirement under the conditions of these studies, and its solubility could be conveniently adjusted by an adjustment of pH.

The sign and magnitude of the rate of change of area of an element of surface on a solid, as the surface is uniformly eroded, is dependent upon its curvature. The proper balance of convex and concave regions on the surface of a pellet can result in a constant surface area as the pellet is consumed. As has been pointed out, unequal rates of surface erosion, due to different effective diffusion layer thicknesses, complicates the application of this concept.

Consider a circular cylindrical tube having a concentric bore. Neglecting the ends, a given length of such a tube will not change in surface area as material is uniformly eroded from its inner and outer surfaces and will maintain its area until completely consumed. This is true, of course, since the rate of change of the outer surface area with respect to its radius of curvature is exactly balanced by that of the inner surface. Unfortunately however, the inner surfaces of such pellets, of a size suitable for oral administration, will dissolve much more slowly than the outer surfaces when subjected to a turbulent flow of solvent, and the pellets will decrease in surface area during dissolution.

It is apparent, neglecting end effects, that any right cylindrical surface will have an instantaneous rate of change of area, with re-

Table I—Relative Changes in Pellet Dimensions

Pellet Type	Dimension	Relative Change <sup>a</sup>
Circular cylinder	Length <sup>b</sup>	1.00
Circular cylinder	Radius	1.14
Clover leaf	Length <sup>b</sup>	1.00
Clover leaf	Convex surface	1.35
Clover leaf	Concave surface	-0.84
Cross	Length	1.00
Cross	Width	1.22

<sup>a</sup> Relative dimensional changes calculated from initial and final measurements of the pellets. <sup>b</sup> One half the net change in pellet length was used as the basis of comparison for pellet dimensions which correspond to radii.

Table II—Initial Dissolution Rates of Pellets

Pellet Type	Initial Rate $\times 10^2$ (mg./cm. <sup>2</sup> sec.)	Rate Relative to Cylinder
Circular cylinder	1.37	1.00
Clover leaf	1.09	0.80
Cross	0.99	0.72
Clover leaf <sup>a</sup>	0.82	0.60
Cross <sup>a</sup>	0.79	0.58

<sup>a</sup> Pellets partially coated with lacquer as shown in Fig. 3.

spect to its radius of curvature, proportional to its cross sectional length in subtended radians. Thus, maintenance of surface area requires the equal availability to solvent of an equal number of radians of both concave and convex surface. The concave regions are best placed on outer more exposed areas on the surfaces of the pellets. In this way, the diffusion pathway from such areas is reduced from that which would result from relatively deep holes in the pellets.

In the absence of an internal surface, an exact balance between concave and convex surfaces cannot be achieved since the latter must be in excess by  $2\pi$  subtended radians. This may be seen from the consideration of a continuous closed curve having a continuous first derivative. Such a curve corresponds to the cross-sectional outline of a pellet having no infinitely sharp corners; a physical requirement met by pellets, regardless of their initial shape, following a short exposure to solvent action. The tangent line to such a curve must rotate through a net angle of  $2\pi$  radians (in the direction of travel) as the tangent point is moved in a complete cycle around the curve. Inasmuch as the normal vector to the curve is perpendicular to the tangent at all points, it too must have a net rotation of  $2\pi$  radians. It follows then that the radius of curvature, which lies along the normal vector, must behave in the same manner, resulting in an excess of  $2\pi$  subtended radians of convex surface along the cross section. In spite of this geometrical limitation, it is possible to obtain cylinders having convoluted surfaces which are superior to right circular cylinders in area maintenance.<sup>2</sup>

Pellet shapes were selected for study as possessing surface features representative of those which have been discussed. As such, they are not intended as examples of ultimate design. As indicated earlier, cylinders having circular, cross shaped, and clover leaf cross sections (Fig. 3) were studied. Additional studies were conducted with clover leaf and cross-shaped pellets having their outermost surfaces coated with lacquer to prevent dissolution from those regions.

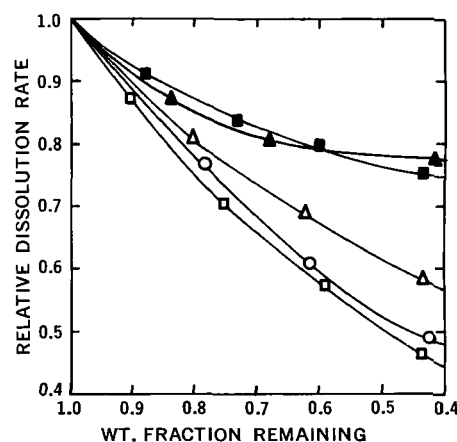


Figure 4—Plots showing the relative dissolution rates, expressed as a proportion of the initial rate, versus the weight fraction of pellet remaining undissolved. Key:  $\circ$ , circular cylinder;  $\Delta$ , clover leaf;  $\square$ , cross;  $\blacktriangle$ , coated clover leaf;  $\blacksquare$ , coated cross.

<sup>2</sup> Thin disks are also known to maintain their surface area well during dissolution.

**Table III—Residual Dissolution Rates after 60% Dissolution of Pellets**

Pellet Type	Relative Residual <sup>a</sup> Dissolution Rate	Relative <sup>b</sup> Efficiency
Circular cylinder	48	1.00
Clover leaf	54	1.12
Cross	45	0.94
Clover leaf <sup>c</sup>	74	1.54
Cross <sup>c</sup>	75	1.56

<sup>a</sup> The rate of dissolution following 60% mass loss as a percentage of the starting dissolution rate. <sup>b</sup> The residual dissolution rate following 60% mass loss as a ratio of that observed for the circular cylinder. <sup>c</sup> Pellets partially coated with lacquer as shown in Fig. 3.

## RESULTS AND DISCUSSION

**Mass Loss from Pellet Surfaces**—To provide an estimate of the relative average rates of dissolution from the various type surfaces, the net dimensional changes in the pellets after 70% dissolution were determined. The relative dissolution rates, calculated from initial and final measurements of the pellets, are presented in Table I as ratios of the decrease in overall length. It can be seen that the outer cylindrical surfaces dissolve more readily than do the pellet end surfaces. The concave surfaces of the clover leaf form showed a significantly lower rate of dissolution. No attempt was made to determine the decrease in thickness of the arms of the cross-shaped pellets as this varied widely over their length. The final cross-sectional aspect of the pellets is shown in Fig. 3. It is quite apparent from this figure alone that significant differences in dissolution rate exist between the various regions on the pellet surfaces. The effect of pellet shape on dissolution rate can be seen also from Table II where average initial rates per unit area are presented. A higher proportion of partially occluded surface area can be seen to result in a generally lower dissolution rate. This in itself is not undesirable, but rather reflects again the fact that concave surfaces do not erode as rapidly as those which are more exposed to the turbulence of the solvent. It is this behavior which seriously limits the practical application of the principle under discussion. In an attempt to overcome this obstacle, the outer surfaces of clover leaf and cross-shaped pellets were coated with clear lacquer, as shown in Fig. 3, so as to prevent reduction of area over these surfaces.

**Maintenance of Dissolution Rate**—The relative efficiencies of the several pellet forms in maintaining a uniform dissolution rate can be seen from Fig. 4. The incremental rates of dissolution over a major portion of the dissolution process, expressed as a proportion of the initial incremental rate, are plotted as a function of the fraction of pellet mass remaining. Although the clover leaf shape exhibits a higher relative rate after 60% dissolution, than either the circular or cross form, it must be considered ineffective under the experimental conditions employed.

A significant improvement in retained available surface was observed with the partially coated pellets as shown in Fig. 4. This may be seen also from Table III where the fractional rates after 60% dissolution are listed for the various pellet forms. The 74% and 75% retained dissolution rates of the partially coated forms, with 40% undissolved solids remaining, represents approximately a 55% relative improvement over a right circular cylinder.

## CONCLUSIONS

It is clearly evident from these limited studies that the long-term dissolution rate of solid pellets can be modified significantly through proper control of available surface. It is equally apparent that the rate of dissolution from a given element of surface is a complex function of the changing size and shape of the pellet itself as well as of the fluid dynamics of the adjacent solvent layer. In view of this complexity, no attempt has been made to submit the data obtained here to a detailed mathematical analysis. This is not to say that such an analysis could not be conducted of a properly restricted and defined system.

While the *in vitro* system employed in these studies differs both chemically and hydrodynamically from conditions encountered in the human gastrointestinal tract, the results indicate the potentialities as well as the limitations of this approach to sustained release for orally administered medication.

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