Dissolution Kinetics of Gallstones: Physical Model Approach

W. I. HIGUCHI[▲], F. SJUIB, D. MUFSON, A. P. SIMONELLI, and A. F. HOFMANN

Abstract □ Recent studies suggested that *in situ* dissolution of gallstones in man might be dissolution rate controlled. In this work, several physical models for the dissolution rate of cholesterol-type stones were developed. One is based upon simple diffusion-controlled dissolution and another upon a leaching process. Two others relate to interfacial coat-type barriers. Calculations were carried out employing models with reasonable input parameters. The results show, for example, that the theoretical dissolution rate based on the simple dissolution model would predict that a 2.5-mm. stone should dissolve in several days into an undersaturated bile solution. Both clinical and *in vitro* experiments show that much longer times, *e.g.*, months, are needed.

Keyphrases □ Gallstones—dissolution kinetics, various physical models proposed and discussed, calculations □ Dissolution rate, gallstones—proposed physical models, calculations □ Cholesterol-type stones—proposed physical models, dissolution kinetics, calculations □ Diffusion—in dissolution kinetics of gallstones, physical models proposed, calculations □ Interfacial barriers—as a factor in dissolution kinetics of gallstones, physical models proposed, calculations

Cholesterol is transported in vertebrate bile dissolved in bile acid–lecithin micelles. Recently, the phase equilibria present in bile acid–lecithin–cholesterol–water systems were defined and shown to relate to human cholesterol cholelithiasis (1, 2). In man, cholesterol cholelithiasis appears to be associated with the formation of bile by the liver which is saturated or supersaturated with cholesterol (3, 4). Recent work by Thistle and Schoenfield (5) indicated that the administration of chenodeoxycholic acid to patients with cholesterol gallstones results in a significant reduction in the ratio of cholesterol to bile acids and lecithin. Nevertheless, despite the achievement of altering bile composition from saturated to unsaturated with respect to cholesterol, gallstone size appears to diminish only slightly or not at all during several months of treatment, indicating that rapid equilibrium between gallstones and bile may not occur. That is, stone dissolution appears to be rate limiting *in vivo*.

This report presents various possible physical models for gallstone dissolution kinetics. This study was expected to be useful in several ways with regard to gallstone dissolution. First, a semiquantitative perspective developed from these models should help identify possible rate-limiting situations and establish preliminary correlations with already published clinical and *in vitro* data. Second, these models, in conjunction with suitable experiments involving "synthetic" gallstones, should be valuable in designing significant clinical or *in vitro* experiments. And third, the models and the related mathematics should provide the vehicle for the appropriate mechanistic analysis of the data, both clinical and *in vitro*.

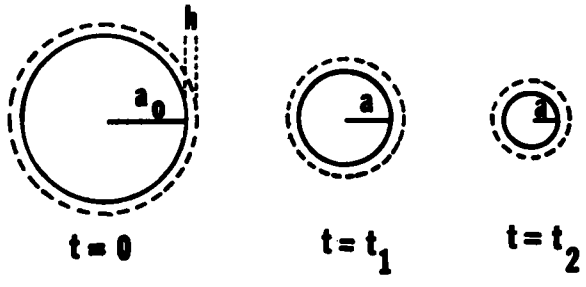

Figure 1—*Simple dissolution case. The radius of the sphere* a *changes with time* t; h *is the liquid diffusion layer thickness.*

Figure 2—*Simple matrix case. Cholesterol embedded in a spherical matrix is dissolved and leached out as a function of time.*

PHYSICAL MODELS

The present discussion is restricted to the problem of the rate of dissolution of "cholesterol" gallstones where the principal constituent of the stones is cholesterol (~70–98%). Thus, the primary processes under consideration are the dissolution and transport of cholesterol from the gallstone and into the solvent. It is assumed that the other constituents (*e.g.*, bile pigments, proteins, and calcium salts) may be important only to the extent that they may provide a barrier to transport of cholesterol.

The fastest dissolving gallstone would be essentially pure cholesterol, where the rate-determining step is the transport of cholesterol from the surface into the solvent. This implies that no significant barriers to transport are present at the solid–solution interface.

This maximum rate situation can be decreased significantly by such factors as interfacial barriers and inert residues which can form a diffusion barrier. Interfacial barriers may arise from intrinsically slow (6) crystal–surface solution equilibria or from adsorbed or deposited substances (7, 8) on the stone surfaces. Gallstones containing appreciable amounts of noncholesterol components may lead to the formation of residue-type barriers (9–12). These barriers arise when the cholesterol is dissolved and leached faster than the slower dissolving or disintegrating noncholesterol substance. The residues then can form a continuous matrix through which the cholesterol must be transported.

Case I: Simple Dissolution Model (No Matrix-Diffusion Barriers or Interfacial Barriers)—This model would be appropriate if either: (*a*) the stone is pure cholesterol or (*b*) the other constituents of the stone slough off sufficiently rapidly from the gallstone surface during cholesterol dissolution.

For simplicity, let the stone have a spherical geometry so that the situation illustrated in Fig. 1 would apply. This model then assumes that during dissolution the solvent adjacent to the surface of the stone is saturated with cholesterol and that the rate of dissolution, J, is governed by the diffusion of cholesterol across the solvent diffusion layer of thickness h. The dissolution rate J is then expressed mathematically by Eq. 1:

$$J = \frac{AD(C_s - C_B)}{h} \qquad \text{(Eq. 1)}$$

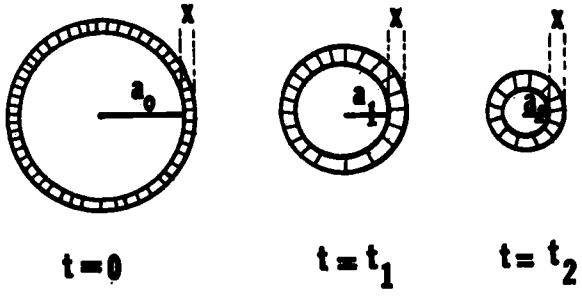

Figure 3—*Interfacial "coating" Model I: gallstone dissolution in the presence of interfacial barrier of thickness* x.

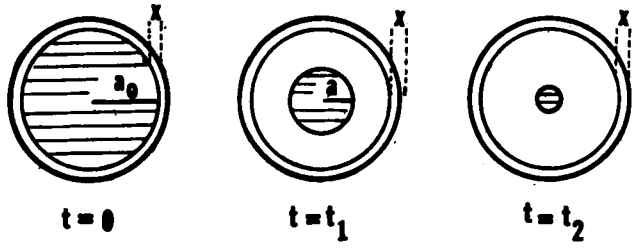

Figure 4—*Interfacial "coating" Model II: gallstone dissolution in the presence of indestructive coating.*

where A = surface area of the sphere, D = diffusion coefficient for cholesterol in the solvent, C_s = solubility of cholesterol, and C_B = concentration of cholesterol in the bulk solvent. J may be also related to the rate of change in mass, W, expressed by Eq. 2:

$$J = -dW/dt = 4\pi a^2 \rho(da/dt) \qquad \text{(Eq. 2)}$$

where ρ = density of cholesterol, and a = radius of the sphere. Therefore, by combining Eqs. 1 and 2 and noting that $A = 4\pi a^2$:

$$\rho \frac{da}{dt} = \frac{D(C_s - C_B)}{h} \qquad \text{(Eq. 3)}$$

In the special case where C_B is constant, Eq. 3 may be integrated to give:

$$a = a_0 - \frac{D(C_s - C_B)}{\rho h} t \qquad \text{(Eq. 4)}$$

where a_0 is the initial ($t = 0$) radius of the gallstone. Equation 4 may also be expressed on a weight basis:

$$W^{1/3} = W_0^{1/3} - \frac{D(C_s - C_B)}{\rho h} \left(\frac{4\pi\rho}{3}\right)^{1/3} t \qquad \text{(Eq. 5)}$$

where W_0 is the initial ($t = 0$) weight of the gallstone, and W is the weight at time t. Equation 5 is a form of the well-known Hixon-Crowell cube-root law (13).

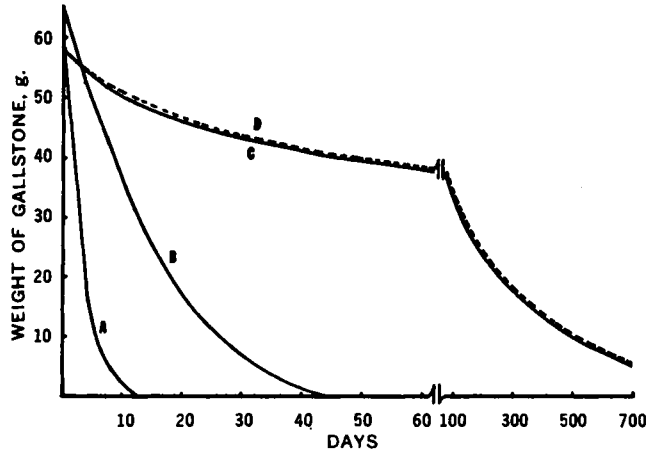

Figure 5—*Calculated dissolution of gallstone of radius* a_0 = *2.5 cm. and solubility* C_s = *26.4 mM/l. with A for Case I and* h = *50 μ, B for Case I and* h = *200 μ, C for Case II and* h = *50 μ, and D for Case II and* h = *200 μ.*

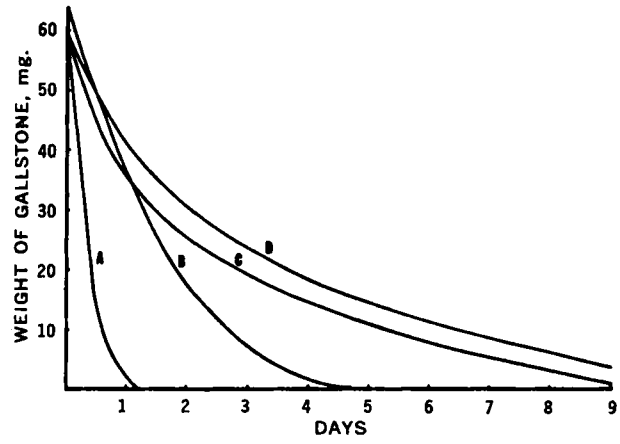

Figure 6—*Calculated dissolution of gallstone of radius* a_0 = *2.5 mm. and solubility* C_s = *26.4 mM/l. See Fig. 5 for meaning of A, B, C, and D.*

The general solution to Eq. 3, *i.e.*, where C_B is not a constant, may easily be obtained (13). If, for example, C_B changes appreciably during the dissolution period, it may be necessary to use the more general equation which is somewhat unwieldy. However, in most of the present discussion, Eqs. 1 and 4 are sufficient.

Case II: Leaching of Cholesterol from Uniform Matrix Model—If an insoluble, nondisintegrating, porous residue remains in place of the original gallstone substance when cholesterol dissolves into the solvent, this model may be appropriate. Figure 2 illustrates this problem for the sphere geometry case.

In this model, the dissolution rate is governed by diffusion of cholesterol from the surface ($r = a$, where r is the distance from the center of the sphere outward) of the cholesterol core through the solvent-filled but leached (no cholesterol) portion ($a \leq r \leq a_0$) of the gallstone and through the solvent diffusion layer of thickness h. It is again assumed that the solvent at $r = a$ is saturated with cholesterol. The rate of cholesterol transport, J, for this case is given by Eq. 6, where it is again assumed that C_B, the cholesterol concentration in the bulk solvent, remains constant during dissolution:

$$J = \frac{4\pi a_0^2 aD}{(\tau/\epsilon)a_0(a_0 - a) + ha}(C_s - C_B)t \qquad \text{(Eq. 6)}$$

where ϵ and τ are the porosity and tortuosity of the leached region ($a \leq r \leq a_0$), respectively. The other symbols have already been defined. Equation 6 thus considers both the effects of the solvent diffusion layer resistance and the matrix-diffusion resistance to cholesterol dissolution.

When Eq. 6 is combined with Eq. 2, one obtains the final expression which relates the size of the cholesterol core to time:

$$-2\left(\frac{h}{a_0} - \frac{\tau}{\epsilon}\right)\left(\frac{a}{a_0}\right)^3 - 3\frac{\tau}{\epsilon}\left(\frac{a}{a_0}\right)^2 + \frac{\tau}{\epsilon} + 2\frac{h}{a_0} = \frac{6D(C_s - C_B)}{a_0^2 S} \qquad \text{(Eq. 7)}$$

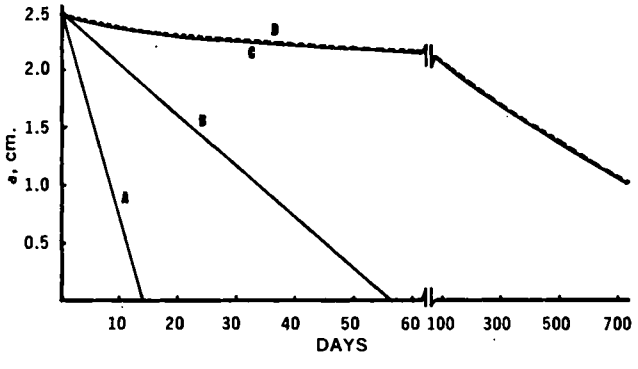

Figure 7—*Calculated dissolution of gallstone with radius* a versus *time* t. *Values of* a_0 = *2.5 cm. and* C_s = *26.4 mM/l. were used. See Fig. 5 for meaning of A, B, C, and D.*

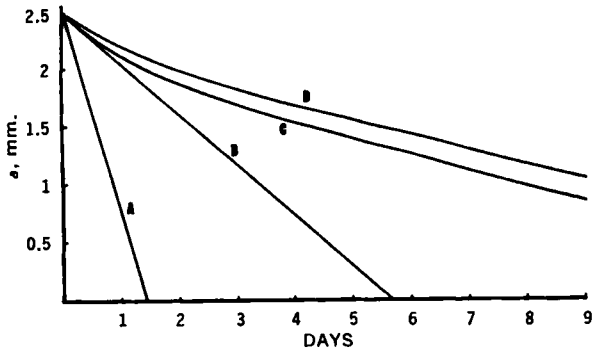

Figure 8—*Calculated dissolution of gallstone with radius* a versus *time* t. *Values of* a_0 = *2.5 mm. and* C_s = *26.4 mM/l. were used. See Fig. 5 for meaning of A, B, C, and D.*

where S = solid concentration of cholesterol in the gallstone matrix. Equation 7 may also be expressed on a weight basis:

$$-2\frac{(4\pi\rho)^{1/3}h}{(3W_0)^{1/3}}-\frac{W}{W_0}-3\frac{\tau}{\epsilon}\left(\frac{W}{W_0}\right)^{2/3}+\frac{\tau}{\epsilon}+\frac{2(4\pi\rho)^{1/3}h}{(3W_0)^{1/3}}=\frac{6(4\pi\rho)^{2/3}D(C_s-C_B)}{(3W_0)^{2/3}S} \quad \text{(Eq. 8)}$$

Case III: Interfacial Barrier or Coat Model I—Figure 3 illustrates a model that may be appropriate when: (*a*) a moderate degree of disintegration and/or dissolution of a residue (matrix) barrier (Case II) takes place, or (*b*) a reversible or collapsible barrier film is present on the stone surface during dissolution. Equation 9 describes the dissolution rate behavior for the sphere situation:

$$W^{1/3}=W_0^{1/3}-\frac{P(C_s-C_B)}{\rho}\left(\frac{4\pi\rho}{3}\right)^{1/3}t \quad \text{(Eq. 9)}$$

It is assumed that the permeability coefficient P of this barrier remains constant. All symbols in Eq. 9 have been defined. The physical meaning of the permeability coefficient P depends upon the particular situation (see *Discussion* section).

Case IV: Interfacial Barrier or Coat Model II—This situation (Fig. 4) might arise if a stable coating (*e.g.*, proteins, calcium phosphates, or calcium carbonate) is present on the stone surface. The outer dimensions do not change with time, while the inner cholesterol dissolves. Equation 10 describes the time change in the weight for this situation:

$$\frac{\epsilon}{\tau}+\frac{2(4\pi\rho)^{1/3}D}{P(3W_0)^{1/3}}-3\frac{\epsilon}{\tau}\left(\frac{W}{W_0}\right)^{2/3}+\left\{2\frac{\epsilon}{\tau}-\frac{2(4\pi\rho)^{1/3}D}{P(3W_0)^{1/3}}\right\}\frac{W}{W_0}=\frac{6(4\pi\rho)^{2/3}(C_s-C_B)\epsilon D}{\tau(3W_0)^{2/3}S} \quad \text{(Eq. 10)}$$

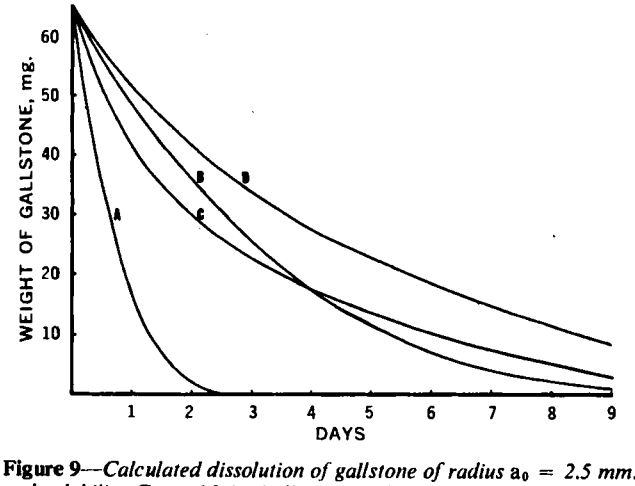

Figure 9—*Calculated dissolution of gallstone of radius* a_0 = *2.5 mm. and solubility* C_s = *26.4 mM/l. with A for Case III and* P = *2* × *10⁻⁴ cm./sec., B for Case III and* P = *5.0* × *10⁻⁵ cm./sec.; C for Case IV and* P = *2* × *10⁻⁴ cm./sec., and D for Case IV and* P = *5.0* × *10⁻⁵ cm./sec.*

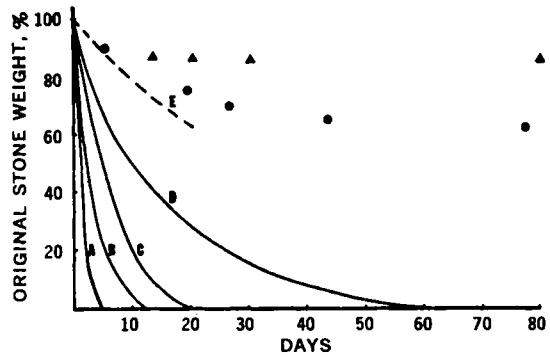

Figure 10—*Comparison of calculated percent gallstone dissolved for cases of* h = *200 μ and Small's (2) data with A for Case I and* C_s = *26.4 mM/l., B for Case II and* C_s = *26.4 mM/l., C for Case I and* C_s = *5.6 mM/l., and D for Case II and* C_s = *5.6 mM/l. Key (Small's data):* ▲, *dissolution in bile salt;* ●, *dissolution in bile salt–lecithin (2:1); and E, bile salt–lecithin corrected to sink condition by changes in* ΔC *with time.*

Here again the physical meaning of the permeability coefficient P depends upon the particular situation.

Other Models—Other models may be developed that relate to physical situations not already presented. Also, very complex combinations are possible. Before much serious consideration is given to very elaborate models, however, those presented in this paper should be evaluated thoroughly.

THEORETICAL CALCULATIONS

While the models and equations in the preceding section may be utilized in a rather rigorous and quantitative manner with experiments on "synthetic" and real gallstones, the present applications of the theoretical relations are concerned primarily with the identification of and "range-finding" in a number of situations. These "order-of-magnitude" calculations should be helpful in suggesting preliminary correlations and expectations and establishing limiting behavior.

Results Involving Case I—Some results of calculations with Eqs. 5 and 6 are shown in Figs. 5–8 (curves A and B). In these calculations, meaningful values for the parameters were selected that correlate to either *in vivo* or *in vitro* situations. The two values for h (50 and 200 μ) should represent reasonable[1] lower and upper limits for moderate and low agitation conditions (14). The two values for a_0, the initial stone radius, are typical of cholesterol stones. The value for the cholesterol solubility (C_s = 26.4 mmoles/l.) was reported to be that for gallbladder bile (15). For the diffusion coefficient D, a value of 1×10^{-6} cm.²/sec. was selected because this is close to that observed for bile salt–cholesterol micelles (16).

These calculations, being based on Case I and sink conditions ($C_B = 0$), represent optimum or maximum dissolution rates. Thus, it is probably significant from a clinical standpoint that it may take about a week to a month for a significant reduction in size of large gallstones ($a_0 \sim 2.5$ cm.) under such optimal conditions. The calculations predict that smaller stones ($a_0 \simeq 0.25$ cm.) may dissolve in a few days under these optimal (Case I and sink) conditions.

Results with Other Models—In curves C and D of Figs. 5–8, results of calculations with Eqs. 7 and 8 (Case II) are presented. As expected, the rates are lower than those for simple dissolution. The effect of agitation (*i.e.*, dependence upon h) is significant for small gallstones following this model but not for large stones.

Figure 9 shows the results of some calculations based on Cases III and IV.

DISCUSSION

The models considered and the equations deduced in this paper should serve as baselines for research on the dissolution kinetics of gallstones *in vitro* and *in vivo*. Experimental results in these laboratories have shown, for example, that gallstones dissolve according

[1] If the medium is much more viscous than water, however, these values should be greater.

to Model I in ethanol–water and acetone–water solvent mixtures. In 5% cholate, the rates appear to be somewhat slower than the predictions of Model I; in bile salt–lecithin solutions, the rates appear to be more than a factor of 10 slower. In Fig. 10, the data of Small (2) are compared to some theoretical calculations. As can be seen, rates based upon Model I appear to be significantly greater than Small's *in vitro* results. These preliminary comparisons of experimental results with the theoretical relationships show that under physiologically important conditions, the simple diffusion-controlled model may or may not be applicable and that careful scrutiny of the various factors is necessary.

From the clinical standpoint, the idea that a 2.5-mm. gallstone might be dissolved in a few days is very appealing. Therefore, the question of why the observed rates might be significantly slower than diffusion controlled is important clinically.

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Mechanisms of Dissolution of Human Cholesterol Gallstones

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Abstract □ Experiments were designed for investigating and comparing the *in vitro* dissolution kinetics of human cholesterol gallstones and cholesterol monohydrate compressed pellets. The dissolution rates were determined in 66% acetone–water, in 63% ethanol–water, in bile acids, and in bile acid–lecithin solutions. It was found that the rates of dissolution of the stones compared well with the dissolution rates obtained with the cholesterol monohydrate pellets in all solvents investigated. The dissolution rates for both stones and pellets in the organic–aqueous solvents were extremely rapid and of the order of magnitude expected for a bulk diffusion-controlled process. In sodium cholate solutions, the dissolution rates were about 2–3 times slower than rates predicted by diffusion theory and the data suggested a modest interfacial resistance to dissolution. The rates obtained in 2% bile acid–1% lecithin solutions were about 17 times slower than diffusion-controlled processes, and these results point to an interfacial barrier to dissolution that may be very important clinically.

Keyphrases □ Gallstones, human—mechanisms of dissolution, dissolution rates in different media, compared to prepared cholesterol pellets, existence of interfacial barriers □ Cholesterol gallstones, human—mechanisms of dissolution, dissolution rates in different media, compared to prepared cholesterol pellets, existence of interfacial barriers □ Dissolution, human cholesterol gallstones—mechanisms, dissolution rates in different media, compared to prepared cholesterol pellets, existence of interfacial barriers □ Diffusion—role in dissolution of human cholesterol gallstones, existence of interfacial barriers □ Interfacial barriers—as a factor in the dissolution of human cholesterol gallstones, mechanisms of dissolution

During recent years much research has been done to evaluate the thermodynamic equilibria existing in the bile acid–lecithin–cholesterol–water systems and their relation to cholelithiasis (1, 2). It has been shown that the degree of cholesterol saturation or supersaturation in gallbladder bile is a critical factor in the formation or dissolution of cholesterol gallstones *in vivo*. While it is now clear that thermodynamic factors can play important roles, relatively little is known about the kinetic factors involved. Questions concerning the *kinetics* of gallstone dissolution have become especially important since the finding of Thistle and Schoenfield (3) and Danzinger *et al.* (4) that oral administration of chenodeoxycholic acid in patients with gallstones can result in the simultaneous "normalization" of bile and the dissolution of stones.

The present article reports results of initial physicochemical investigations on the mechanisms of dissolution of cholesterol gallstones. An attempt was made to determine: (*a*) whether or not the rate of cholesterol gallstone dissolution *in vitro* compares closely to the dissolution rate of "synthetic" gallstones of compressed cholesterol monohydrate pellets, and (*b*) whether or not the dissolution rates of gallstones in various solvent media are governed by diffusion in the bulk or by interfacial factors (5).