A second equation for prediction of dynamic flow rates was developed, similar in form to Eq. 2 for static flow:

$$W_2 = \frac{\pi\rho\sqrt{g}}{4}\left(\frac{P}{1.52 + 4.12d}\right)^{(2.79+6.68d)} \quad \text{(Eq. 4)}$$

Again, measurements of dynamic flow through the largest orifice were excluded. Now, the exponent n is a function of the particle diameter. The flow rates predicted with Eq. 4 were larger than experimentally measured values in five of 12 cases. The average of the differences between calculated and experimental values (expressed as a percent of experimental data) for dynamic flow rates was −0.4%.

In Eqs. 2–4, which are based on the Brown–Richards equation, the static and dynamic flow rates are expressed in terms of orifice diameter, particle diameter, and particle density. If static and dynamic flow rates are not dependent on any dimensions of the apparatus except the orifice size, it should be possible to combine the relationships. Then dynamic flow rate can be expressed as a function of static flow. If Eqs. 2 and 3 are combined, dynamic flow rates can be predicted using:

$$W_2 = \frac{\pi\rho\sqrt{g}}{4}\left[\left(\frac{1.65 + 2.34d}{2.11 + 0.12\ln d}\right)\left(\frac{4W_s}{\pi\rho\sqrt{g}}\right)^{(0.24-0.038\ln d)} + \left(\frac{0.0009d^{-1.25}}{2.11 + 0.12\ln d}\right)\right]^{3.33} \quad \text{(Eq. 5)}$$

If the predicting power of Eq. 5 is good:

1. There should be the same number of positive and negative differences between calculated and experimental values (+5 and −7).
2. The average of the differences (expressed as a percent of experimental data) should be close to zero (−1.2%).
3. The arithmetic mean of the absolute value of these differences should be small (6.0%).

Thus, Eq. 5 appears to be appropriate for predicting dynamic flow rates for the granular material studied.

When Eqs. 2 and 4 are combined, another algebraic expression is obtained that describes dynamic flow rate as a function of static flow:

$$W_2 = \frac{\pi\rho\sqrt{g}}{4}\left(\frac{1.65 + 2.34d}{1.52 + 4.12d}\right)^{(2.79+6.68d)} \times \left(\frac{4W_s}{\pi\rho\sqrt{g}}\right)^{(0.67+1.60d-0.11\ln d-0.25d\ln d)} \quad \text{(Eq. 6)}$$

If the predicting power of Eq. 6 is good:

1. There should be the same number of positive and negative differences between calculated and experimental values (+0 and −12).
2. The average of the differences (expressed as a percent of experimental data) should be close to zero (−6.2%).
3. The arithmetic mean of the absolute value of these differences should be small (6.2%).

Thus, Eq. 6 appears to have fair predicting power for dynamic flow rates of the granular materials studied, although it is somewhat less accurate than Eq. 5. The limited amount of data precludes selection of the more appropriate general form for an equation to predict dynamic flow rates from static flow data.

The form of Eqs. 2–4 for static and dynamic flow is comparable to equations reported by other investigators (9, 10). While Eqs. 5 and 6 are more cumbersome, they also are of a similar form; the orifice diameter (P) was written implicitly as a function of the static flow rate (W_s). An important observation of Eqs. 5 and 6 is that dynamic flow is not first order in static flow (W_s) if the exponents on the $(4W_s/\pi\rho\sqrt{g})$ term are different than unity. In Eq. 5, the exponent $[(0.24 - 0.038\ln d)\ (3.33)]$ is greater than unity for all d values of <0.21 cm. Similarly, for Eq. 6, the exponent $(0.67 + 1.60d - 0.11\ln d - 0.25d\ln d)$ has a value greater than 1 for all particles sizes (d) of <598 cm. Therefore, for particle sizes commonly found in tablet formulations, both equations predict that the dynamic flow is not first order in static flow. In addition, the dynamic flow is nonlinear with respect to both preexponential terms, which are related indirectly (*i.e.*, through particle density) or directly to the particle diameter.

The direct applicability of Eqs. 5 and 6 to other granulations and dynamic flow systems is questionable. However, the form of the equations explains why the dynamic flow rates are not easily predicted from static flow data. The relationships also suggest that static and dynamic flow rates are dependent on many of the same measurable parameters; these parameters should be considered in the development of other mathematical models for dynamic flow rates.

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Mesophase Formation during *In Vitro* Cholesterol Gallstone Dissolution: A Specific Effect of Ursodeoxycholic Acid

Keyphrases □ Cholesterol—gallstones, mesophase formation during *in vitro* gallstone dissolution □ Gallstones, cholesterol—effect of bile acid on gallstone dissolution *in vitro* □ Ursodeoxycholic acid—effect on cholesterol gallstone dissolution *in vitro*, compared with chenodeoxycholic acid □ Dissolution—cholesterol gallstones, effect of bile acid

To the Editor:

Ursodeoxycholate (I), the 7β-epimer of chenodeoxycholate (II), has been shown to be equal or superior to II when used as oral medication for the dissolution of cho-

lesterol gallstones (1–4). The clinical efficacy of I is curious since *in vitro* it is a relatively poor solubilizer of cholesterol, either alone or as mixed bile acid–lecithin micelles (5–8).

The contradiction between the poor solubilization of cholesterol monohydrate by I *in vitro* and yet its successful use for the dissolution of human gallstones *in vivo* led us to investigate the dissolution behavior of cholesterol monohydrate in media containing I conjugates (9, 10). The data showed that initial dissolution rates of cholesterol monohydrate in powder and pellet forms were always lower in lecithin–ursodeoxycholylglycine (III) solutions than in the corresponding lecithin–chenodeoxycholylglycine (IV) solutions. This finding is in agreement with previous investigations (5–8). However, in these experiments, cholesterol release into the lecithin–III-containing medium continued far beyond the apparent equilibrium solubility in the isotropic phase by formation of a turbid, liquid crystalline phase (mesophase).

These experiments were extended to determine whether such mesophase formation might occur during the *in vitro* dissolution of cholesterol gallstones.

Gallstones were obtained at surgery from two patients. The first group of stones (Fig. 1A) was removed from the gallbladder of a patient 40 years old, and the second group (Fig. 1B) was obtained from a patient 85 years old with a typical history of recurrent biliary colic. All stones were washed and kept moist in water until the dissolution studies were begun. Preoperative oral cholecystograms revealed radiolucent stones, and chemical analyses of both groups of stones showed the cholesterol contents to be close to 100%.

A single stone was placed in a test tube containing either 2 or 2.5 ml of solution. The tubes were shaken at 37°, and samples were taken at suitable time intervals. Cholesterol was assayed enzymatically[1], and an organic phosphate assay (11) was employed for lecithin.

Figure 1A shows the dissolution behavior of two stones, removed from the same patient, in lecithin–III medium. The dotted line shows the apparent equilibrium solubility of cholesterol monohydrate from pellet studies[2] in the corresponding medium. The arrows in Fig. 1 show the beginning of turbidity in the media. Microscope observations under cross-polarized light of a sample of the turbid medium revealed liquid crystals. In one experiment, the entire solution was replaced by 2.0 ml of fresh medium on the 10th day, and mesophase formation was observed to continue perhaps even at a higher rate. In these experiments, the total amount of cholesterol released far exceeded the thermodynamic micellar saturation value for cholesterol monohydrate.

Figure 1B shows data for the dissolution behavior of cholesterol gallstones from another patient; the difference in behavior for stone dissolution in III and IV solutions is clearly illustrated. For IV, the initial micellar dissolution rate was relatively rapid and the curves leveled off close to the apparent solubility value for cholesterol monohydrate[2]. In contrast, the stone dissolution in III initially proceeded much more slowly (as in Fig. 1A), and the dissolution curve did not level off at the apparent solubility

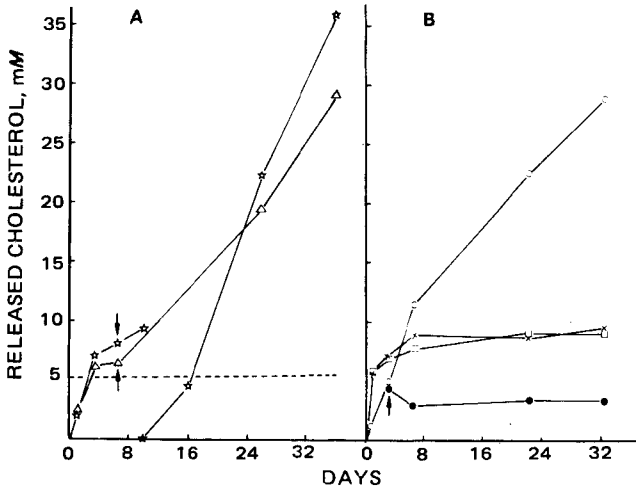


Figure 1—*Effect of bile acid type on cholesterol gallstone dissolution in 32 mM lecithin, 0.1 M NaCl, and 0.01 M phosphate buffer at pH 7.4 and 37°. Key: △, 126-mg stone in 2 ml of solution containing 87 mM III; ☆, 172-mg stone in 2 ml of solution containing 87 mM III (old medium was replaced by fresh medium on the 10th day); ○, 873-mg stone in 2.5 ml of solution containing 87 mM III; ×, 891-mg stone in 2.5 ml of solution containing 87 mM IV; □, 910-mg stone in 2.5 ml of solution containing 87 mM IV; and ●, 873-mg stone in 2.5 ml of solution containing 87 mM III (after centrifugation of the supernate).*

but proceeded to much higher values. In III solution, the beginning of turbidity was observed after about 3 days (see arrows), but cholesterol released from the stone continued far beyond the apparent solubility value. As in Fig. 1A, the polarizing microscope examination of the mesophase (which separates to the top of the isotropic solution after centrifugation) showed liquid crystal properties. Solid circles in Fig. 1B show the supernatant (isotropic phase) cholesterol levels after centrifugation (8000×*g* for 10 min).

Table I shows that the lecithin levels in the experiments involving IV remained relatively constant with and without centrifugation. In the experiments with III, the lecithin levels in the supernate (isotropic phase) obtained after centrifugation decreased greatly with time. Calculations based on the lecithin data in Table I and the cholesterol data in Fig. 1B showed that the separated phase(s) possessed an average cholesterol to lecithin ratio of 1:1 to 3:1. In addition, the cholesterol level obtained for the supernate (isotropic phase) after centrifugation was somewhat lower than the value corresponding to the dotted line in Fig. 1A. This finding is consistent with observed lecithin depletion from the media during mesophase formation.

Other gallstones, which are under investigation in these

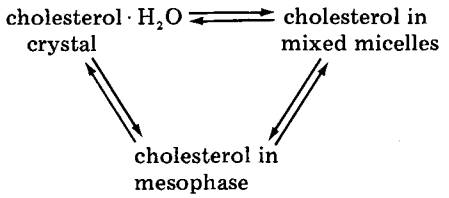
Table I—Data Showing Lecithin Concentration (Millimolar) Changes during *In Vitro*[a] Cholesterol Gallstone Dissolution in Solutions Containing III

Days	Lecithin–IV		Lecithin–IV		Lecithin–III	
	Before[b]	After	Before	After	Before	After
0	32.0	32.0	32.0	32.0	32.0	32.0
3.1	33.3	33.2	28.3	29.8	25.2	22.0
7.0	32.6	29.4	27.6	30.6	25.0	12.6
22.5	32.8	29.8	27.0	27.4	25.2	11.8
32.7	31.0	31.5	28.1	31.0	25.2	12.0

[a] Changes in cholesterol concentration are shown in Fig. 1. The initial concentration of lecithin was 32 m*M*; the concentrations of IV and III were 87 m*M*. [b] The concentration of lecithin before centrifugation denotes lecithin in both the mesomorphic and isotropic phases; after centrifugation, the lecithin concentration refers to the isotropic phase because the mesophase has risen to the top of the tube.

[1] Bio-Dynamics, Indianapolis, Ind.
[2] Manuscript in preparation.

laboratories, also show that the cholesterol release in media containing III and lecithin may follow the pattern described in Scheme I.



Scheme I

The process effectively represents a substantial mass transfer rate of cholesterol from the gallstone into the medium. Although this process is significantly slower than the micellar dissolution rate of a cholesterol gallstone in a lecithin–IV solution, after some time (several days in these experiments) the extent of dissolution and disintegration by this process may be greater.

These studies imply that the phase equilibria in III–lecithin–cholesterol–water differ from that in IV–lecithin–cholesterol–water. Conjugates of ursodeoxycholic acid apparently have a much weaker tendency to disperse mixed lecithin–cholesterol bilayers than those of chenodeoxycholic acid. The data do not answer directly the question of whether mesophase formation may occur during gallstone dissolution induced by ursodeoxycholate in humans since biliary bile acids become only moderately enriched in ursodeoxycholic acid (60–70%) during continuous ursodeoxycholate administration; therefore, further studies are needed. Mesophase formation during gallstone induction does occur in the cholesterol-fed prairie dog (12) whose bile contains predominantly cholate conjugates, and mesophases were reported to occur in some samples of human bile (13, 14).

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BOOKS

REVIEWS

Pharmaceutical Calculations, 7th Ed. By MITCHELL J. STOKLOSA and HOWARD C. ANSEL. Lea & Febiger, 600 Washington Square, Philadelphia, PA 19106. 385 pp. 15 × 23 cm. Price $15.00.

The seventh edition is in the same format as earlier ones but contains an expanded chapter on dosage calculations and additional chapters on interpreting the prescription and calculations involving parenteral admixtures. The material from the "Chemical Problems" chapter in the 6th edition is found in the appendix of the new edition. Many new practice problems have been added to appropriate chapters.

The addition of a new chapter, "Interpretation of the Prescription or Medication Order," is very good. The interpretation presented is aimed specifically at helping the student solve problems presented in the prescription, medication order, or formula and does not duplicate information given in other chapters, as one might expect. The subject matter is presented in a direct manner with enough examples to be easily understood.

Additions to the "Calculation of Doses" chapter include an expansion of the surface area method with the two DuBois and DuBois nomograms for finding body surface areas for children and adults. This is a considerable improvement over the 6th edition which contained a table of body weights and surface areas. Unfortunately, the reference to the use of this method (Harry Shirkey) uses the West nomogram, which gives results different from that of DuBois. Perhaps an expanded discussion could cover this point in the next edition.

The inclusion of calculations involving lean body mass, loading dose, maintenance dose, and the use of creatinine clearance rate is an excellent choice of subject to update the book. The explanations and examples are all clear and precise except for the calculation and use of creatinine