had been determined since often only the free and nonionized drug establishes an equilibrium between blood and saliva concentrations (3, 4). For example, Killman and Thaysen (3) found that unbound sulfonamides in human saliva were proportional to the concentration of unbound drug in the plasma. Similar findings were reported for phenytoin (6). Thus, we are presently developing methods to study unbound quinidine in plasma so that these values can then be compared to saliva levels to determine if even better plasma–saliva level correlation exists for this drug.

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Dissolution of Model Gallstones in Bile Acid Solutions I: Implications for T-Tube Infusion Treatment of Retained Common Duct Stones with the Cholate System

Keyphrases □ Dissolution—gallstones, *in vitro*, T-tube infusion treatment with sodium cholate □ Gallstones—*in vitro* dissolution, T-tube infusion treatment with sodium cholate □ Sodium cholate—infusate for *in vitro* dissolution of gallstones by T-tube infusion

To the Editor:

The problem of retained common bile duct stones affects about 5% of the patients undergoing cholecystectomies (1–3). Considerable effort has been directed by clinicians[1] (2–6) to find a nonsurgical solution to the problem which will save the patient a high risk operation.

One study (2) showed that retained common bile duct stones can be dissolved using a T-tube infusion; sodium cholate solution was used as the infusate. The investigators were able to dissolve retained stones in 12 of 22 patients within 14 days of continuous infusion at a rate of 30 ml/hr. With the same technique and a similar formula, retained stones were dissolved in five of six patients within 5 days (3).

However, recent controlled T-tube infusion studies were less successful[1]. Only two of six patients showed dissolution of the retained stones. This difference in results between the studies was not expected since there was only a 25% difference in the cholate concentration levels between the formulations tested.

This communication presents a probable physical–chemical explanation for the differences observed. This explanation is based upon the surface resistance to the cholesterol dissolution in bile acid media and the influence of electrolytes upon it.

Compressed cholesterol monohydrate pellets were used as model cholesterol stones. Infusion media were prepared according to Way *et al.* (2) and La-Russo *et al.*[1], using a purified grade of cholic acid[2]. The pH of the media was adjusted to pH 7.5 with sodium hydroxide.

Dissolution experiments were conducted using the apparatus and procedures reported previously (7). Equilibrium solubilities were measured after allowing excess amounts of ^{14}C-cholesterol monohydrate to equilibrate with the infusion media with continuous shaking at 37°.

Dissolution rates and solubility values are shown in Table I. The resistance to dissolution, R, was calculated from the equation:

$$\frac{J}{A} = \frac{C_s}{R} \qquad \text{(Eq. 1)}$$

where J/A is the dissolution rate per unit surface area, and C_s is the solubility.

The data show that the rate of cholesterol dissolution in the Way *et al.* (2) and Lansford *et al.* (3) infusion medium is about nine times faster than that in the La Russo *et al.*[1] medium. This large difference in the rate of dissolution cannot be explained on the basis of a diffusion-controlled mass transport mechanism, because the solubility increases by only about a factor of two (Table I) and the diffusivities are not expected to vary significantly.

These results, therefore, point to the likely importance of surface kinetic factors in the dissolution process. A significant interfacial resistance has been shown (7–11) to govern the rate of cholesterol monohydrate and cholesterol gallstone dissolution in bile media generally, and it is proposed that interfacial resistance is the primary factor responsible for the difference in cholesterol dissolution and, hence, the

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Table I—Dissolution Rates, Solubilities, and Resistances to Dissolution of Cholesterol Monohydrate in Sodium Cholate Infusion Media

Infusion Medium	$(J/A)\ 10^4$, mg/(cm² sec)	C_s, mg/ml	$R \times 10^{-3}$, sec/cm
Way *et al.* (2) and Lansford *et al.* (3) (100 m*M* sodium cholate + 154 m*M* sodium chloride)	2.038	1.440	7.066
La Russo *et al.*[a] (75 m*M* sodium cholate + 77 m*M* sodium chloride)	0.236	0.710	30.085
75 m*M* sodium cholate	0.061	0.452	74.10
100 m*M* sodium cholate	0.201	1.032	51.34
100 m*M* sodium cholate + 77 m*M* sodium chloride	0.682	1.315	19.282
75 m*M* sodium cholate + 154 m*M* sodium chloride	0.744	0.974	13.091

[a] See Footnote 1.

T-tube infusion efficacy between the two solutions.

Previous investigations in our laboratories (11–13) showed that the interfacial barrier to cholesterol transport in bile acid systems may be highly sensitive to electrolytes. It is proposed, therefore, that the difference in the electrolyte levels of the two formulations is primarily responsible for the efficacy difference in retained stones dissolution.

Additional data supporting this interpretation can be seen in Table I. For example, in 75 m*M* sodium cholate, the cholesterol dissolution rate increased fourfold when 77 m*M* sodium chloride was added and an additional threefold when the sodium chloride concentration was doubled.

The results of this study should open the door for a much broader systematic investigation of the formulation–activity relationships of solutions for T-tube infusion in patients with retained common duct stones.

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Vehicle for Stabilizing Aluminum Hydroxide Gel

Keyphrases □ Aluminum hydroxide gel—vehicles for stabilization □ Stability—aluminum hydroxide gel, vehicles investigated □ Antacids—vehicles for stabilizing aluminum hydroxide gel

To the Editor:

A recent research article (1) demonstrated that aluminum hydroxide gel loses acid reactivity depending on the vehicle used for dilution and the degree of dilution. A significant loss of acid reactivity occurred when the gel was diluted with double-distilled water. Dilution with dioxane or mother liquor had no effect on reactivity. It was suggested that a carefully designed diluting solution could minimize the loss of acid reactivity normally observed and result in a dosage form with increased efficacy and a longer shelf-life. We now wish to demonstrate the stabilizing effect of a vehicle suitable for use in aluminum hydroxide gel dosage forms.

An aluminum hydroxide gel was prepared as previously described (1) by the reaction of aluminum chloride, sodium bicarbonate, and sodium carbonate at pH 6.5. The gel was divided into four portions and diluted to 3.3% Al_2O_3. One portion was diluted with a saturated aqueous solution of potassium chloride (equivalent to 72 mEq/15 ml). The second portion was diluted with propylene glycol. The third portion was diluted with distilled water saturated with carbon dioxide, and the fourth portion was diluted with double-distilled water to serve as the control.

The acid reactivity was monitored by an automated[1] pH-stat technique similar to the method described by Steinberg *et al.* (2). An appropriate volume of water was added to the reaction vessel and brought to pH 3.0. A volume of sample containing 38 mg of aluminum oxide was then added. The volume of water was adjusted for each sample to produce a reaction volume of 22 ml. The instrument was set to maintain pH 3.0 by adding 1.0 *N* HCl from the autoburet. The instrument was activated simultaneously with the sample injection. The recorder plotted milliliters of 1.0 *N* HCl added *versus* time. The acid reactivity of each sample is expressed as T_{50}: the time re-

[1] PHM 26; TTT 11; ABU 12, 2.5 ml; TTA 3; SBR 2; Radiometer, Copenhagen, Denmark.