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 mM sodium cholate + 154 mM sodium chloride)	2.038	1.440	7.066
La Russo et al.[a] (75 mM sodium cholate + 77 mM sodium chloride)	0.236	0.710	30.085
75 mM sodium cholate	0.061	0.452	74.10
100 mM sodium cholate	0.201	1.032	51.34
100 mM sodium cholate + 77 mM sodium chloride	0.682	1.315	19.282
75 mM sodium cholate + 154 mM 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 mM sodium cholate, the cholesterol dissolution rate increased fourfold when 77 mM 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.

(1) F. Glenn, *Surg. Gynecol. Obstet.*, **134**, 249(1972).

(2) L. Way, W. Admirand, and J. E. Dunphy, *Ann. Surg.*, **176**, 347(1972).

(3) C. Lansford, S. Mehta, and F. Kern, *Gut*, **15**, 48(1974).

(4) B. Gardner, *Ann. Surg.*, **177**, 240(1973).

(5) R. Mazzariello, *Surgery*, **73**, 299(1973).

(6) S. J. Galloway, W. J. Casarella, and W. B. Seaman, *Surg. Gynecol. Obstet.*, **137**, 55(1973).

(7) W. I. Higuchi, S. Prakongpan, and F. Young, *J. Pharm. Sci.*, **62**, 945(1973).

(8) W. I. Higuchi, S. Prakongpan, V. Surpuriya, and F. Young, *Science*, **178**, 633(1972).

(9) W. I. Higuchi, V. Surpuriya, S. Prakongpan, and F. Young, *J. Pharm. Sci.*, **62**, 695(1973).

(10) W. I. Higuchi, S. Prakongpan, and F. Young, *ibid.*, **62**, 1207(1973).

(11) S. Prakongpan, W. I. Higuchi, K. H. Kwan, and A. M. Molokhia, *ibid.*, in press.

(12) V. Surpuriya and W. I. Higuchi, *ibid.*, **61**, 375(1972).

(13) V. Surpuriya and W. I. Higuchi, *Biochim. Biophys. Acta*, **290**, 375(1972).

Abdulla M. Molokhia [x]
William I. Higuchi

College of Pharmacy
University of Michigan
Ann Arbor, MI 48104

Alan F. Hofmann
Mayo Clinic
Rochester, Minn.

Vehicle 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-
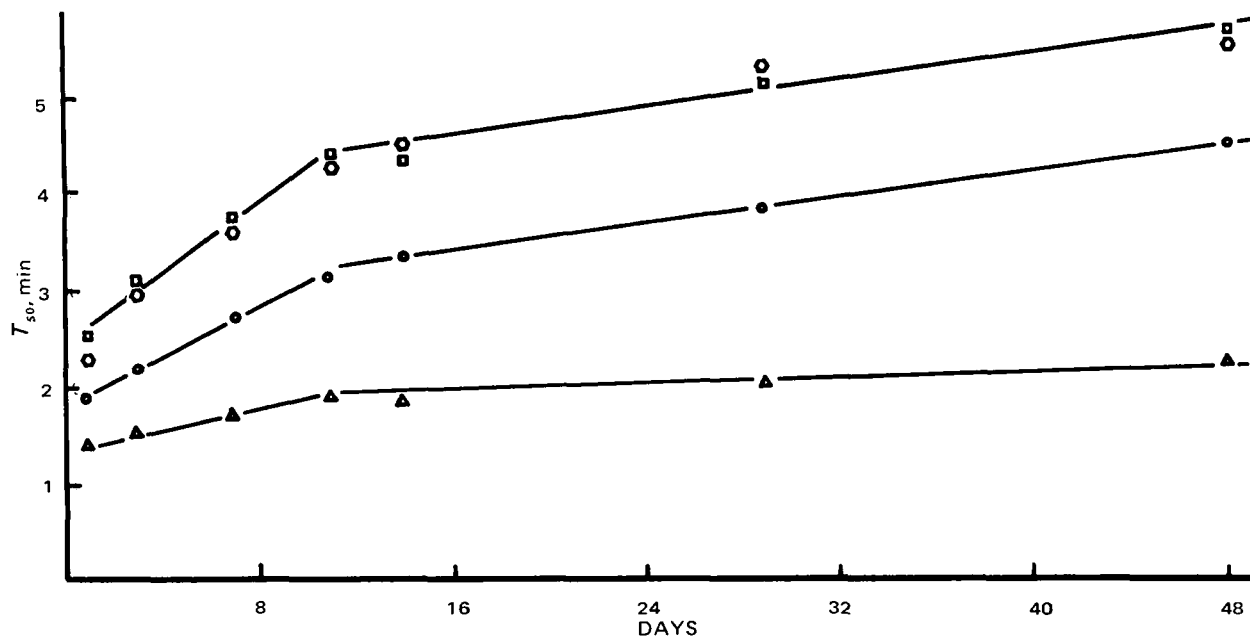
Figure 1—*Effect of diluting vehicle on acid reactivity of aluminum hydroxide gel aged at 25°. Gels were diluted to 3.3% Al_2O_3 with:* □, *distilled water;* ○, *carbon dioxide-saturated distilled water;* ○, *propylene glycol; and* △, *saturated aqueous solution of potassium chloride.*
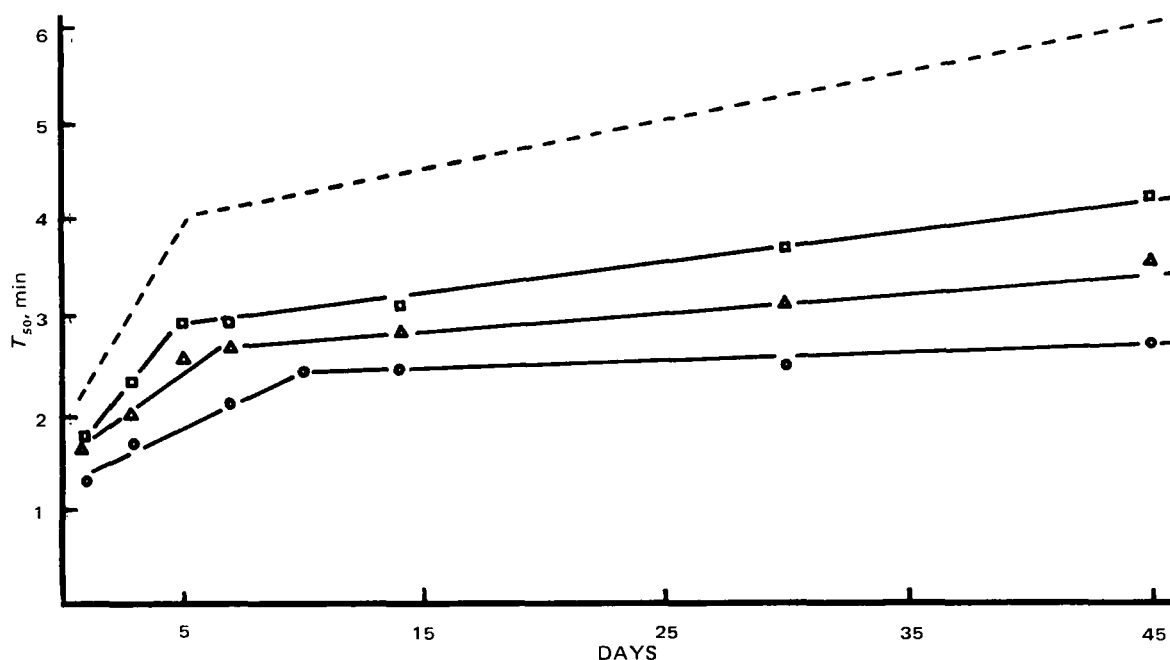

Figure 2—*Stabilization of aluminum hydroxide gel by dilution with potassium chloride solutions. Gels were aged at 25° and diluted to 3.6% Al_2O_3 with:* ○, *40 mEq of potassium chloride/15 ml;* △, *20 mEq of potassium chloride/15 ml;* □, *10 mEq of potassium chloride/15 ml; and - - -, distilled water.*

quired to add 50% of the total 1.0 *N* HCl needed to neutralize the aluminum hydroxide gel at 25°.

As seen in Fig. 1, the acid reactivity of the gel diluted with saturated potassium chloride was virtually unchanged. The sample diluted with propylene glycol was more stable than the portions diluted with distilled water or carbon dioxide-saturated water.

Lower levels of potassium chloride also significantly improve the stability of aluminum hydroxide gel. A second aluminum hydroxide gel was prepared as before, divided into three portions, and diluted to 3.6%

Al_2O_3 with solutions equivalent to 40, 20, and 10 mEq of potassium chloride/15 ml. The stabilization by the potassium chloride solution was directly related to the potassium chloride concentration of the diluting solution (Fig. 2).

The samples continue to be monitored, and at 120 days the correlation coefficient for the linear portion commencing at 7 days was 0.999, 0.998, and 0.987 for the gels diluted with 10, 20, and 40 mEq of potassium chloride/15 ml, respectively. The 10-mEq/15-ml dilution resulted in a 30% improvement in T_{50} after 120

days at 25° compared to dilution with distilled water.

The 10 mEq of potassium chloride/15-ml dilution does not have an objectionable taste and could be suitably flavored to produce an acceptable pharmaceutical product. The OTC Antacid Review Panel report (3) stated that potassium presents no problem to normal persons, but that products containing 25 mEq or more of potassium per maximum daily dose must include a warning to patients with kidney disease. Thus, a vehicle designed to maintain the stabilizing ions in the aluminum hydroxide gel appears to be a feasible approach to improving the stability of aluminum hydroxide gel.

(1) N. J. Kerkhof, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, 64, 940(1975).
(2) W. H. Steinberg, H. H. Hutchins, P. G. Pick, and J. S. Lazar, *ibid.*, 54, 625(1965).
(3) *Fed. Reg.*, 38 (65), 8714(Apr. 5, 1973).

Nicholas J. Kerkhof
Stanley L. Hem ˣ
Department of Industrial and
Physical Pharmacy
School of Pharmacy and
Pharmacal Sciences
Purdue University
West Lafayette, IN 47907

Joe L. White
Department of Agronomy
Purdue University
West Lafayette, IN 47907

BOOKS

REVIEWS

Alicyclic Chemistry, Volume 2—A Review of the Literature Published during 1972. Senior Reporter, W. PARKER. The Chemical Society, Burlington House, London WIV OBN, England, 1974. 470 pp. 14 × 22 cm. Price $35.

This book is part of a series of 32 Specialist Periodical Reports designed, according to the Chemical Society, to give an in-depth coverage of the whole field of chemistry. Ultimately some 40 titles are contemplated. The first volume was published in three reports covering aliphatic, alicyclic, and saturated heterocyclic chemistry from January 1970 to December 1971. Other reports of interest to medicinal chemists are: Aliphatic Chemistry, Saturated Heterocyclic Chemistry, Aromatic and Heteroaromatic Chemistry, Organic Compounds of Sulfur, Selenium and Tellurium (all Volume 2), and Organophosphorous Chemistry, already up to Volume 5.

The present volume consists of four chapters. Chapter 1 covers three- and four-membered rings. The first 10 pages are devoted to theoretical and structural considerations including X-ray studies, MO calculations, and energetics. The remainder of the chapter is divided into syntheses and reactions of three- and four-membered carbocyclic compounds. The coverage is thorough. The reactions considered include those with electrophiles, nucleophiles, thermal reactions, cycloadditions, rearrangements, eliminations, functional group modifications, and radicals. Chapter 2 views five- and six-membered rings in light of structural and conformational considerations, followed by an in-depth overview of their reactivities. A 10-page section also considers fused rings. Thus, the reactions of decalyl tosylates and amines are described in terms of acetolyses, deaminations leading to twist conformers, and ring contractions. Bicyclo[4.3.0]nonane and bicyclo[4.2.0]octane systems are also discussed.

Chapter 3 is devoted to medium and large ring compounds. It has 16 sections. Energies and conformations of seven- to 10-membered rings are covered, followed by synthetic routes to such systems. Intramolecular photochemical electrocyclic and cycloaddition reactions, as well as intermolecular photochemical reactions, are surveyed. Transannular reactions, ring contractions, and ring-opening reactions are briefly covered. Finally there is a section on general reactions, *e.g.*, of cycloalkenes, cyclic ketones, amines, alcohols, and esters. Organometallic derivatives complete the chapter.

The final chapter is titled Bridge Carbocyclics. A lengthy introductory section discusses physical methods and energy calculations. This is followed by a section on bicyclic and polycyclic structures. Of particular interest to medicinal chemists are some references to bornane chemistry and extensive coverage (11 pages) of adamantanes. Extensions of known methods of syntheses for this carbon skeleton are reported. The chapter further details cycloadditions, photo- and organometallic chemistry, and solvolytic reactions. Finally, several miscellaneous reactions, including a new stereospecific reducing agent (lithium tris-s-butyl borohydride) and an enzymatic reduction (horse liver dehydrogenase and NADH), are referred to. An author index is included.

The book is profusely endowed with structural formulas; the reader need not fumble with vast quantitites of IUC nomenclature. Its value to the medicinal chemist would be mainly as an adjunct reference source for new developments in those alicyclic ring systems of potential biological interest either as pharmacophores (adamantanes) or as useful carriers for such groups.

Reviewed by Alex Gringauz
Brooklyn College of Pharmacy
Long Island University
Brooklyn, NY 11216