be free of endotoxin, *e.g.*, by treating this carefully cleaned equipment at 180° for several hours.) Ten microliters of the sample is added and mixed with the aid of the capillary tube (a special pipet holder with a punched rubber cap is recommended[3]). A negative control and a positive control are placed in the same manner on two separate test fields. Air bubbles should be prevented or eliminated using a needle, which has been previously heated to red heat and then allowed to cool. All of the small droplets placed on a slide must show some slight movement when the plate is gently vibrated. The slide is then placed in a "moist chamber" consisting, for example, of a flat plastic box, the bottom of which has been covered with a piece of moistened cellulose. Two glass rods serve as support of the slide.

The whole assembly is incubated at 37° for 30 min. After 30 min, the slide is observed against a bright background. The slide is always held in a horizontal position and may be gently tilted or vibrated through an angle of a few degrees only. A solid gel or an increase in viscosity is easily detected. The incubation may be prolonged, but usually the result remains unchanged. Very hygroscopic solutions tend to increase the volume of the droplets upon prolonged standing and, therefore, to reduce the sensitivity of the test. A nonsaturated moist chamber might be used in these cases.

(1) J. F. Cooper, J. Levin, and H. N. Wagner, *J. Lab. Clin. Med.*, **78**, 138(1971).
(2) J. Eibert, *Bull. Parenteral Drug Ass.*, **26**, 253(1972).
(3) H. D. Hochstein, R. J. Elfin, J. F. Cooper, E. B. Seligman, and S. M. Wolff, *ibid.*, **27**, 139(1973).

P. Frauch
Regional Hospital
CH 7000 Chur
Switzerland

Received December 6, 1973.
Accepted for publication February 11, 1974.
Presented in part at the semiannual meeting of the Society of Swiss Hospital Pharmacists, Chur, Switzerland, October 1973.
The skilled technical assistance of Mr. John D. Contesse is acknowledged.

[3] Micropipets and holder, Hirschmann GmbH, Eberstadt, West Germany.

Rapidly Dissolving Forms of Digoxin: Hydroquinone Complex

Keyphrases □ Digoxin—rapidly dissolving digoxin-hydroquinone complex, bioavailability characteristics □ Hydroquinone-digoxin complex—dissolution, bioavailability characteristics □ Bioavailability—digoxin from digoxin-hydroquinone complex

To the Editor:

Numerous recent publications attested to the wide variance in bioavailability found among commercial digoxin tablets (1–5). The main cause of unsatisfactory performance seems to be directly related to the extremely low water solubility of the active substance. Although significant improvements in the efficiency of absorption from oral dosage forms have been obtained through formulation technology, it appears that intrinsically more rapidly dissolving forms of digoxin would provide greater assurance of more reproducible and more bioavailable digoxin products.

In this preliminary communication, we report the development of such forms of digoxin. The approach is based on an earlier concept reported by our group, which utilized free energy of dissolution of molecular complexes to elicit substantially faster dissolution of relatively insoluble solids (6, 7).

Figures 1 and 2 show phase solubility diagrams in water of hydroquinone in the presence of digoxin at

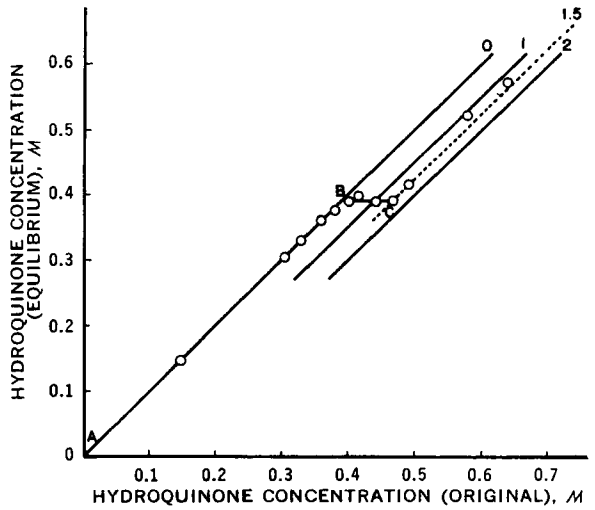

Figure 1—*Plot of hydroquinone concentrations in solution at equilibrium in the presence of 0.05 mole solid digoxin/liter against original concentrations of hydroquinone. The system was equilibrated at 25°. Point B corresponds to the triple point. Line 1 corresponds to the formation of a 1:1 complex, line 1.5 to a 2:3 complex, and line 2 to a 1:2 complex.*

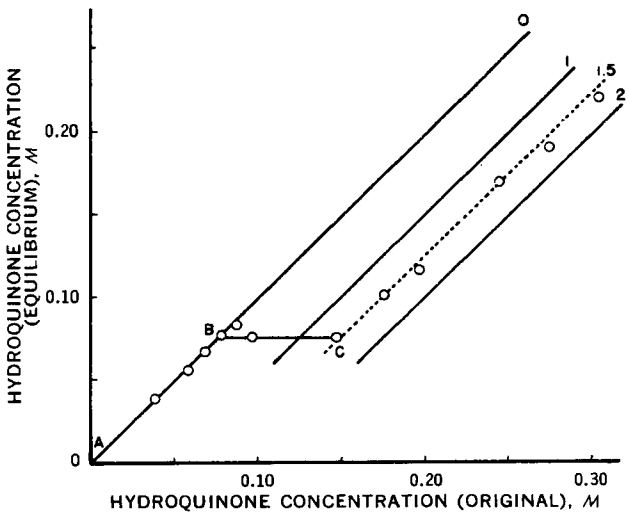

Figure 2—*Plot of hydroquinone concentrations at equilibrium* versus *original concentrations equilibrated at 1.5°. All samples initially contained 0.05* M *(39 mg/ml) of digoxin.*

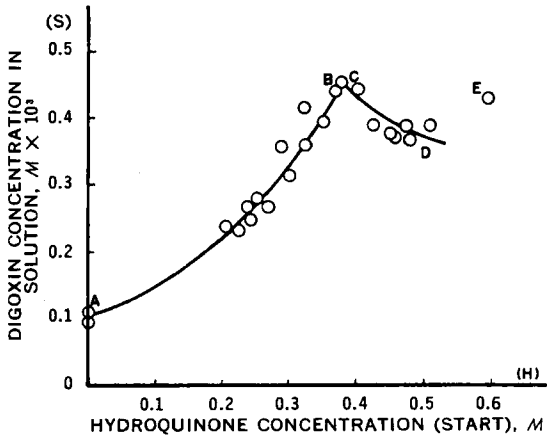

Figure 3—*Apparent solubility of digoxin as a function of hydroquinone concentration at 25°. The system contained 5.12 × 10⁻³ mole digoxin/liter.*

25 and 1.5°, respectively. The more conventional type of plot used to follow complexation reactions of organic species (Fig. 3) is less meaningful in these instances because of the extremely low water solubility of digoxin and the very high solubility of hydroquinone. In both Figs. 1 and 2, the initial total concentration of hydroquinone in solution increases linearly with a slope of one, corresponding exactly to the amount of hydroquinone originally present. At a critical triple point (solution, solid digoxin, and solid complex) corresponding to a solution concentration of approximately 0.38 *M* at 25° and 0.08 *M* at 1.5°, the plots flatten. Following the break, the curves appear to blend into straight lines, again with slopes equal to one.

The total amount of hydroquinone incorporated into digoxin corresponds to the distance between the two parallel lines shown in Figs. 1 and 2. In both instances, the values correspond very closely to formation of a complex species containing two molecules of digoxin and three of hydroquinone. In our studies, variation of conditions led to stoichiometry ranging from 1:1 to 1:2. The usual difficulty of isolating such complexes from their mother liquor without incorporating into the final recovered solid significant amounts of the more concentrated species contained in the adhering mother liquor prevents exact analytical studies on the pure complex. It is, of course, impractical to attempt recrystallization or washing to remove the adhering liquid, since the complex is much more soluble than one of the constituents. Analysis of the unwashed complex corresponded very closely to the indicated chemical compositions.

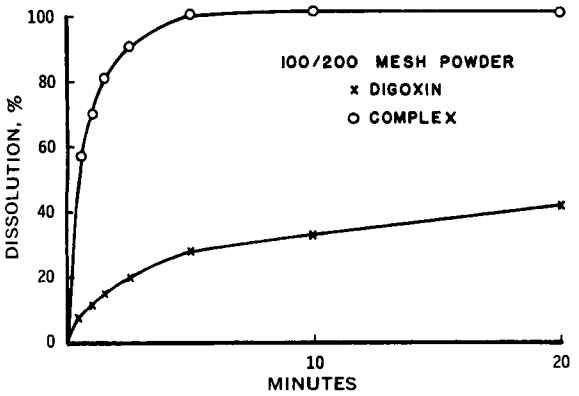

Figure 4—*Dissolution rate profiles obtained for the hydroquinone-digoxin complex and for digoxin itself under comparable conditions.*

The mathematical analysis of dissolution behaviors of complexes of this type was already treated in depth (6, 7). The general equation that applies to dissolution rates of molecular complexes cannot be solved exactly if the diffusivities of the component molecules are significantly different and for other than 1:1 complexes. The form of the equation indicates, however, that for 2 digoxin:3 hydroquinone complex the rate of dissolution per unit area under given stirring conditions will be greater than $(K_{sp})^{1/5}(S_{DG})^{-1}$ than that of pure digoxin, where $K_{sp} = [DG]^2[HQ]^3$, where both concentrations are those of free species at the triple points, and where S_{DG} is the solubility of digoxin alone in water. For the 3:2 complex, $(K_{sp})^{1/5}(S_{DG})^{-1}$ is approximately 140 at 25°, which strongly suggests that its intrinsic rate of dissolution may be as large as several hundred times that of digoxin itself.

In Fig. 4, the relative rates of dissolution of digoxin powder and digoxin-hydroquinone complex are shown[1]. The dissolution measurements were made on the equivalent of 5 mg of digoxin as a 100–200-mesh powder in 500 ml water containing two drops of polysorbate 80[2]. The dissolution medium was maintained at 25° and stirred at 100 rpm. Under these conditions, it is evident that the complexed form of digoxin dissolved much more rapidly, as expected, than digoxin itself. The observed increase in rate has been shown to carry over into tablet formulation.

Since the improved dissolution characteristic is the property of the new form of digoxin and the overall release behavior would be less subject to minor variation in processing, the complex may prove to be the answer to the current problems associated with digoxin solid dosage forms. Moreover, since the complex exists as such only in the solid state and is essentially totally dissociated when dissolved, it only serves as a delivery mechanism. Any toxicity attributable to the amount of hydroquinone present in the final dosage form is, of course, negligible.

We have also formed and isolated a resorcinol complex, but our studies have been quite limited.

(1) *Fed. Regist.*, **39**, 2471(1974).

(2) J. Lindenbaum, M. G. Mellow, M. D. Blackstone, and V. P. Butler, *N. Engl. J. Med.*, **285**, 1344(1971).

(3) T. G. Vitti, D. Banes, and T. E. Byers, *ibid.*, **285**, 1433(1971).

(4) J. G. Wagner, M. Christensen, E. Sakmar, D. Blair, J. D. Yates, P. W. Willis, III, A. J. Sedman, and R. G. Stoll, *J. Amer. Med. Ass.*, **224**, 199(1973).

(5) J. Skelly and G. Knapp, *ibid.*, **224**, 243(1973).

(6) T. Higuchi, "Teacher's Seminar of American Association of Colleges of Pharmacy," 1961, p. 119.

(7) E. Shefter and T. Higuchi, *J. Pharm. Sci.*, **52**, 781(1963).

[1] These plots were obtained for us by Dr. Richard Shaffer of INTERx Research Corp., Lawrence, Kan.

[2] Tween 80.

Takeru Higuchi[x]
Masaru Ikeda
Pharmaceutical Chemistry Laboratory
University of Kansas
Lawrence, KS 66044

Received January 31, 1974.
Accepted for publication March 13, 1974.
Supported by a grant from INTERx Research Corporation of Lawrence, Kan.

[x] To whom inquiries should be directed.

BOOKS

REVIEWS

Current Concepts in the Pharmaceutical Sciences: Dosage Form Design and Bioavailability. Edited by JAMES SWARBRICK. Lea & Febiger, Philadelphia, PA 19106, 1973. xi + 230 pp. 18 × 26 cm. Price $19.50.

The first volume in this series [reviewed in *J. Pharm. Sci.*, **61**, 319(1972)] dealt with several general aspects of biopharmaceutics and pharmacokinetics and partly laid the groundwork for this second volume. The contributors orient their chapters toward assessing bioavailability, showing the significance of variable bioavailability, and indicating ways in which such variability might be overcome.

The first of the six chapters of the book is by S. A. Kaplan who provides a useful review of biopharmaceutics in the preformulation stages of dosage form development. It begins with a brief consideration of how the physicochemical properties of the drug and *in vitro* tests such as dissolution and permeability measurements provide useful input into planning a dosage form. Protocol design, execution of bioavailability studies, pharmacokinetic methods of data analysis, and demonstration of bioavailability problems are the major topics covered.

W. H. Barr takes a unique systems analysis approach to examine the variables that are interspersed between the dosage form and the ultimate clinical effects of the drug. Physiological, pathological, and pharmacokinetic functions including bioavailability are expressed as linear or nonlinear gains which relate the system input and output. A large number of clinically relevant bioavailability problems are provided in this systematic approach to clarification of the role of bioavailability as a primary variable in a sequence of pharmacokinetic and pharmacological factors which ultimately determine both the clinical effects and the risks of drug usage in diverse patient populations.

The third chapter is a useful survey of the effect of formulation additives on drug bioavailability from oral solutions and suspensions by S. L. Hem. Factors that can alter the dissolution and bioavailability of drugs are considered such as type of vehicle and buffer system and presence of sugars, surface-active agents, chelating agents, viscosity-inducing agents, dyes, adsorbents, and crystal growth inhibitors.

W. G. Gorman and G. D. Hall provide a comprehensive treatment of drug absorption from inhalation aerosols. They initially review the normal and pathological anatomy and physiology of the respiratory system. Much of the chapter is concerned with the physicochemical factors of importance in aerosol biopharmaceutics with respect to the formulation of particles and their deposition in various parts of the respiratory system. The final section deals with the complexities and limitations of current mathematical models for inhalation and lung clearance of drugs and drug particles.

Statistical considerations in the design and interpretation of bioavailability trials are crucial topics which have previously lacked clarification by someone with expertise in both pharmacokinetics and biostatistics. W. J. Westlake furnishes an excellent chapter which should provide rational statistical guidelines for all scientists who perform bioavailability studies. The major performance characteristics of a drug formulation are identified as the bioavailability, the blood concentration *versus* time pattern (a multivariate characteristic), and particular univariate properties (*e.g.*, peak blood level). The use of statistics in the design and analysis of bioavailability studies to compare such parameters is lucidly presented and a detailed set of analyzed data nicely demonstrates the statistical methodology.

M. Rowland authors the sixth chapter which is a quantitative examination of the influence of various physiological factors on drug bioavailability from oral dosage forms. Events prior to hepatic distribution, including GI biotransformation and local blood flow, and the influence of hepatic elimination, including use of clearance concepts and the role of hepatic extraction of drugs, are reviewed. A number of linear and nonlinear pharmacokinetic relationships are provided along with data simulations which complement examples from the literature describing most physiological factors affecting bioavailability.

All chapters of the book are amply illustrated, currently documented, and the approach to many of the topics is often innovative. The present clinical, governmental, and industrial activities in seeking optimal bioavailability of drug products, make it a useful and timely publication. The editor and authors have succeeded in providing both an extensive review of the area as well as basic methodology for recognizing and avoiding bioavailability problems with new products.

Reviewed by William J. Jusko
Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo, NY 14214

Aliphatic, Alicyclic, and Saturated Heterocyclic Chemistry, Specialist Periodical Reports, Volume 1 (in three parts). **Part I: Aliphatic Chemistry.** vii + 213 pp. **Part II: Three- and Four-Membered Rings (Carbocyclic and Saturated Heterocyclic).** ix + 517 pp. **Part III: Five- and Six-Membered Rings; Medium Sized Rings; Bridged and Caged Systems (Carbocyclic and Saturated Heterocyclic).** xi + 567 pp. Senior Reporter, W. PARKER. The Chemical Society, Burlington House, London, WIV OBN, England, 1973. 14.5 × 22 cm. Price £20.00 (all three parts).

This volume, the first of the Specialist Periodical Reports of the Chemical Society published under this title, surveys the literature published during the 2-year period of 1970–1971. Subsequent Reports on the areas included in the three Parts of this volume are to be published annually. Part I consists of three chapters. Chapter 1 by R. S. Atkinson deals with acetylenes, allenes, and alkenes. Chapter 2 by E. W. Colvin reviews aliphatic compounds