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Methodological Differences in Correlating Digoxin Dissolution with Bioavailability

Keyphrases □ Digoxin—correlating dissolution and bioavailability, differences in methods, paddle-water method and rotating-basket apparatus □ Dissolution—digoxin, methods of determination, correlation with bioavailability □ Bioavailability—digoxin, correlation with dissolution, methods of dissolution determination

To the Editor:

A recent report by Klink *et al.* (1) indicated that the "paddle-water" method for determining dissolution rates for digoxin tablets failed to reflect the comparative bioavailability properties of two commercially available digoxin products. Specifically, large differences in dissolution rates were observed which failed to reflect the similar bioavailabilities of the two brands studied.

A number of reports have appeared indicating successful *in vivo–in vitro* correlation employing different methods (2–8), including the method recently adopted by the USP (9). Thus, the purpose of this communication is to report the results of recent dissolution rate studies carried out on the same batches of tablets employed by Klink *et al.* (1) using the USP dissolution rate test method.

The dissolution properties of six tablets each from Treatment I[1] and Treatment II[2] tablets were determined using the USP rotating-basket apparatus and employing the conditions specified in the USP (9). Samples were withdrawn and assayed by a fluorometric method (10) at 15, 30, 60, and 120 min after commencement of the studies.

The results of these studies are summarized in Table I, which lists the amount of digoxin in solution at various times for both the USP method and the paddle-water method (1). As indicated by these results, the two brands showed fairly similar dissolution properties, especially at the 60- and 120-min sampling times, when the USP method was employed. This finding is in contrast to the large differences observed at all sampling times when the paddle-water method was employed; Treatment I tablets dissolved much more rapidly than did Treatment II tablets.

These results are of significance when the *in vivo* performance of the two brands is considered. As reported by Klink *et al.* (1), the bioavailabilities of Treatment I and Treatment II tablets, as determined by the area under the serum level–time curves from 0 to 48 hr relative to similar areas obtained from digoxin in elixir data, were 106.38 ± 10.27 and 100.75 ± 24.09%, respectively. Similar relationships between the two brands were observed when the 0–5-, 0–12-, and 0–24-hr areas were compared.

Thus, from the dissolution data presented, it appears that, in the case of the specific lots of the two brands of digoxin tablets studied, the USP method for determining dissolution rates is of greater reliability than is the paddle-water method in predicting bioavailability. Based on these findings and the findings of others (2–8), it appears that much work remains to be done before the acceptance of a single *in vitro* dissolution test for the prediction of digoxin bioavailability from compressed tablets.

Table I—Mean Percent (±Standard Error) of Labeled Digoxin in Solution at Various Times following *In Vitro* Dissolution by Two Different Methods

	USP Method[a]		Paddle-Water Method[b]	
Minutes	Treatment I	Treatment II	Treatment I	Treatment II
15	65.1 ± 2.4	29.6 ± 2.7	—[c]	—
30	76.6 ± 1.8	60.0 ± 4.1	34.9 ± 4.3	6.0 ± 1.2
60	83.7 ± 3.0	77.0 ± 1.4	46.9 ± 6.1	8.0 ± 0.8
120	92.2 ± 0.9	86.7 ± 0.9	59.1 ± 3.9	19.4 ± 3.5

[a] Mean of six tablets. [b] Data from Ref. 1; mean of five tablets. [c] Samples not taken.

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BOOKS

REVIEWS

Quality Control in the Pharmaceutical Industry, Vol. 2. Edited by M. S. COOPER. Academic, 111 Fifth Ave., New York, NY 10003, 1973. 332 pp. 15.5 × 23.5 cm. Price $22.00.

This volume is composed of six chapters covering quality control of aerosol products and veterinary biologicals, the quality control test program of the National Center for Drug Analysis for drug products, pyrogen testing, stability, and sterilization. As in any multiauthor book, certain chapters stand out in comparison with others.

The chapter on Pyrogen Testing of Parenteral Pharmaceuticals by G. R. Personeus provides an excellent comprehensive in-depth discussion of the variables that can influence pyrogen test results and provides the scientist concerned or interested in pyrogen testing with information of how to best use this test. This chapter best fulfills the aim of the editor of the book in dealing in depth with a distinct aspect of the subject of quality control of pharmaceuticals.

The chapter on Pharmaceutical Product Stability by C. J. Lintner provides a general condensed review on stability of pharmaceuticals. Information is provided in this chapter on regulations applicable to stability, types of degradation (hydrolysis, oxidation–reduction, *etc.*,) physical stability of different dosage forms, preservatives, antioxidants, chelating agents, isothermal *versus* nonisothermal reactions, containers and closures, and computer programs for treating and storing stability data; there are also short synopses on stability attributes of specific drug compounds. Because of the considerable amount of information the author provides, no one area of his presentation could be given in depth. The author of this chapter has provided an excellent comprehensive bibliography on his subject.

The chapter on Quality Control of Veterinary Biologics by G. R. Sharpless is concerned for the most part with potency testing of bacterial, viral, sera, toxoid and bacterin–toxoid, and diagnostic products. It also provides a brief review of the tests and procedures outlined by the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture, Veterinary Services Branch, which is responsible for the government regulation of veterinary biologics.

The chapter on the Control of Sterilization Procedures by R. R. Ernst does not discuss sterility tests or testing methods, but instead gives an in-depth presentation of the various factors involved in steam and gaseous sterilization and the types of equipment utilizing these two methods of sterilization. Sterilization by radiation, filtration, and dry heat is treated superficially.

The chapter on Quality Control for Pharmaceutical and Cosmetic Aerosol Products by J. J. Sciarra has only a minor portion related to the quality control of aerosol products and components. The major portion of the chapter is concerned with the general philosophy and principles of quality control and assurance in the pharmaceutical industry.

The chapter on The Test Program of the National Center for Drug Analysis on the Quality Control of Drug Products by A. W. Steers discusses the FDA regulations pertaining to drug quality, the organization of the National Center for Drug Analysis (NCDA), the Retail-Based Drug Monitoring Program, and the Formulator-Oriented Rx Drug Studies (FORDS) Program. Data are presented on the drug products evaluated from the retail-based and formulator-based studies at the NCDA.

Certain chapters of this volume provide the pharmaceutical scientist, quality control chemist, and biologist with pertinent information not readily found in other books which should be of use in their daily work.

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Analytical Profiles of Drug Substances, Vol. 4. Edited by KLAUS FLOREY. Academic, 111 Fifth Ave., New York, NY 10003, 1975. 16 × 23.5 cm. 526 pp. Price $26.50.

Volume 4 of this unique series provides coverage of 20 additional drugs including cefazolin, estradiol valerate, methaqualone, norethindrone, and tybamate. Utilizing a monograph format, these volumes provide frequently difficult to locate information on physical and chemical data, methods of synthesis, pathways of physical and biological degradation, metabolism, and methods of analysis.

Each monograph is amply illustrated and well referenced. Considerable information concerning the drugs is compiled and presented in an easy-to-use format. These volumes should be available to everyone working in pharmaceutical research.

Staff Review