and NMR (D_2O) spectra were superimposable with an authentic specimen of *(RS)*-carnitine chloride[4].

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COMMUNICATIONS

Bioavailability of Digoxin Tablets in Relation to Their Dissolution *In Vitro*

Keyphrases □ Digoxin tablets—dissolution data compared to bioavailability □ Bioavailability of digoxin tablets—relationship to dissolution

To the Editor:

The bioavailability of digoxin tablets has been claimed to be related to their dissolution *in vitro*. Many investigators have correlated the dissolution rate of digoxin tablets to concentration of digoxin in serum or plasma and to values for areas under the serum level–time curves of tablets (1–6). They have concluded that the dissolution rate *in vitro* is adequate for predicting the bioavailability of commercial digoxin tablets. It has been reported recently, however, that despite the different dissolution rates of two different brands of digoxin tablets, the total amount of digoxin absorbed from these tablets was quite similar to that from digoxin elixir USP (7). The present paper reports that the dissolution test according to the USP (8) is not always effective for evaluating the bioavailability of commercial digoxin tablets.

The experiment was carried out with eight healthy volunteer female subjects, ranging in age from 23 to 50 years and in weight from 57 to 68 kg. The subjects had no history of GI, liver, or kidney disease, and none admitted to taking any medication regularly. One digoxin tablet[1] (0.25 mg) or 10 ml of digoxin standard solution[2] (0.025 mg/ml) was given with 100 ml of water to each subject at 9 am for 10 days under laboratory supervision in a crossover manner. Tablets were determined to meet USP specifications as to purity, disintegration time, and content uniformity.

After taking the drug, the subjects were not allowed to eat for 2 hr and were asked to abstain from alcoholic beverages during the experiment. For measuring serum digoxin levels, venous blood samples were taken on the 8th, 9th, and 10th mornings just previous to the next dose of the drug. After the last dose, samples were drawn at intervals of 0.5, 1, 2, 4, 8, and 24 hr.

[1] Digoxin Novum, Star Ltd., Pinnink. 53, SF-33100 Tampere 10, Finland.

[2] Digoxin, 0.00025 g (International Chemical Reference Substance Digoxin, WHO Centre for Chemical Reference Substances, Apotekens Centrallaboratorium, Solna 3, Sweden); propylene glycol, 0.4 g; alcohol, 0.1 g; and sterile water, a sufficient quantity to make 10 ml.

Table I—Percentage of Labeled Digoxin Found in Solution after 60 min, Basal Concentration of Serum Digoxin (Mean of the Last 4 Experimental Days), and Areas under the Serum Level–Time Curves (for 24 hr) on the 10th Experimental Day (Values are Means ± *SE*)

	Percent of Labeled Amount in Solution (n = 12)	Basal Concentration of Serum Digoxin (n = 8)		Areas under the Serum Level–Time Curves (n = 8)	
		ng/ml	Compared with Standard, %	ng/ml × hr	Compared with Standard, %
Digoxin tablets	57.8 ± 1.6	0.59 ± 0.05	95.2 ± 10.6	4.43 ± 0.69	95.0 ± 8.9
Digoxin standard solution	98.4 ± 0.7	0.62 ± 0.04		4.60 ± 0.46	
Probability level	$p < 0.0005$	$p > 0.3$[a]		$p > 0.6$[a]	

[a] Not significant.

The serum samples were analyzed for digoxin radioimmunologically utilizing specific antiserum[3], ^{3}H-digoxin[4], and a liquid scintillation spectrometer[5]. The bound radioactivity separated from free ^{3}H-digoxin during the assay procedure was counted for 10 min/sample. The dissolution of digoxin tablets was performed according to the USP method (8). Twelve tablets were dissolved individually in a cylindrical stainless-steel basket[6], which was dipped into 500 ml of diluted hydrochloric acid (3 in 500) and rotated for 60 min at 120 rpm. After dissolution medium samples were filtered with a filter of 0.45-μm porosity[7], digoxin concentration was measured fluorometrically[8].

The percentage of digoxin dissolved after 60 min from the tablets was compared with the percentage of drug recovered from the dissolution medium containing dissolved digoxin (10 ml of standard solution) equivalent to the labeled amount in the tablets. For this comparison, the Student t test was used. Data from *in vivo* experiments were tested by a t test for paired observations. Areas under the serum level–time curves were determined by a planimetrical technique.

The amount of digoxin dissolved after 60 min from the tablets corresponded to 57.8 ± 1.6% (mean ± *SE*) of the declared amount and varied from 49.0 to 69.5% (Table I). The respective percentage of drug recovered from the dissolution medium containing standard solution (10 ml) was 98.4 ± 0.7% (from 94.0 to 101.5%). Despite the rapid disintegration of each tablet in this medium (1–2 min), four tablets dissolved less than the required 55% of the labeled amount of drug.

The basal digoxin concentration in serum and areas under the serum level–time curves during the last experimental day are shown in Fig. 1 and Table I. During the treatment with tablets, the basal digoxin level was 95.2 ± 10.6% of that caused by the standard solution (mean of the last 4 experimental days), and the area under the serum level–time curve describing digoxin absorption from tablets in the alimentary tract was 95.0 ± 8.9% of that of the standard solution. There was no statistically significant difference between tablets and standard solutions in these parameters.

Previously, Klink *et al.* (7) demonstrated that the bioavailability of digoxin tablets may be excellent despite the poor dissolution *in vitro*. They did not, however, report whether their tablets disintegrated rapidly during the dissolution test or whether digoxin was released slowly from the surface. In the present study, the poor dissolution percentage may be partly explained by the fact that during the test an essential part of the grains of the disintegrated tablets fell through the wall of the rotating basket into a nonagitated part of the apparatus where the release of digoxin from the grains probably was negligible or too slow.

Although the tablets tested did not meet USP specifications for dissolution (8), the basal digoxin concentration in serum and the area describing digoxin absorption during the treatment with tablets did not differ significantly from those caused by the standard solution. These results agree with the concept of Klink *et al.* (7) that a single dissolution test may not show a good correlation between the GI ab-

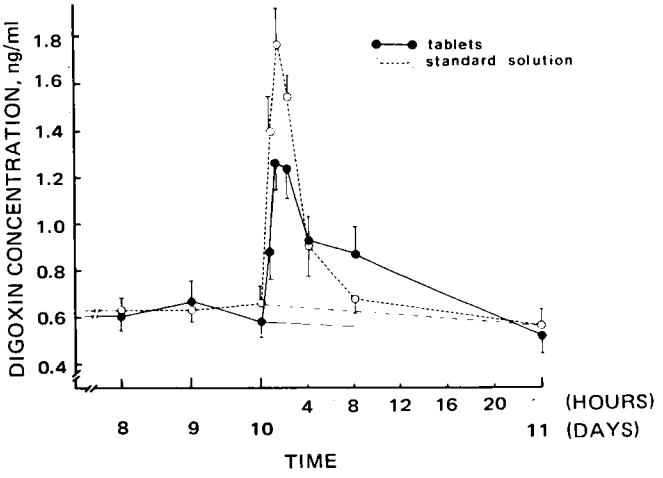

Figure 1—*Basal concentration of serum digoxin during the last 4 experimental days and the serum digoxin levels at each time of collection on the 10th experimental day following 10 consecutive daily administrations of 0.25 mg of digoxin (n = 8; values are means ± SE).*

[3] Laboratory Kvantti, Hallitusk. 28-30, SF-90100 Oulu 10, Finland.
[4] Digoxin 12-^{3}H, New England Nuclear, Boston, MA 02118
[5] Packard Tri-Carb scintillation spectrometer, Packard Instrument Co., Downers Grove, IL 60515
[6] A 40-mesh woven wire cloth formed into a cylinder 3.66 cm high and 2.5 cm in diameter; Hanson Research Corp., Northridge, CA 91324
[7] Sartorius-Membranfilter Ltd., Weender Landstrasse 94-102, 34 Göttingen, Germany.
[8] Aminco-Bowman spectrophotofluorometer, American Instrument Co., Inc., Silver Spring, MD 20910

sorption of digoxin from all commercially available compressed tablets and their dissolution *in vitro*. The results also indicate the poor applicability of the USP (8) dissolution test in predicting the bioavailability of this particular brand of commercial digoxin tablets.

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BOOKS

REVIEWS

Proceedings of the USP Conference on Radiation Sterilization, The United States Pharmacopeia, Inc., Rockville, MD 20852, 224 pp. 16 × 22 cm. Price $10.00.

This volume consists of 15 papers devoted to an area of pharmaceutical and biomedical technology in which the United States has lagged behind several European nations, largely because of strict controls on testing of safety and efficacy imposed by federal agencies. Among the subjects considered in detail are instrumentation and experimental conditions employed in radiation sterilization, chemical dosimetry, the effects of ionizing radiations on microorganisms, and the evaluation of microbiological control systems for the determination of the efficacy of radiation sterilization.

Ionizing radiation offers an advantage over heat in the sterilization of thermally degradable materials. However, the high doses and dose rates required to effect sterilization, especially against radio-resistant bacteria, represent a problem because of the susceptibility of many materials to chemical and structural alterations as a result of their interactions with ionizing radiations. The treatment of bacteria-containing samples with UV light prior to high-energy irradiation provides a solution to this problem, at least in some cases, as bacteria preirradiated with UV light appear to require smaller doses of ionizing radiations to produce the same degree of sterilization observed in untreated bacterial samples. The cobalt-60 γ-ray source which, historically, was the first sterilization source employed on a wide scale is still preferred over other isotopic sources because of its high radiation flux, long-term stability, and relatively low cost and is favored over electronuclear sources such as the linear accelerator because of the high cost of the latter. It is suggested by several contributors to the volume that the cobalt-60 source is expected to maintain its preeminence for the forseeable future. It is also suggested that the search for and evaluation of better dosimeters and microbiological standards will be a major area of endeavor for some time to come. The need for improved microbiological controls is particularly acute because much of the testing of the efficacy of radiation sterilization has been carried out with bacteria which are unrepresentatively sensitive to radiation damage.

"Proceedings of the USP Conference on Radiation Sterilization" is a comprehensive, authoritative, and very readable account of a subject which is probably the major industrial application of ionizing radiations. Although it deals primarily with applications to biological test systems and surgical products, it is worthwhile reading for all pharmaceutical and biological scientists.

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The United States Pharmacopeia, Nineteenth Revision. Prepared and Published by The United States Pharmacopeial Convention, Inc., Distributed by Mack Publishing Co., 20th & Northampton Sts., Easton, PA 18042, 1974. l + 824 pp. 21.5 × 28 cm. Price $25.00.

This latest revision of the *United States Pharmacopeia* (USP XIX) continues its respected tradition by providing legally recognized standards for identity, strength, quality, and purity for nearly 1300 important and well-established drugs and their dosage forms in use in the United States. Additionally, about one-fourth of this volume is devoted to general chapters, reagent specifications, and tables.