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Thiazides VIII: Dissolution Survey of Marketed Hydrochlorothiazide Tablets

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Abstract □ The dissolution profiles of 50-mg hydrochlorothiazide tablets representing all approved manufacturers (at the time of the study) were determined in two vehicles [purified water and dilute (1:100) hydrochloric acid] by three methods (rotating basket at 150 rpm; spin filter at 300 rpm; paddle method at 50 rpm). The paddle method was preferred on the basis of overall ease of operation, reproducibility, and discrimination. The paddle data were validated in both vehicles on the same lots of tablets by a second laboratory. A standard of not <80% dissolution in 60 min by the paddle method in water is proposed for hydrochlorothiazide tablets.

Keyphrases □ Hydrochlorothiazide tablets—dissolution studies, paddle method, basket method, spin filter method □ Dissolution—paddle method, basket method, spin-filter method, hydrochlorothiazide tablets □ Paddle method—dissolution of hydrochlorothiazide tablets □ Basket method—dissolution studies of hydrochlorothiazide tablets □ Spin-filter method—dissolution studies of hydrochlorothiazide tablets

Hydrochlorothiazide is a member of the benzothiadiazine class of orally effective diuretics widely used in the treatment of hypertension, congestive heart failure, and other edematous conditions. As a class, these compounds generally are poorly wetted and have limited solubility. Thus, it is not surprising that they have been identified in the Federal Register (1) as a class of drugs with a potential for bioavailability/bioequivalency problems and for which dissolution standards should be developed. For such standards to be meaningful and reflect bioavailability performance, the dissolution system must be capable of generating data that consistently correlate with *in vivo* performance. However, the dissolution of a drug from its dosage form is dependent on many factors, which include not only the physicochemical properties of the drug, but also how the dosage form is formulated and processed. Thus, even in the absence of a correlation between *in vivo* and *in vitro* data, dissolution data provide a desirable aid in controlling formulation and manufacturing variables and should be a reliable indicator of uniformity of manufacture. The objectives of this study were to (*a*) survey the dissolution performance of marketed hydrochlorothiazide products by various methods, (*b*) select an appropriate dissolution method, and (*c*) develop acceptable dissolution standards based on the performance of the marketed products. The results of this study should form a basis for the consideration of other members of the benzothiadiazine class.

EXPERIMENTAL

Materials—Commercial 50-mg hydrochlorothiazide tablets[1] (representing all approved manufacturers at the time of the study) were used.

Reagents and Chemicals—Distilled water was used throughout, and all other chemicals or reagents were either official grade or reagent grade. Hydrochlorothiazide USP was the reference standard.

[1] Product 1, Abbott Laboratories Lot No. 55-116AF22; Product 2, Barr Lot No. 6C02013; Product 3, Ciba Lot No. 10721; Product 4, Danbury Lot No. 12357; Product 5, Heather Lot No. 61088; Product 6, Merck Sharp and Dohme Lot No. V2487; Product 7, Towne Paulsen Lot No. 037652; Product 8, Zenith Lot No. A208313.

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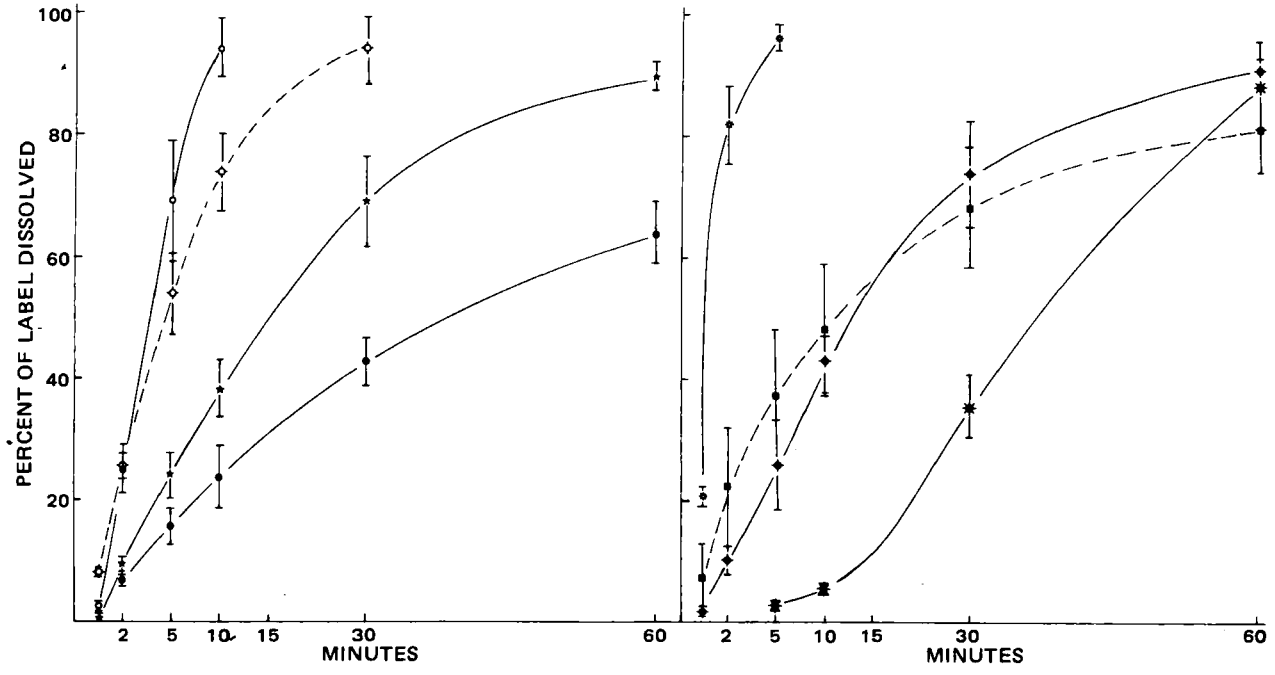

Figure 1—*Dissolution of hydrochlorothiazide tablets in purified water—paddle method (50 rpm). Key: product 1 (★); product 2 (☼); product 3 (○); product 4 (◇); product 5 (■); product 6 (●); product 7 (◆); product 8 (✹).*

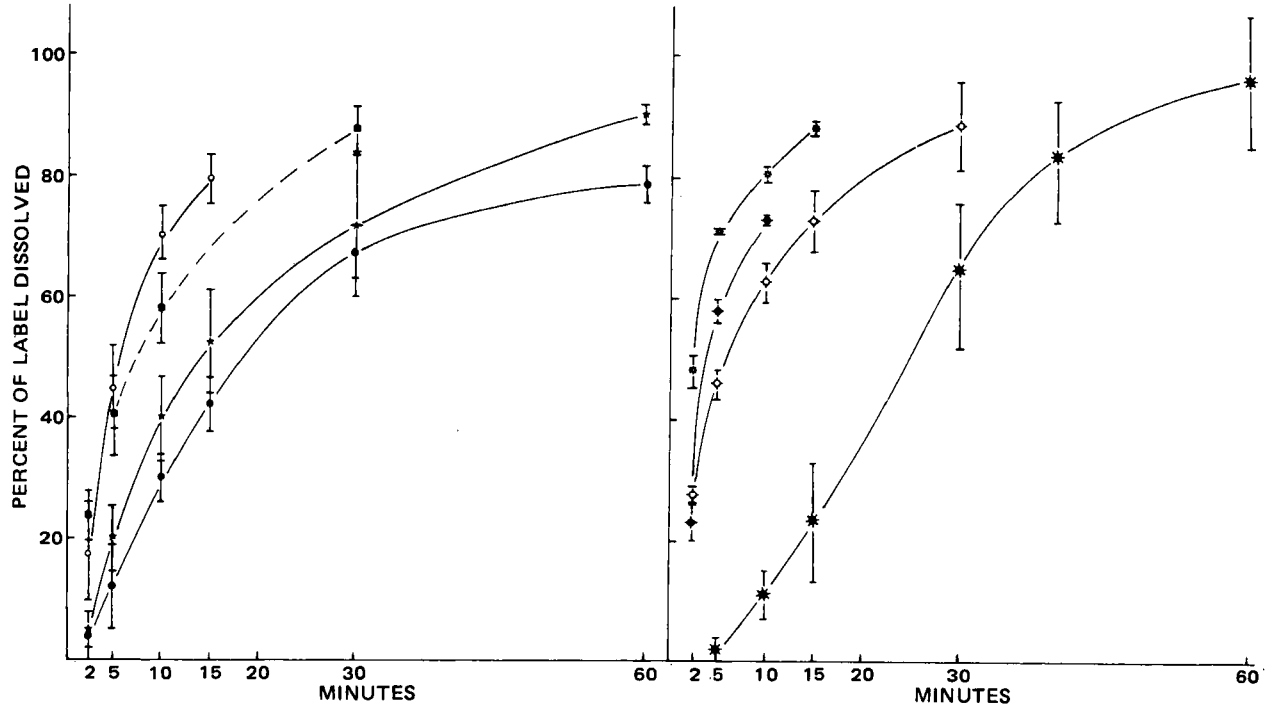

Figure 2—*Dissolution of hydrochlorothiazide tablets in purified water—rotating basket method (150 rpm). See Fig. 1 for key to graph.*

Dissolution Methods—The dissolution tests were carried out in two laboratories using UV spectrophotometry[2]. Dissolution was monitored by continuously circulating the filtered medium from each flask to and through a 0.1-cm path-length flow cell mounted in the spectrophotometer, and then back to the flask. The filter was mounted on the intake end of the hosing and consisted of a 13-mm fiberglass pad held in a plastic holder.

Dissolution was carried out in distilled water and in dilute (1:100) hydrochloric acid: 900 ml at 37°.

Rotating Basket (USP XIX, Method 1)—The basket assemblies were rotated in resin flasks by means of a multiple-spindle drive system[3]. Official specifications (2) were adhered to, including the 150-rpm stirring rate noted in the hydrochlorothiazide monograph.

Paddle Method (USP XX, Method 2)—The paddles were rotated in round-bottom flasks by suitable adaptation of the multiple-stirrer head. All official specifications (2) were followed. A paddle speed of 50 rpm was selected.

Spin-Filter Method—This method is essentially the stationary basket, spinning-filter method described by Shah *et al.* (3). The apparatus[4] was obtained commercially. The geometry relating the position of the basket to the filter is fixed by the apparatus design; however, the filter unit was always set 2 mm from the bottom of the flask, as recommended (3). Filter rotational speed was 300 rpm.

[2] Beckman 25/7 Spectrophotometer, Beckman Instruments, Fullterton, Calif.

[3] Easilift Dissolution Test Station Model 63-734-100, Hanson Research Corp., Northridge, Calif.

[4] Magne-Drive Dissolution Test Apparatus, Series 74, Coffman Industries, Inc., Kansas City, Kan.

Table I—Dissolution of 50-mg Hydrochlorothiazide Tablets by Paddle Method at 50 rpm in Water and Acid

Product	% Dissolved in Water				% Dissolved in Acid			
	30 min		60 min		30 min		60 min	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
1	68.9	7.4	89.4	2.5	86.7	2.3	95.3	1.4
2	95.8[a]	2.2	—	—	94.3[a]	5.9	—	—
3	93.7[a]	5.3	—	—	94.1[a]	4.6	—	—
4	93.7	4.9	—	—	91.5	5.3	—	—
5	68.4	10.3	81.1	6.7	86.3	9.6	—	—
6	42.5	3.9	63.8	4.9	66.0	11.0	78.0	6.9
7	73.5	8.6	90.5	2.3	97.8	2.2	—	—
8	35.5	5.3	88.0	7.3	80.0	4.5	95.5	3.2

[a] — 15-min value.

Except for the spin-filter runs, the media were not deaerated. Concentrations were determined at 272 nm. Laboratory I used all three methods; laboratory II validated laboratory I results using only the paddle method. Six or more tablets from each lot were evaluated by each laboratory.

Stability of Hydrochloride in the Dissolution Media—Stability studies were conducted in purified water and dilute hydrochloric acid (1:100) for 90 min at 37°. The samples were analyzed for diazotizable substances (hydrolyzed product) using both the Bratton–Marshall colorimetric technique (4) and a specific high-performance liquid chromatographic (HPLC) method. For the HPLC method, a C_{18} reverse-phase column, a 254-nm detector, and a methanol–water eluant (60:40) were used.

Table II—Dissolution of 50-mg Hydrochlorothiazide Tablets by Basket Method at 150 rpm in Water and Acid

Product	Water % Dissolved in 30 min		Acid % Dissolved in 30 min	
	Mean	*SD*	Mean	*SD*
1	71.8	12.4[a]	83.2	2.9[b]
2	88.3[c]	1.4	94.3[c]	4.3
3	79.2[c]	4.5	94.0[c]	5.7
4	88.7	7.2	81.0[c]	5.3
5	87.7	3.9	87.0[c]	5.6
6	67.5	4.6[d]	90.8	7.1
7	73.3[c]	0.5	78.8	4.0[e]
8	64.8	12.0[f]	93.2	1.9

[a] 90.5 ± 2.1 in 60 min. [b] 94.5 ± 2.3 in 60 min. [c] In 15 min. [d] 88.8 ± 3.5 in 60 min. [e] 88.3 ± 3.7 in 60 min. [f] 83.2 ± 10.3 in 60 min.

For the purposes of identity and determining the extent of hydrolysis under dissolution conditions, USP reference hydrolyzed products were used. Less than 5% hydrolysis was found in either medium after 90 min.

RESULTS AND DISCUSSION

One of the first requirements of a dissolution study is to determine the equilibrium solubility of the compound. The solubility test gives the maximum expected dissolution of less soluble compounds and provides information as to whether sink conditions are being approximated in the test or not. In earlier investigations, it was accepted that the maintenance of sink conditions (or the approximation) increases the chances for *in vitro–in vivo* correlation, although lack of sink conditions does not necessarily prohibit such a correlation. Equilibrium solubility studies carried out showed that hydrochlorothiazide is soluble to the extent of 1.05 mg/ml in water and 1.06 mg/ml in dilute hydrochloric acid, which approximates to only 5.3% saturation for a 50-mg tablet in 900 ml of the medium.

The dissolution of all marketed hydrochlorothiazide tablets was surveyed using both dilute (1:100) hydrochloric acid and water as the dissolution media: water is the simplest possible medium, and dilute acid has physiological significance owing to the pH of the gastric contents.

The USP rotating basket at 150 rpm was selected since it was the official method used for hydrochlorothiazide tablets in USP XIX. The paddle method has been gaining popularity in recent years and is currently recognized as Method 2 in the official compendia. The paddle speed of 50 rpm was selected on the basis of preliminary experiments and the experience of the Food and Drug Administration with this method. It was felt that this low degree of agitation would not only enhance the chances for *in vitro–in vivo* correlation, but also enhance discrimination between brands. The stationary basket-spinning filter method was se-

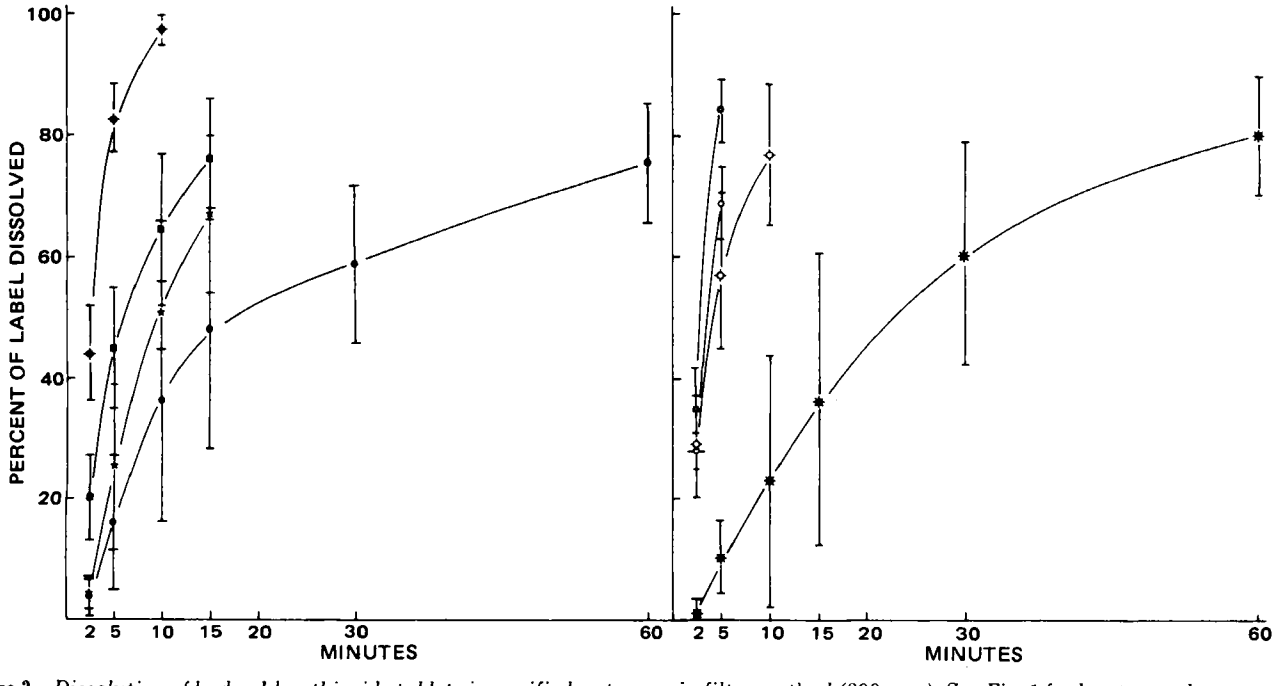

Figure 3—*Dissolution of hydrochlorothiazide tablets in purified water—spin filter method (300 rpm). See Fig. 1 for key to graph.*

Table III—Dissolution of 50-mg Hydrochlorothiazide Tablets by Spin-Filter Method at 300 rpm in Water and Acid

Product	Water % Dissolved			Acid % Dissolved		
	Minutes	Mean	*SD*	Minutes	Mean	*SD*
1	15	67.3	13.4	15	80.2	5.5
2	5	84.2	5.4	5	85.3	5.5
3	5	69.0	6.2	10	94.7	3.2
4	10	76.7	11.8	10	79.0	12.6
5	15	75.9	10.4	10	96.4	5.3
6	30	59.4	13.4[a]	15	83.6	3.4
7	5	82.7	5.8	10	80.0	4.9
8	30	58.4	18.1[b]	15	65.5	11.5

[a] 75.7 ± 10.0 in 60 min. [b] 78.0 ± 9.6 in 60 min.

lected largely on the basis of the encouraging results reported by Shah *et al.* (3).

The dissolution results by all three methods in both media are summarized in Tables I–III and Figs. 1–6. The final procedure for validation in laboratory II was selected based on the reproducibility of the method, its ability to discriminate brands, and ease of operation.

The data in Tables I–III show that the dissolution results in water and acid were similar, although some products (1, 5, 6, and 8) apparently contain acid-soluble excipients and, therefore, tend to show faster dissolution in this medium. For example, with the paddle method, the eight hydrochlorothiazide products dissolved in the range of 35–96% in 30 min in water, whereas in acid the same products dissolved in the range of 66–97% in 30 min (Table I). However, all products exhibited at least 60% dissolution in 60 min in both media. Dissolution by the basket method at 150 rpm was faster than the paddle method, but the spin-filter method showed the fastest dissolution. Most of the products showed 70–80% dissolution in 10 min by the spin-filter method.

The same lots were evaluated by each of the methods. The relative standard deviations were comparable for the paddle and basket methods; however, variability tended to be somewhat higher in the spin-filter apparatus. Furthermore, a comparison of the percent-dissolved figures reveals that both the paddle and basket methods tended to separate the tablet brands reasonably well. A somewhat more distinct separation was realized with the paddle method. In the case of the spin-filter apparatus, the dissolution rates of nearly all tablets were quite high, but the separation of brands was somewhat poorer. These distinctions can be visualized by comparing the dissolution profiles of the products in Figs. 1–6. The bar around each point represents the standard deviation. The results in Tables I–IV also show that regardless of the method, a somewhat clearer separation of the brands results when water is the dissolution medium.

In general, the paddle method was easier to set up and use. The disintegrated-tablet components tended to remain localized under the paddle in the concavity of the round-bottomed flask, where they presumably received a uniform degree of agitation during the course of the run. In addition, the paddle method was the easiest of the three methods to clean up.

In contrast, the basket method required insertion of the tablets into individual baskets prior to starting. As particles from the disintegrated tablet gradually pass through the basket screen during the test, it appeared that not all of the tablet material received uniform agitation.

The most difficult method to set up and use was the spin-filter apparatus. This method requires careful adjustment of the spinning filter to maintain a clearance of 2 mm from the bottom of the flask. Even after careful tightening of the lock nuts, the filter was found to drop at times to the bottom of the flask. This alters the rotational speed and contributes to variability. The most troublesome problem was the tendency of the

Table IV—Validation Studies on 50-mg Hydrochlorothiazide Tablets (Paddle Method, 50 rpm)

Product	% Dissolved in 60 min			
	Water		Acid	
	Mean	*SD*	Mean	*SD*
1	94	1.4	94	1.0
2	100	1.9	99	0.8
3	99	1.5	100	1.9
4	90	8.1	97	1.4
5	90	7.8	99	1.3
6	59	9.1	101	2.6
7	100	1.6	101	3.0
8	87	7.2	97	2.6

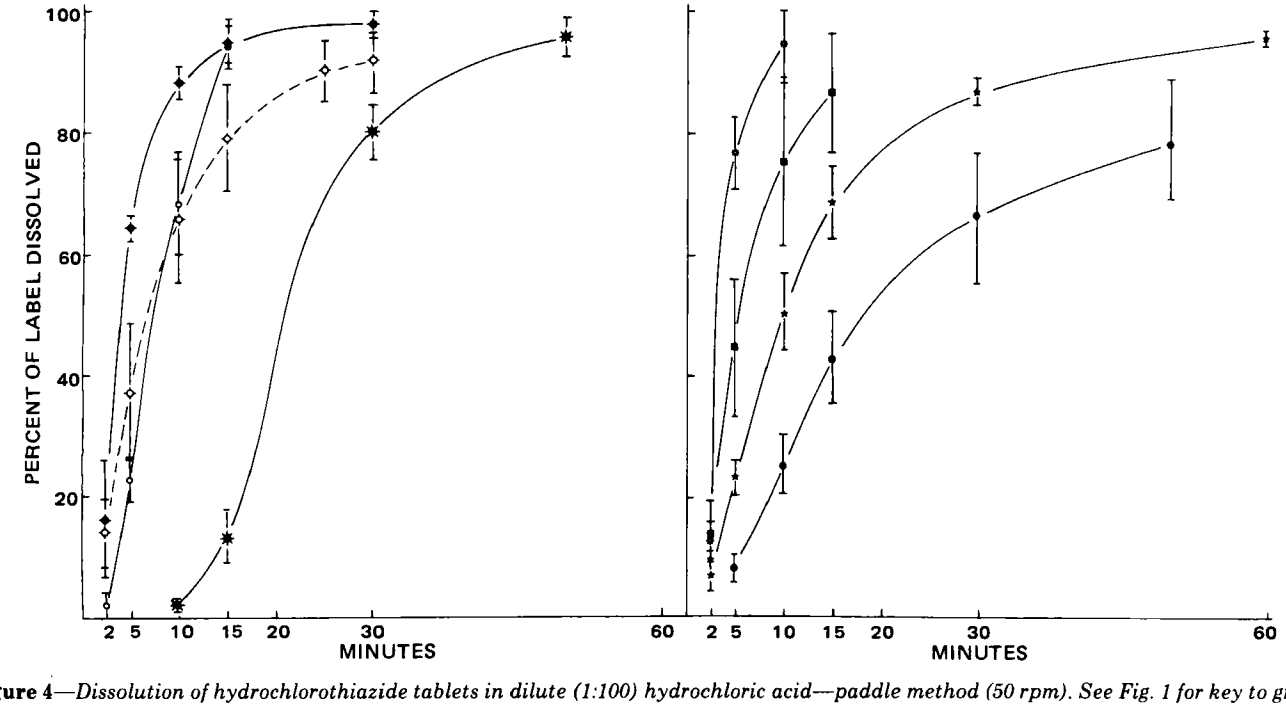

Figure 4—*Dissolution of hydrochlorothiazide tablets in dilute (1:100) hydrochloric acid—paddle method (50 rpm). See Fig. 1 for key to graph.*

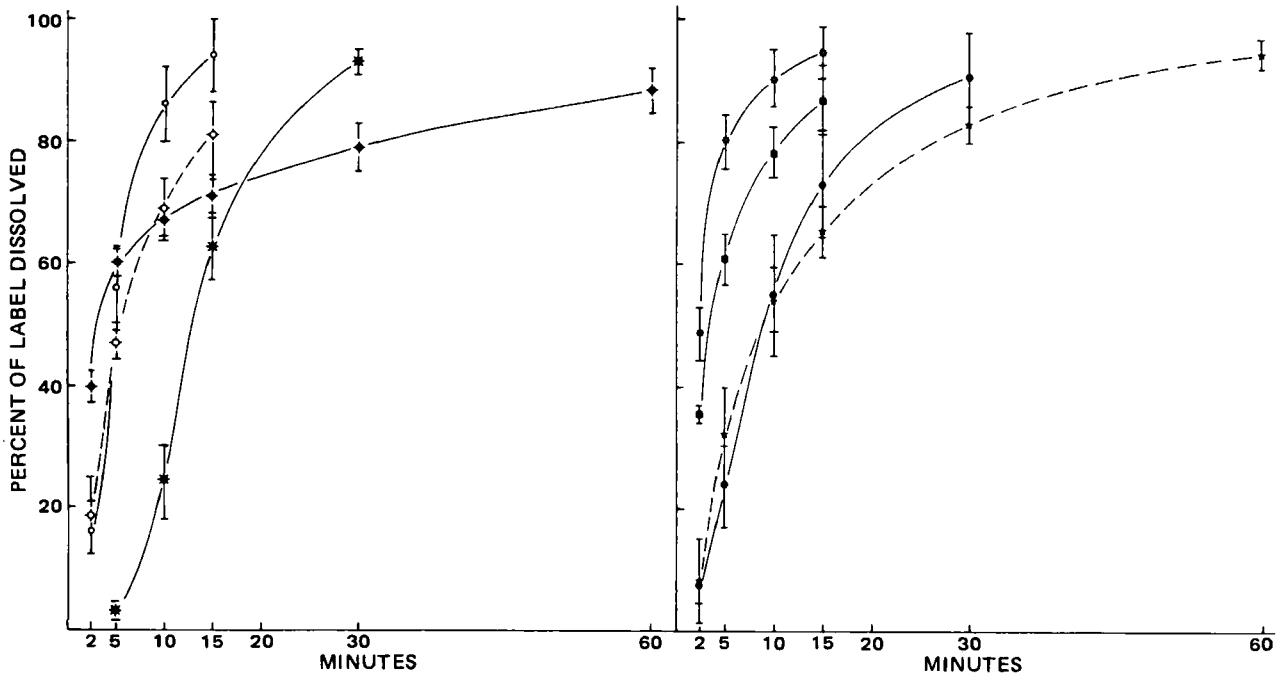

Figure 5—*Dissolution of hydrochlorothiazide tablets in dilute (1:100) hydrochloric acid—rotating basket method (150 rpm). See Fig. 1 for key to graph.*

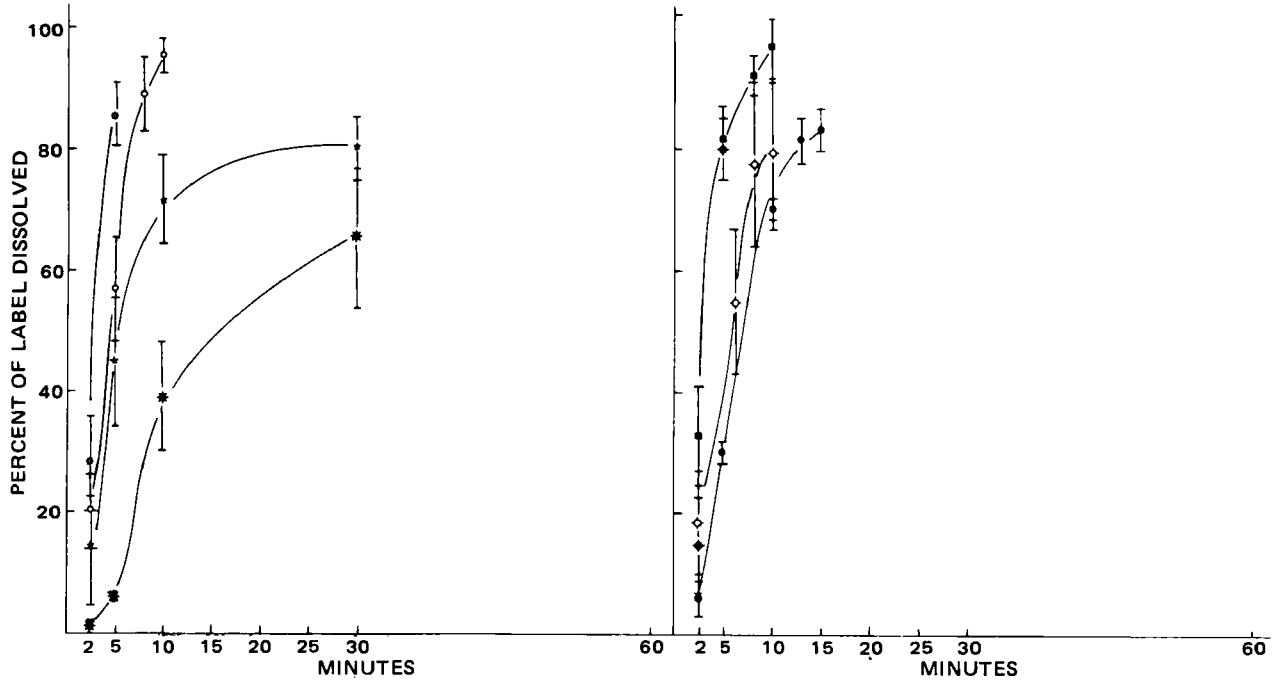

Figure 6—*Dissolution of hydrochlorothiazide tablets in dilute (1:100) hydrochloric acid—spin filter method (300 rpm). See Fig. 1 for key to graph.*

spinning filter to create air bubbles in the flow lines which interfered with spectrophotometric readings. Careful cleaning of the filters in an ultrasonic bath and thorough deaeration of the medium reduced the air bubble problem to manageable levels; however, they could not be eliminated entirely.

In conclusion, on the basis of data reproducibility (lower standard deviation) and ease of operation, as well as enhanced separation of the dissolution results for all products tested, the paddle method at 50 rpm was selected (preferred) over the basket method at 150 rpm and the spin-filter method at 300 rpm.

The same lots of hydrochlorothiazide tablets were validated by another laboratory using the paddle method with water and dilute hydrochloric acid as the dissolution media. The results from these studies (Table IV) show good agreement between data from the two laboratories. All eight products studied show a good dissolution profile. Additional batches of products 6 and 8 were also studied, and they showed faster dissolution.

At present, there is no documented evidence of any bioavailability problem from the marketed products studied. The dissolution survey described herein indicated that it is possible to manufacture products that dissolve not <80% in 60 min by the paddle method at 50 rpm in water. The dissolution methodology presented herein is simple. In addition, it is evident that the limit specified is achievable. These two facts show that the method could be useful in a quality assurance program.

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Synthesis and Structural Study of *N*-Substituted Nortropane Spirohydantoins

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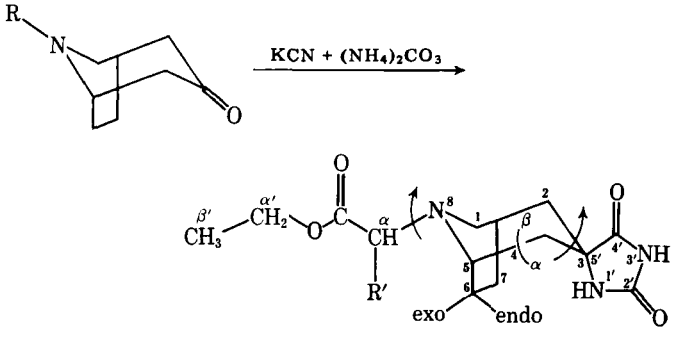
Abstract □ A series of N^8-alkyloxycarbonylalkyl-nortropane-3-spiro-5′-hydantoins has been synthesized and studied by spectral and crystallographic methods. The crystal and molecular structure of one [8(γ-ethoxycarbonylpropyl)nortropane-3-spiro-5′-hydantoin, VI] was determined by X-ray diffraction. The preferred conformations of these compounds and subsequent changes on protonation were determined from ^{1}H-NMR and ^{13}C-NMR data.

Keyphrases □ *N*-Substituted nortropane spirohydantoins—synthesis, structural studies using IR, NMR, and X-ray crystallography □ NMR spectroscopy—analysis of *N*-substituted nortropane spirohydantoins □ IR spectroscopy—analysis of *N*-substituted nortropane spirohydantoins □ X-Ray crystallography—analysis of *N*-substituted nortropane spirohydantoins

In a previous paper (1), ^{1}H- and ^{13}C-NMR studies of a pharmacologically interesting series of tropane- and *N*-substituted nortropane-3-spiro-5′-hydantoins were reported. The structure of tropane-3-spiro-5′-hydantoin (determined by X-ray methods) also has been described (2). In this study the synthesis and structural determination of a series of N^8-ethoxycarbonylalkyl-nortropane-3-spiro-5′-hydantoins and their corresponding hydrochlorides is reported (Scheme I). Treatment of the appropriate N^8-substituted nortropinone[1] with potassium cyanide and ammonium carbonate in aqueous ethanol gave the desired hydantoins.



I: R′ = H
II: R′ = $-CH_3$
III: R′ = $-CH_bH_cC_6H_5$
IV: R′ = $-CH_2CH_2CO_2CH_2CH_3$
V: R′ = $-CH(CH_3)_2$
VI: $>N^8-CH_2CH_2CH_2CO_2CH_2CH_3$
VII: $>N^8-C_6H_4$-*p*-$CO_2CH_2CH_3$

Scheme I

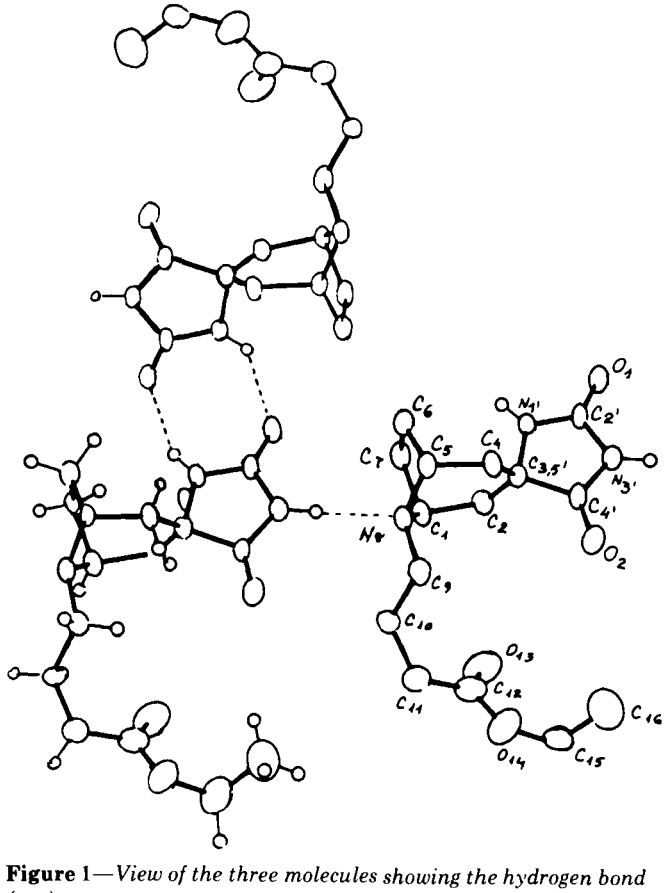


Figure 1—*View of the three molecules showing the hydrogen bond (---).*

[1] G. G. Trigo, M. Martinez and E. Galvez, unpublished results.

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