cedure can result in considerable savings in cost and time over the duration of the drug screening. In judging whether or not an impurity test is required, comparison is made with a reference impurities assay chromatogram (Fig. 1). In the present work, the GLC determination of II and III was carried out on all capsule formulations. A larger amount of chlordiazepoxide hydrochloride was used for the impurities test to increase the concentrations of II and III in the final solution to afford increased peak areas and improved accuracy.

The data given in Table II show that, by the GLC procedure, Formulations 1 (7.1% of II) and 3 (3.4% of II) failed to comply with the USP purity requirement of 3.0% of II. Impurity III was detected at a level of 0.02% in Formulation 1 but was not observed in others. The products were old samples selected to demonstrate the merits of the GLC method and are not representative of the quality of chlordiazepoxide capsule preparations currently on the market. A chromatogram of an impurity calibration solution containing the maximum levels of II and III allowed in the USP monograph for chlordiazepoxide hydrochloride capsules is shown in Fig. 2.

Identity—USP identity tests for chlordiazepoxide hydrochloride capsules and diazepam tablets involve nonspecific UV absorbance scans of the assay solutions and chemical tests on aliquots of the sample powders. The NF identity of flurazepam in capsule formulations is confirmed by these tests and also by an IR trace of a carbon disulfide extract of the drug. While this test is highly specific, it can be time consuming if numerous samples are to be monitored.

In the GLC procedure, identity was established during the analytical run by comparing the retention time and peak area of the drug in the sample solution with those of the reference standard in the calibration solution, the latter having been prepared at the concentration assumed for the sample solution. The probability of an artifact compound in a formulation labeled to contain the drug of interest having coincident retention time and peak area to those of the reference standard is considered remote. This manner of confirming the identity of the drug is suitable for screening programs, and it is not only quicker than the pharmacopeial tests but also is generally more specific and allows verification of the identity of the drug in each dosage unit. However, in rare instances where the identity of the product might be questioned or otherwise still be in doubt, absolute identification of the drug can be confirmed by IR spectroscopy.

REFERENCES

(1) R. C. Basalt, C. B. Stewart, and S. J. Franch, *J. Anal. Toxicol.*, **1**, 10 (1977).

(2) J. Besic, M. Grims, I. Sernhorst-Staresinic, I. Beus, and J. Rulnjevic, *Acta Pharm. Jugosl.*, **26**, 99 (1976).

(3) J. P. Cano, J. Guintrand, C. Aubert, and A. Viala, *Arzneim.-Forsch.*, **27**, 338 (1977).

(4) J. L. Ferguson and D. J. Couri, *J. Anal. Toxicol.*, **1**, 171 (1977).

(5) B. E. Pape and M. A. Ribick, *J. Chromatogr.*, **136**, 127 (1977).

(6) G. J. G. Parry and D. G. Ferry, *ibid.*, **128**, 166 (1976).

(7) D. M. Rutherford, *ibid.*, **137**, 439 (1977).

(8) J. A. F. de Silva, I. Bekersky, C. V. Puglisi, M. A. Brooks, and R. E. Winefeld, *Anal. Chem.*, **48**, 10 (1976).

(9) A. J. Bugge, *J. Chromatogr.*, **128**, 111 (1976).

(10) K. Harzer and R. J. Barchet, *ibid.*, **132**, 83 (1977).

(11) L. C. Bailey, *Am. J. Pharm. Educ.*, **42**, 63 (1978).

(12) A. G. Butterfield, F. F. Matsui, S. J. Smith, and R. W. Sears, *J. Pharm. Sci.*, **66**, 684 (1977).

(13) M. Emery and J. Kowto, *ibid.*, **68**, 1185 (1979).

(14) J. T. Stewart and J. L. Williamson, *Anal. Chem.*, **48**, 1182 (1976).

(15) W. Lund and L. Opheim, *Anal. Chim. Acta*, **88**, 275 (1977).

(16) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, pp. 80, 136.

(17) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., pp. 292, 293.

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Stability-Indicating Assay for Hydrochlorothiazide

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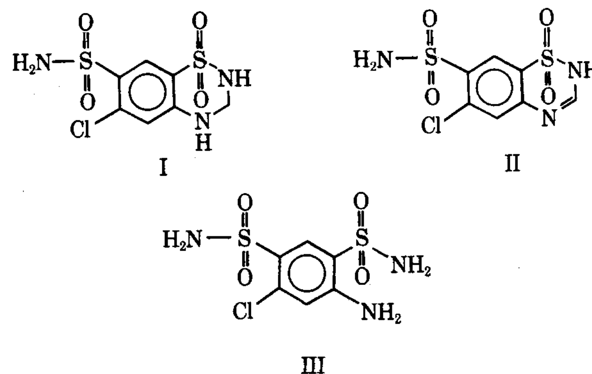
Abstract □ A stability-indicating method for determining hydrochlorothiazide in tablet formulations and in the bulk form is described. Hydrochlorothiazide is dissolved or extracted using methanol. An aliquot of the solution, containing sulfadiazine as an internal standard, is chromatographed on a 10-μm C_{18} column with an aqueous mobile phase containing 5% methanol as the modifier. The pH is adjusted to about 4.5 with acetic acid. The method gave accurate results for nine lots (four different suppliers) of tablets and two bulk drug lots (two different suppliers). The assay has a relative standard deviation of about 1%. The method can also be used as a test for impurities in hydrochlorothiazide. The data in this study indicate that the test should give accurate results for impurities between 0.1 and 5%.

Keyphrases □ Hydrochlorothiazide—stability-indicating high-pressure liquid chromatographic method □ Degradation—stability-indicating high-pressure liquid chromatographic assay of hydrochlorothiazide □ High-pressure liquid chromatography—stability-indicating assay of hydrochlorothiazide

Hydrochlorothiazide is a common diuretic. It is used as an antihypertensive by itself and in combination with other compounds. It is available in a wide range of dosage forms (25–100-mg tablets) and in combination tablets (*e.g.*, hydrochlorothiazide and guanethidine).

The assay listed in USP XIX is a titration with sodium methoxide. This method cannot distinguish hydrochlo-



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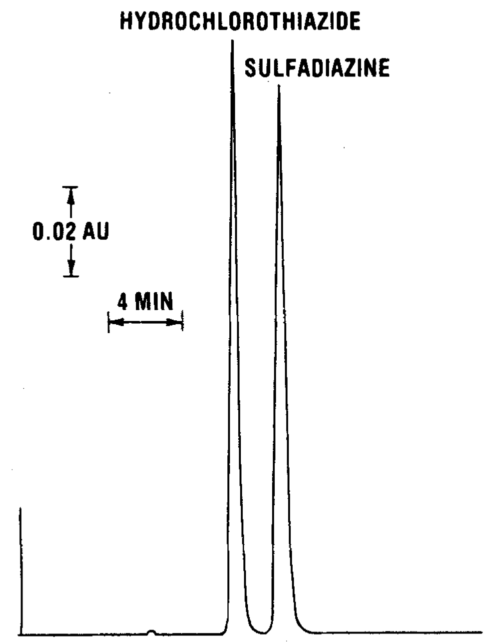

Figure 1—*Typical chromatogram for the hydrochlorothiazide assay. The mobile phase is 5% methanol in water at pH 4.5.*

rothiazide (I) from likely degradation and process impurities such as chlorothiazide (II) and 4-amino-6-chloro-1,3-benzenedisulfonamide (III).

Liquid chromatographic methods for quantitating thiazides have been developed for tablet formulations (1) and the determination of hydrochlorothiazide in serum, plasma, and urine (2, 3). This report describes a new reversed-phase high-pressure liquid chromatographic (HPLC) method that is specific for hydrochlorothiazide and has adequate sensitivity for the determination of impurities.

EXPERIMENTAL

Materials—Sulfanilamide[1], chlorothiazide[1] (II), hydrochlorothiazide[2,3] (I), sulfadiazine[1], and 4-amino-6-chloro-1,3-benzenedisulfonamide[1] (III) were obtained in pure form and dissolved in methanol for chromatography and spectroscopy. Solvents and reagents were commercial analytical grade. Tablets from four sources[2–5] were used.

Chromatographic Conditions—A liquid chromatograph[6] with a low volume septumless injector, a fixed-wavelength detector[7] (254 nm), and a minicomputer[8] were used. Commercial 10-[9] and 5-μm[10] C_{18} columns (30 cm × 4 mm i.d.) were used at ambient temperature. The mobile phase consisted of 5% (v/v) methanol in double-distilled water. The pH was adjusted to 4.5–5.0 with 0.1 *M* acetic acid, and then the solution was filtered and deaerated. The flow rate was adjusted to 2.0 ml/min.

Internal Standard Solution—A solution of methanol containing ~0.7 mg of sulfadiazine/ml was used.

Standard Preparation—About 20 mg of USP hydrochlorothiazide reference standard[1] was weighed accurately, and 10.0 ml of internal standard solution was added.

Sample Preparation—*Tablets*—Ten tablets were weighed accurately, and the average tablet weight was determined before they were

[1] United States Pharmacopeial Convention, Rockville, Md.
[2] Abbott Laboratories, North Chicago, Ill.
[3] Ciba Pharmaceutical Co., Summit, N.J.
[4] Barr Laboratories, Northvale, N.J.
[5] The Upjohn Co., Kalamazoo, Mich.
[6] ALC 202, Waters Associates, Milford, Mass.
[7] Model 440, Waters Associates, Milford, Mass.
[8] PDP11-40, Digital Equipment Corp., Marlborough, Mass.
[9] μBondapak C_{18}, Waters Associates, Milford, Mass.
[10] Ultrasphere ODS, Altex Scientific, Berkeley, Calif.

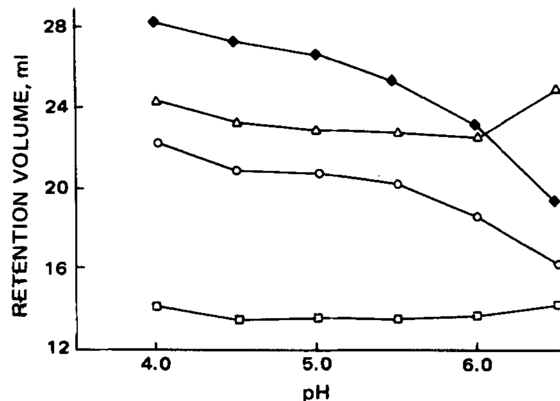

Figure 2—*Effect of pH on the retention volume of I (△), IV (♦), II (○), and III (□) in water–methanol (95:5).*

crushed gently using a mortar and pestle. An amount equivalent to about 20 mg of hydrochlorothiazide was weighed, 10.0 ml of internal standard solution was added, and the solution was shaken for 35–40 min. The solution was filtered or centrifuged to remove the particulate matter.

Bulk Drug—The samples were prepared in the same way as the reference standard.

Impurities Test—About 10.0 mg of sample was weighed, and 10 ml of reagent grade methanol was added.

Procedure—The sample or standard preparation, 6–10 μl, was chromatographed using conditions described. The reference standard was run in duplicate at the beginning and end of the run and between every seventh sample. The detector attenuation was set at 0.2–0.5 aufs. To observe the impurities on a 10-mv recorder, the attenuation was adjusted to 0.01 aufs.

Calculations—*Tablets*—The hydrochlorothiazide (I) content, expressed in milligrams per tablet, is calculated from:

$$\mathrm{I} = (R_{sam}/R_{std}) \times (W_{std}/W_{sam}) \times (F1/F3) \times F2 \times P \quad \text{(Eq. 1)}$$

where:

R_{sam} = ratio of hydrochlorothiazide peak height to internal standard peak height in sample preparation
R_{std} = ratio of hydrochlorothiazide reference standard peak height to internal standard peak height in standard preparation
W_{std} = weight of hydrochlorothiazide reference standard in milligrams
W_{sam} = weight of sample in milligrams
$F1$ = volume of internal standard used in sample preparation in milliliters
$F2$ = average tablet weight in milligrams
$F3$ = volume of internal standard used in standard preparation in milliliters
P = purity of hydrochlorothiazide reference standard expressed as a decimal

Bulk Drug—The percent hydrochlorothiazide is found using:

$$\mathrm{I} = (R_{sam}/R_{std}) \times (W_{std}/W_{sam}) \times (F1/F3) \times P \times 100 \quad \text{(Eq. 2)}$$

Impurities Test—The content of the impurities in the sample, expressed as percent by weight, is calculated from:

$$\text{impurities} = \frac{H_3R_3 + H_2R_2 + \ldots H}{H_1 + H_3R_3 + H_2R_2 + \sum H} \times 100 \quad \text{(Eq. 3)}$$

where:

H_3 = height of 4-amino-6-chloro-1,3-benzenedisulfonamide (III) peak
R_3 = response factor for III (about 0.3 on a weight basis)
H_2 = height of chlorothiazide (II) peak
R_2 = response factor for II (about 1.6 on a weight basis)
H_1 = height of hydrochlorothiazide peak
H = height of any unknown peaks

Recovery Studies—Recovery studies were performed by adding 10–30 mg of I to 180 mg of a placebo mix. If no placebo mix was available, 13–50 mg of I was added to the crushed tablet mix. The samples were then treated as described under *Sample Preparation*.

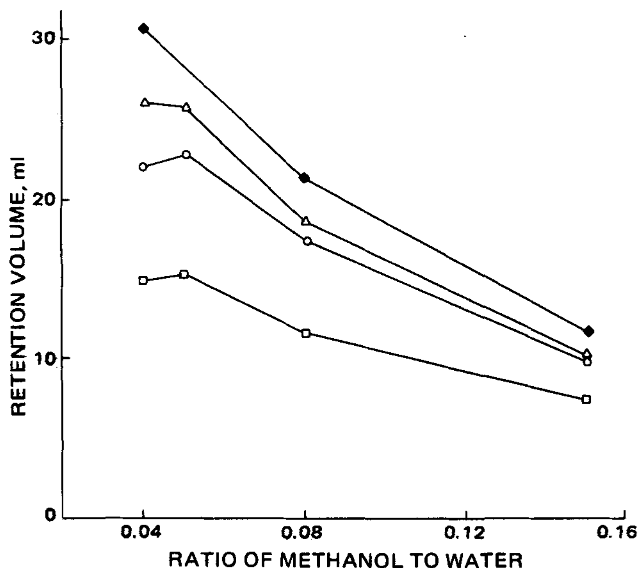

Figure 3—*Effect of methanol concentration on the retention volume of I (△), IV (♦), II (○), and III (□) at pH 5.*

Response Factors—Samples of II and III were weighed and added to 10 mg of I (accurately weighed). These mixtures were dissolved in about 10 ml of methanol. The samples were then chromatographed under the conditions described. The response factors were calculated using:

$$R = \frac{Wt_{sam}}{Wt_{I}} \times \frac{X_{I}}{X_{sam}} \quad \text{(Eq. 4)}$$

where:

Wt_{sam} = weight of a sample of II or III in milligrams
Wt_{I} = weight of I in milligrams
X_{sam} = height or area of II or III peak
X_{I} = height or area of I peak

RESULTS

Chromatography and Specificity—The mobile phase was adjusted to obtain good retention of hydrochlorothiazide (I) and baseline separation of the sulfadiazine (IV) internal standard. The chromatogram of I and IV (Fig. 1) indicates that, under the recommended experimental conditions, the method is free of interference and gives symmetrical chromatographic peaks. Apparently, none of the excipients was extracted into the methanol during the I extraction step. In fact, no peaks were observed when the placebo was extracted with methanol for 30 min. The placebo sample was rerun at a much higher sensitivity (0.01 aufs), and only a small peak due to the methanol solvent (at about 2-ml retention volume) was observed.

During the search for the optimum chromatographic conditions, it was observed that pH had a pronounced effect on the retention volume of the internal standard (IV), especially between pH 5 and 6. Therefore, a study was done to determine the effect of pH on I, IV, and the two known impurities of I (II and III). The results (Fig. 2) indicate that the pH has a definite effect on all compounds except III. Its retention volume remained about the same between pH 4 and 6.5. The order of elution of I and IV reversed between 6 and 6.5. Between pH 4 and 5, the relative retention

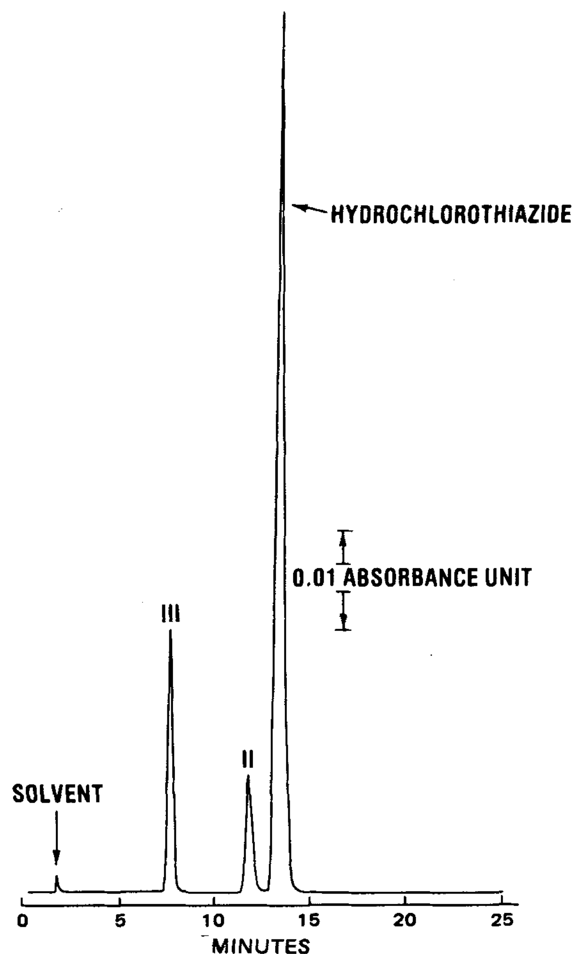

Figure 4—*Chromatogram of hydrochlorothiazide spiked with 7% III and 17% II.*

times of all compounds remained about the same. It is recommended that the pH be kept between these values for reproducibility.

Methanol was used as the organic modifier for the aqueous mobile phase. The retention data obtained by chromatographing I–IV are shown in Fig. 3. The results, when plotted as the ratio of methanol to water, are about linear up to a point corresponding to 4% methanol in water. This level of methanol gave the best combination of resolution and analytical results. Assay specificity was tested by chromatographing a mixture of I–III (Fig. 4).

Several other benzenesulfonamides were chromatographed to test further the method specificity. The results in Table I indicate that there are large differences in retention volume even for closely related compounds. Sulfamerazine differs from sulfadiazine only by one methyl group on the heterocyclic ring. These data also illustrate that the procedure is highly specific.

The chromatographic method was also tested by performing the assay with a different column. Table II and Fig. 5 show the results obtained on a 5-μm C_{18} column compared to the results normally obtained on the 10-μm column. The retention times for the 5-μm column were longer,

Table I—Specificity of the HPLC Method

Compound	Retention Volume, ml	Capacity Factor[a]
Guanadrel sulfate	3.6	—
Sulfanilamide	6.8	0.9
III	15.4	3.2
II	23.0	5.4
I	26.0	6.2
IV	35.5	8.9
Sulfamerazine	68.8	18.0

[a] Void volume is 3.6 ml; capacity factor = (volume − void volume)/void volume.

Table II—Comparison of Chromatography on a 10- and 5-μm Column

Parameter	C_{18}[a], 10 μm[b]	C_{18}[c], 5 μm[d]
IV retention time, min	16.5 ± 0.4	22.1 ± 0.3
I retention time, min	12.1 ± 0.2	16.6 ± 0.1
Theoretical plates[e]	1080 ± 130	3150 ± 580
Resolution[f]	2.7 ± 0.2	3.2 ± 0.2

[a] μBondapak C_{18}, Waters Associates, Milford, Mass. [b] Average of 59 values; error is 2 *SD*. [c] Ultrasphere ODS, Altex Scientific, Berkeley, Calif. [d] Average of nine values; error is 2 *SD*. [e] Theoretical plates = $5.54\,(T/w)^2$. [f] Resolution = $[2|T_1 - T_2|]/1.67\,(w_1 + w_2)$, where T is the retention time and w is the peak width at half height.

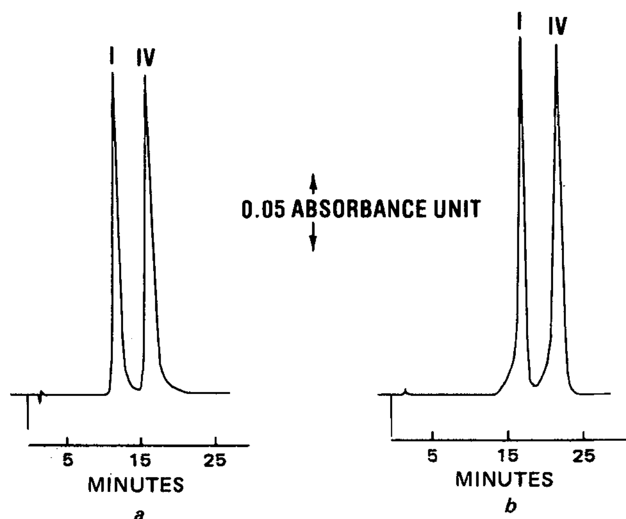

Figure 5—*Separation of I and IV on 10-μm (a) and 5-μm (b) C_{18} reversed-phase columns.*

resulting in more theoretical plates, but there was essentially no increase in the resolution. In fact, on a new 10-μm C_{18} column, the resolution between hydrochlorothiazide and the internal standard was 3.9. However, the data do serve to illustrate the ruggedness of the chromatographic conditions.

Recovery and Linearity—The effectiveness of the extraction step was tested by adding I to the powdered placebo mixture (Table III). A plot of the amount of I added *versus* the amount of I recovered indicates that the slope is 1 (0.97 ± 0.02) within experimental error and that the intercept is 0 (0.25 ± 0.31). These data, a correlation coefficient of 0.999, and complete recovery of I (99.1 ± 1.7%) show that the assay is linear and accurate between 50 and 150% of the tablet formulations (25 mg of I/225-mg tablet) tested.

The method was further tested by spiking several different formulations with additional I. Fifty percent of the label amount was added to three different formulations (from two different manufacturers) containing 25, 50, and 100 mg of I. The results (Table IV) indicate that complete recovery was obtained for all three formulations. The validity of the measurement was tested by changing the concentration of I relative to the internal standard (IV). Eight 8-μl aliquots (concentration range was 0.76–3.06 mg of I/ml) were chromatographed. The plots of both height and area ratio of I/IV *versus* the amount of I were linear (correlation coefficients > 0.98) and showed no bias (intercepts were 0 ± 2 *SD*).

Table III—Hydrochlorothiazide (I) Extraction Study

Sample	Amount of I Added, mg	Amount of I Recovered, mg	Recovery, %
	Samples Extracted 30 min		
100% Std.	20.3	20.1	99.0
100% Std.[a]	20.3	20.6	101.7
100% Std.	20.4	19.7	96.7
100% Std.[a]	20.4	19.9	97.7
50% Std.	9.8	9.9	101.1
80% Std.	16.4	16.4	99.8
90% Std.	18.7	18.4	98.2
110% Std.	22.8	22.2	97.4
120% Std.	24.0	23.4	97.5
150% Std.	30.6	30.3	99.2
Average			99.1
RSD			1.7
	Samples Extracted 45 min		
50% Std.	10.4	10.5	101.0
100% Std.	20.8	20.7	99.5
150% Std.	30.1	29.4	97.7
80% Std.	16.7	16.5	98.8
Average			99.2
RSD			1.4

[a] Repeat of previous standard.

Table IV—Standard Addition Results for Tablet Formulations

Unspiked I per Tablet, mg	Amount of I Added, mg	Measured I per Tablet, mg	Recovery, %[a]
24.4	13.1	37.5	99.8
50.2	26.7	76.3	99.2
97.5	50.2	144.3	97.7

[a] Percent recovery = [measured I/(unspiked I + added I)] × 100.

Table V—Response Factors for Known Impurities

Impurity Concentration, % by weight	Response Factor Area	Response Factor Height
III		
0.3	0.46	0.28
2.5	0.50	0.29
7.1	0.54	0.31
Average	0.50	0.29
RSD, %	8	5
II		
0.5	1.66	1.56
4.6	1.84	1.61
16.8	2.03	1.76
Average	1.84	1.64
RSD, %	10	6

These results indicate that the assay is accurate over a fourfold concentration range.

A study of I–III was performed to determine their absorptivity at 254 nm. The results show that the most sensitive region was between 220 and 226 nm. However, at 254 nm, all three compounds had adequate absorptivity. Since the absorptivities of these compounds differed, it was necessary to determine response factors for II and III relative to I. As shown in Table V, response factors based on peak height and peak area were determined. Since peak height appears to give the more precise data, it is the recommended parameter for quantitative measurements. Although there was a definite concentration effect on the response factor, this effect was significant only at concentrations much higher than would ever be expected in pure I (Table VI).

The detector (UV at 254 nm) gave linear responses for II and III between 0.01 and 5 μg with a correlation coefficient of 0.99 or better. The intercept for both II and III was 0 ± 1 *SD*. The normal injection volume

Table VI—Hydrochlorothiazide Impurities: Recovery Study

Compound	Amount Added, % (w/w)	Amount Observed, % (w/w)	Recovery, % (w/w)
III	0.28	0.30	109.0
	2.50	2.56	102.4
	7.11	6.91	97.2
II	0.51	0.52	102.9
	4.60	4.58	99.6
	16.80	16.09	95.8
	50.00	45.29	90.6

Table VII—Hydrochlorothiazide Assay Results for Tablet Formulations

Formulation	Label per Tablet, mg	Average Tablet Weight, mg	Tablet Potency Amount, mg/tablet	Tablet Potency *RSD*, %	Percent of Label
1A	25.0[a]	224	23.6	0.5	94.4
1A-1	25.0[a]	224	23.8[b]	0.6	95.2
1B	25.0[a]	224	24.0	1.2	96.0
2	25.0	101	24.9	0.4	99.6
3A	25.0[c]	296	24.4	1.0	97.6
3B	50.0	302	49.2	0.6	98.4
3C	100.0	348	97.5	1.0	97.5
4A	25.0	85	25.7	1.1	102.8
4B	25.0	86	24.4	0.4	97.6
4C	50.0	171	50.2	2.8	100.4

[a] Tablets also contained 10 mg of guanadrel sulfate. [b] Results obtained using the 5-μm column. [c] Tablets also contained 10 mg of guanethidine sulfate.

Table VIII—Hydrochlorothiazide Assay Results for Bulk Drug Lots

Lot	Assay (Peak Height)[a] %	Assay (Peak Height)[a] RSD	Assay (Peak Area)[a] %	Assay (Peak Area)[a] RSD	USP Assay
A	98.7	0.7	98.6	1.6	100.7
B	98.2	0.8	98.0	0.9	101.4
C	98.8	0.6	98.6	1.3	99.8
D	100.0	1.1	100.3	1.4	100.3
E	97.8	0.8	97.3	1.6	100.0
F	98.0	1.1	98.4	1.1	99.9
G	97.7	1.8	98.2	1.8	99.5
H	97.6	0.6	96.4	1.4	100.5

[a] Calculated on the anhydrous basis; the results are averages of at least five determinations.

Table IX—Effects of Injection Size and Sample Age

Day	Run	Amount Injected[a], μl	Hydrochlorothiazide Recovered, mg
1	19	8	23.7
2	22	8	23.8
	24	10	23.6
	25	6	23.9
	26	6	23.6
3	29	8	23.5
Mean			23.7
RSD, %			0.6

[a] Concentration = 2 mg/ml.

for the impurities test of about 10 μl of a 1-mg/ml preparation corresponds to 10 μg. The data indicate that the test should give accurate results for impurities between 0.1 and 5%. At higher levels, the response factors used would have to be redetermined. Therefore, the method can be used to determine the purity of bulk hydrochlorothiazide.

DISCUSSION

The method was tested by assaying nine lots of tablets from the four suppliers. Three samples were obtained from each lot and prepared as indicated under *Experimental.* Two aliquots of each sample were chromatographed. The results (Table VII) indicate that the method gives accurate results for the various formulations since there is good agreement with the label concentrations in all cases.

The results also indicate that the assay has good precision. A statistical evaluation of the variability (4), using a χ^2 distribution at the 95% confidence level, indicates that the true relative standard deviation is between 0.7 and 1.1% using peak height. The results for eight lots of bulk drug from two suppliers are listed in Table VIII. The data indicate that the pooled relative standard deviation is about 1.1% for the peak height measurement. This value is in good agreement with the assay precision found for the products listed. The results in Table VIII indicate that equivalent results are obtained using peak height or peak area. However,

Table X—Stability of Hydrochlorothiazide (I)

Sample	Impurities[a], % III	Impurities[a], % Unknown	Impurities[a], % Total
Initial assay[b]	0.04	ND[c]	0.04
3 months at room temperature (10 mg/ml in methanol)	1.52	ND	1.52
1 hr at 100°	0.09	ND	0.09
4 days at 100°	0.11	ND	0.11
16 hr in 0.1 *N* HCl (aqueous)	0.28	1.54	1.82
16 hr in 0.1 *N* NaOH (aqueous)	0.13	0.94	1.07

[a] Chlorothiazide (II) was not detected in any of these samples. [b] Average of five assays where impurity was detected. [c] None detected.

peak area measurements resulted in less precise results (pooled *RSD* = 1.5%). The purity of the lots examined was 97.5–98.5%, except for Lots D and H. For the very pure Lot D (100% by HPLC and USP methods; 99.9% by summation of minor impurities), there was excellent agreement between the HPLC and USP XIX methods; for all other lots, the USP method gave higher results.

The HPLC results indicate that some impurities in hydrochlorothiazide (I) may interfere with the USP method for the following reasons:

1. The HPLC impurity test and the other impurity tests listed in USP XIX indicate that Lot H has impurities present at 1% or more, yet the USP assay gave a purity value of 100.5%.
2. The USP assay is a sodium methoxide titration, which would not distinguish I from II and III.
3. All results using the USP method were 100% or larger, suggesting a positive bias.

A study of injection size and sample stability was performed. The data (Table IX) indicate that 6–10-μl aliquots give accurate and precise results over 3 days. Hydrochlorothiazide stability was examined under several conditions. The data given in Table X show that I is very stable in the powdered form. No significant degradation was observed when the dry powder was kept at 100° for 4 days. Even under severe conditions such as in 0.1 *N* HCl, I only degraded at a rate of about 0.1%/hr. A sample left at room temperature in methanol for 3 months produced about 1.5% III. This result shows that III is a degradation compound of I and that the method is stability indicating.

REFERENCES

(1) A. G. Butterfield, E. G. Lovering, and R. W. Sears, *J. Pharm. Sci.*, **67,** 651 (1978).

(2) M. J. Cooper, A. R. Sinaiko, M. W. Anders, and B. L. Mirkin, *Anal. Chem.*, **48,** 1110 (1976).

(3) E. Redalieu, U. V. Tipnis, and W. E. Wagner, Jr., *J. Pharm. Sci.*, **67,** 726 (1978).

(4) A. H. Bower and G. J. Lieberman, "Engineering Statistics," Prentice Hall, Englewood Cliffs, N.J., 1959.

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