Routine Quality Evaluation of Benzodiazepine Drugs to USP–NF Specifications

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Abstract □ A GLC procedure was developed for the evaluation of diazepam, chlordiazepoxide, and flurazepam formulations to USP–NF specifications for drug content, content uniformity, impurities, and identity by retention times and peak areas. The polyimide column, instrument zone temperatures, gas flows, internal standard solution, extraction solvent, and auxiliary equipment were the same for each drug. No derivatization of the samples was required. The GLC assay values (mean of 10 individual dosage units) for diazepam and flurazepam products were in good agreement with the results obtained by the pharmacopeial composite assays. With chlordiazepoxide capsules, when the levels of the two pharmacopeial impurities determined by GLC were added to the GLC assay results (mean of 10), the aggregate values were consistent with the drug content results found by the nonspecific USP method. The procedure can be made sensitive to impurity levels of ~0.01% for 2-amino-5-chlorobenzophenone and to ~0.2% for 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide. With the equipment used, the estimated potential outputs in lots per working day for a complete quality profile (drug content, content uniformity, purity, and identity) were seven for chlordiazepoxide if no impurity test was required, five if such a test was required, eight for diazepam, and seven for flurazepam.

Keyphrases □ Benzodiazepines—routine quality evaluation for adherence to USP–NF specifications □ Diazepam—routine evaluation of content, uniformity, impurities, and identity by retention times and peak areas □ Chlordiazepoxide—routine evaluation of content, uniformity, impurities, and identity by retention times and peak areas □ Flurazepam—routine evaluation of content, uniformity, impurities, and identity by retention times and peak areas □ GLC—routine evaluation of benzodiazepines

Pharmacopeial test procedures for drug quality generally tend to be tedious and time (money) consuming, and assay methods occasionally lack specificity. Even within the same chemical family of drugs, such methods sometimes require different experimental techniques and apparatus. Compendial procedures, which are legal standards not necessarily designed for speed and efficiency, may not be compatible with the needs of control laboratories that must routinely perform identity, purity, content uniformity, and drug content tests on a large number of drug products.

Most recently published GLC and high-pressure liquid chromatographic (HPLC) methods for benzodiazepines are concerned with their analysis in biological media only (1–10). New procedures reported for the determination of these drugs in pharmaceutical dosage forms include HPLC (11–13), fluorometry (14), and automated polarography (15). However, most of these methods are not suitable for moderate to large-scale drug quality screening programs.

This paper describes a semiautomated multifunctional GLC procedure for the evaluation of three benzodiazepine drugs (chlordiazepoxide, diazepam, and flurazepam) to USP–NF specifications (16, 17) for drug content, content uniformity, impurities, and identity by retention times and peak areas.

EXPERIMENTAL

Material and Equipment—The following were used: chlordiazepoxide hydrochloride[1] (USP reference standard), 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide[1] (II) (USP reference standard), 2-amino-5-chlorobenzophenone[1] (III) (USP reference standard), diazepam[1] (USP reference standard), flurazepam hydrochloride[1] (NF reference standard), dicyclohexyl phthalate[2] (95–99%), toluene[3] (ACS reagent grade, distilled in glass), sodium hydrogen carbonate[4] (analytical reagent), 1 *N* HCl, Acculute solution[5], screw-capped tubes[6] (19 × 150 mm), variable-speed mechanical horizontal shaking apparatus[7], and a 3/4-h.p. centrifuge, 5000 rpm maximum[8].

Solutions—The internal standard solution was dicyclohexyl phthalate in toluene, accurately prepared to contain ~0.25 mg/ml. The stock solution of II was accurately prepared in the internal standard solution to contain ~0.2 mg/ml, and the stock solution of III was accurately prepared in the internal standard solution to contain ~0.02 mg/ml.

The diazepam stock solution was accurately prepared in the internal standard solution to contain ~0.5 mg/ml. The sodium bicarbonate (sodium hydrogen carbonate) solution was prepared in water to contain ~5% (w/v).

GLC System—The gas chromatograph[9] (flame-ionization detector) was fitted with a coiled glass column, 0.91 m × 6 mm o.d. (2 mm i.d.), firmly packed with 3% Poly I-110 on Gas Chrom Q[10] (80–100 mesh) and vibrated so that no cracks or deadspaces were evident. The column was conditioned overnight at 250° with a nitrogen flow of 35 ml/min. Experimental temperature conditions were: column, 250°; injector port, 250°; and detector, 250°. The gas flows were: nitrogen, 29 ml/min; hydrogen, 30 ml/min; and air, 300 ml/min. The maximum loads injected onto the column were ~0.5 μg for chlordiazepoxide and diazepam and 1.5 μg for flurazepam.

The detector output signal was fed to a digital microprocessor, which automatically computed the required information in the preinstructed format. Appropriate slope sensitivity and attenuation settings were entered *via* the keyboard terminal prior to analyses.

Chlordiazepoxide Hydrochloride Analysis—*Preparation and GLC of Chlordiazepoxide Calibration Solutions*—For each dosage level (5, 10, and 25 mg/capsule), a corresponding standard solution containing a similar amount of drug was prepared daily as required. About 5, 10, or 25 mg of chlordiazepoxide hydrochloride was weighed accurately into a screw-capped tube. Distilled water (2 ml), sodium bicarbonate (2 ml), and the internal standard solution (20.0 ml) were added, the contents of the tube were mechanically shaken vigorously for 10 min, and the solution was centrifuged at 3000 rpm for 10 min. To prevent column overloading, the organic layer resulting from the extraction of the 25-mg calibration solution was diluted 2:5 with the internal standard solution. A portion of the final organic layer was transferred to a sample vial[11], which was capped[11] immediately and placed in the sampling tray. About 1 μl of solution was injected in duplicate into the gas chromatograph. The run time was 10 min.

GLC Analysis of Capsule Preparations for Content Uniformity—The

[1] USP–NF Reference Standards, Rockville, Md.
[2] K & K Laboratories, Plainview, N.Y.
[3] Caledon Laboratories Ltd., Georgetown, Ontario, Canada.
[4] BDH Chemicals Ltd., Toronto, Ontario, Canada.
[5] Anachemia Chemicals Ltd., Montreal, Quebec, Canada.
[6] O. H. Johns Glass Co. Ltd., Toronto, Ontario, Canada.
[7] Eberbach Corp., Ann Arbor, Mich.
[8] International Equipment Co., Needham Heights, Mass.
[9] Hewlett-Packard 5840A series reporting gas chromatograph with automatic liquid sampler model 7671A.
[10] Applied Science Laboratories, State College, Pa.
[11] Hewlett-Packard, 1 ml, clear glass with caps (11 mm) and a hand capper (10 mm).

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Table I—GLC Data on Benzodiazepine Compounds on Polyimide Column

Compound	Retention Time, min	Relative[a] Response Factor	CV, %	Number of Data Points	Weight Range[b] Examined, mg
Chlordiazepoxide hydrochloride	4.1[c]	1.2411	1.5	4	5.3–25.5
II	5.3	2.49[illegible]1	2.8	3	1.0–1.8
III	1.0	1.07[illegible]1	6.1	3	0.035–0.088
Diazepam	2.7	1.0715	1.5	3	2.1–10.4
Flurazepam dihydrochloride	4.8[c]	1.4777	1.1	3	11.2–30.3

[a] Relative to the internal standard (dicyclohexyl phthalate, retention time of 1.7 min). [b] Amount extracted into 20.0 ml of the internal standard solution. [c] Eluted as the free base.

Table II—GLC *versus* Pharmacopeial Assay Results for 10-mg Chlordiazepoxide Hydrochloride Capsules

Formulation	Manufacturer	Percent of Label Claim, GLC, I[b] C.U.[a] Range	I[b] CV, %	Mean[c]	II[d]	III[e]	Total	USP XIX[f]
1	A	84.4–91.7	2.4	89.4	7.1	0.02	96.6	96.2
2	B	97.2–106.9	3.0	101.6	0.7	0	102.3	105.9
3	C	93.0–107.5	4.4	97.7	3.4	0	101.1	99.8
4	F	93.6–105.5	4.0	99.3	1.7	0	101.0	98.9
5	G	93.8–105.0	3.6	98.2	1.2	0	99.4	97.4

[a] Content uniformity of 10 individual dosage units. [b] Chlordiazepoxide hydrochloride. [c] Mean of 10 content uniformity values. [d] Pharmacopeial II impurity. [e] Pharmacopeial III impurity. [f] Composite assay on 10 capsules.

Table III—GLC *versus* Pharmacopeial Assay Results for Diazepam Tablets

Formulation	Dosage Level, mg/unit	Manufacturer	Percent of Label Claim, GLC, C.U.[a] Range	CV, %	Mean[b]	USP XIX[c]
1	10	B	98.6–100.7	0.6	99.4	101.0
2	2	D	84.6–113.4	8.1	97.6	98.6
3	5	H	99.0–108.9	3.1	105.9	105.2
4	10	F	96.1–99.2	1.1	97.9	96.4
5	5	I	97.5–106.3	2.7	100.4	104.0
6	10	J	96.3–100.8	1.6	98.3	100.4
7	5	K	89.5–102.3	4.6	97.9	96.5

[a] Content uniformity of 10 individual dosage units. [b] Mean of 10 content uniformity values. [c] Composite assay on 10 powdered tablets.

contents of each of 10 individual capsules were emptied into separate screw-capped tubes labeled 1–10. The contents of each tube were subjected to the same extraction and chromatographic procedures as described for the calibration solutions. For each sample solution, the amount of chlordiazepoxide hydrochloride present, expressed as a percentage of the label claim, was calculated automatically with reference to a calibration solution of approximately the same concentration and chromatographed just prior to the analysis of each batch of 10 dosage units. The mean of the 10 individual results was used as the assay value.

Preparation and GLC of II and III Impurity Calibration Solutions—Various volumes of the stock II and III impurity solutions were pipetted into three separate screw-capped tubes (A–C), each containing about 50 mg of chlordiazepoxide hydrochloride, accurately weighed. The volumes added corresponded to the following impurity levels based on the weight of chlordiazepoxide hydrochloride: A, 2.0% of II and 0.08% of III; B, 2.8% of II and 0.12% of III; and C, 4.0% of II and 0.20% of III. In each tube, the volume of the internal standard required for a total volume of 20.0 ml of organic solution then was added with water (2 ml) and sodium bicarbonate (2 ml). A blank containing ~50 mg of chlordiazepoxide hydrochloride, accurately weighed, the internal standard solution (20.0 ml), water (2 ml), and sodium bicarbonate (2 ml) also was prepared.

Each mixture was shaken mechanically for 10 min and then centrifuged at 3000 rpm for 10 min. Exactly 10.0 ml of each of the four respective organic layers and 1 *N* HCl (2 ml) were pipetted into separate screw-capped tubes, the contents were shaken mechanically for 5 min, and the solution was centrifuged at 3000 rpm for 10 min. An aliquot of each of the four organic layers was chromatographed.

GLC Determination of II and III Impurities in Capsule Formulations—Prior to the determination of II and III, the contents of 20 capsules were emptied, thoroughly mixed, and accurately weighed. An amount of powder equivalent to ~50 mg of chlordiazepoxide hydrochloride was accurately weighed into a screw-capped tube. The internal standard solution (20.0 ml), water (2 ml), and sodium bicarbonate (2 ml) were added, and the contents were subjected to the same bicarbonate–acid double-extraction procedure already described.

About 1 μl of the final organic layer was injected into the gas chromatograph, and the run time was set at 10 min. For each sample, the II and III levels were calculated with reference to the impurity calibration solution closest to the concentration of impurities estimated by inspection of the assay chromatogram and were expressed as a percentage of the drug label claim.

Diazepam Analysis—*Preparation and GLC of Diazepam Calibration Solutions*—The stock diazepam (0.5 mg/ml and 10 mg/20 ml) was successively diluted with the internal standard solution to give solutions of 0.25 mg/ml (5 mg/20 ml) and 0.1 mg/ml (2 mg/20 ml), respectively. About 1 μl of each of the three solutions (including the stock solution) was injected into the gas chromatograph set in the automatic mode with a run time of 5 min.

GLC Analysis of Tablet Preparations for Content Uniformity—Ten tablets (2, 5, or 10 mg/tablet) were selected at random, and each was placed in a separate screw-capped tube and crushed to a fine powder with a blunt-end stirring rod (10 mm in diameter). Exactly 20.0 ml of the internal standard solution was pipetted into each tube, after which the contents were mechanically shaken vigorously for 10 min and then centrifuged at 3000 rpm for 10 min. A 1-μl portion of each supernate was chromatographed with a run time set at 5 min. For each sample, the amount of diazepam present, expressed as a percentage of the label claim, was calculated automatically with reference to a calibration solution of approximately the same concentration. The mean of the 10 individual results was used as the assay value.

Flurazepam Dihydrochloride Analysis—*Preparation and GLC of Flurazepam Calibration Solutions*—For each dosage level (15 and 30 mg/capsule), a corresponding standard solution containing a similar amount of drug was prepared daily as required. About 15 or 30 mg of flurazepam dihydrochloride was weighed accurately into a screw-capped tube. Distilled water (2 ml), sodium bicarbonate solution (2 ml), and the internal standard solution (20 ml) were added, the contents of the tube

were mechanically shaken vigorously for 10 min, and then the solution was centrifuged at 3000 rpm for 10 min. A 1-μl portion of the organic layer was chromatographed with a run time of 10 min.

GLC Analysis of Capsule Preparations for Content Uniformity—The contents of each of 10 individual capsules were emptied into separate screw-capped tubes labeled 1–10. The contents of each tube were subjected to the same extraction and chromatographic procedure as described for the calibration solutions. For each sample, the amount of flurazepam dihydrochloride present, expressed as a percentage of the label claim, was calculated automatically with reference to a calibration solution of approximately the same concentration. The mean of the 10 individual results was used as the assay value.

DISCUSSION

In selecting an appropriate column for this work, the criteria adopted were that the three drugs, their associated impurities, and the internal standard (dicyclohexyl phthalate) should all be eluted quickly as single sharp peaks and should require no derivatization. Poly I-110, a polyimide nonsilicone polymer suitable for the separation of a variety of amine-type drugs and necessitating no pretreatment of the functional groups with derivatizing agents, was the phase of choice. The capacity of the column was ~0.5 μg for chlordiazepoxide and diazepam and ~1.5 μg for flurazepam. While Poly I-110 is claimed to be stable to 275°, some deterioration in column performance, evidenced by darkening of the packing material and peak broadening, particularly with chlordiazepoxide, was noted after 3–4 weeks of operation at 250°. When these symptoms were observed, the column was replaced. Zone temperatures and gas flow conditions were chosen to achieve optimum elution characteristics and minimum run times of the drugs, and instrument settings were adjusted for maximum quantitation accuracy.

Relevant GLC data on the compounds eluted from the polyimide column are listed in Table I. The internal standard was eluted as a sharp, symmetrical peak at 1.7 min and did not interfere with any peak of interest. Detector linearity was established for each drug over weight ranges that approximated the dosage level ranges encountered in their commercial formulations. The associated coefficients of variation for chlordiazepoxide, diazepam, and flurazepam were 1.5, 1.5, and 1.1%, respectively, indicating that any of these calibration solutions would be satisfactory for the analysis of that drug at any of its dosage levels (Table I). Nonetheless, to minimize error, the calibration solutions were prepared to about the same concentration as the sample solutions.

Compounds II and III were studied at concentrations equivalent to levels of 2.0–3.6 and 0.07–0.18% of the weight of chlordiazepoxide hydrochloride, respectively. The USP limits for these impurities in commercial capsules of chlordiazepoxide hydrochloride are 3.0 and 0.1%, respectively. Only trace amounts of chlordiazepoxide were observed in each impurity calibration solution, and no II and III were detected in the blank sample. The toluene layer was back-extracted with 1 *N* HCl to remove the potentially interfering parent drug. Compounds II and III are not soluble in 1 *N* HCl and were extracted completely into toluene since neither was detected in the residual aqueous layer. While the response factor coefficient of variation values were higher for II and III (2.8 and 6.1%, respectively) than for the drugs, the quantitation errors would be small (certainly much less than those of the USP TLC test) considering the low levels of these compounds usually encountered in formulations.

Drug Content and Content Uniformity—The USP limits for chlordiazepoxide hydrochloride and diazepam in commercial capsules and tablets, respectively, and the NF limits for flurazepam in capsule preparations are 90.0–110.0% of the labeled amount of drug. All chlordiazepoxide formulations listed in Table II met the USP requirement when analyzed by the nondiscriminating USP spectrophotometric procedure, but Formulation 1 fell just outside (89.4%) the lower limit when assayed by the GLC method. This product, several years old and containing >7% of II, was chosen to illustrate the greater specificity of the GLC procedure. When the levels of II and III determined by GLC were added to the GLC assay results, the aggregates were in good agreement with the respective USP values. All diazepam products met the compendial assay requirements and gave consistent results by both procedures (Table III). One flurazepam product (15-mg capsules) was examined and afforded values of 96.2% with the GLC procedure and 95.9% with the NF XIV spectrophotometric method.

In the present chromatographic method, the mean of 10 content uniformity values was taken as the assay result. In the pharmacopeial situation, this method of calculating drug content may not be justified since the content uniformity test often entails direct dissolution of the dosage unit in a suitable solvent, leading to possible excipient interference and overestimation of the drug content.

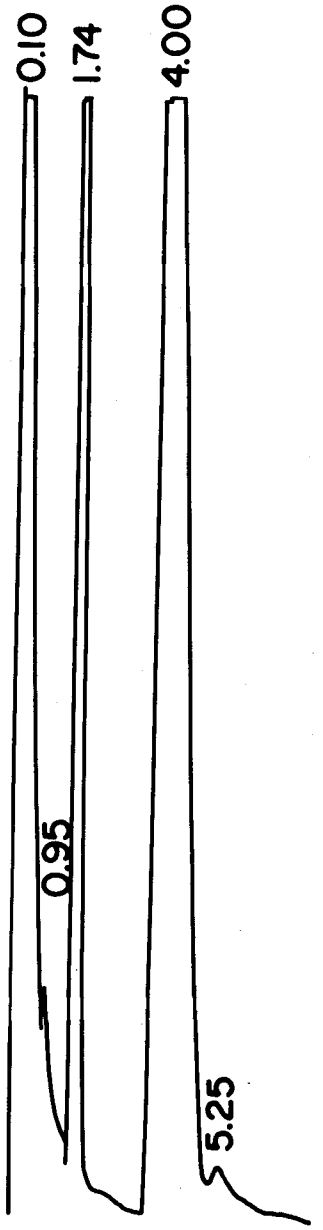

Figure 1—*Chromatogram of a reference impurities assay solution (10 mg of chlordiazepoxide hydrochloride spiked with 3.0% of II and 0.1% of III). The peaks are 0.95 min for III, 1.7 min for the internal standard, 4.0 min for chlordiazepoxide, and 5.25 min for II.*

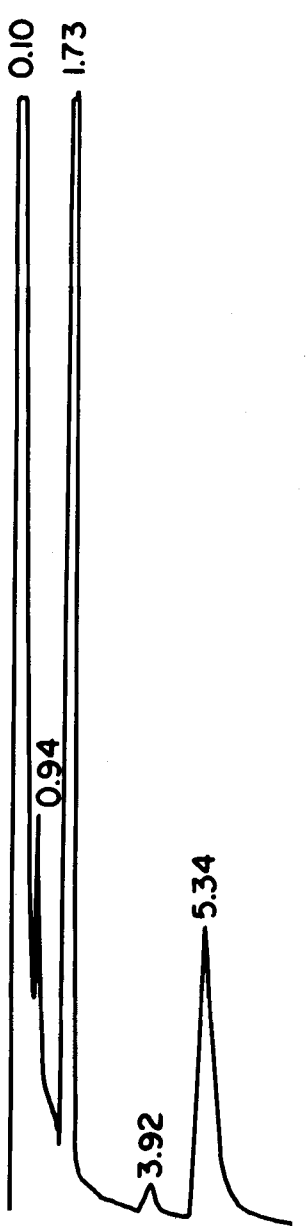

Figure 2—*Chromatogram of an impurities calibration solution at the USP limit for II (3.0%) and III (0.1%). The peaks are 0.94 min for III, 1.7 min for the internal standard, 3.9 min for residual chlordiazepoxide, and 5.34 min for II.*

Content uniformity results were evaluated in terms of the USP–NF specifications for tablets and capsules. One diazepam tablet, Formulation 2 (Table III), gave a value of 84.6%, but 20 additional tablets were not assayed. A satisfactory range of 91.8–101.5% of the label claim was obtained for the flurazepam formulation.

Purity—The USP monograph for chlordiazepoxide hydrochloride capsules includes a TLC test for the related Compounds II and III, and this test must be applied to every formulation since the impurity levels cannot be estimated from the other pharmacopeial tests performed. In the GLC method, the assay chromatogram provides important preliminary information on the product purity and eliminates the impurity test for formulations for which no extraneous peaks are observed. This pro-

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.

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Stability-Indicating Assay for Hydrochlorothiazide

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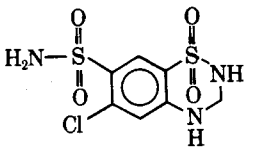
Abstract □ A stability-indicating method for determining hydrochlorothiazide in tablet formulations and in the bulk form is described. Hydrochlorothiazide is dissolved or extracted using methanol. An aliquot of the solution, containing sulfadiazine as an internal standard, is chromatographed on a 10-μm 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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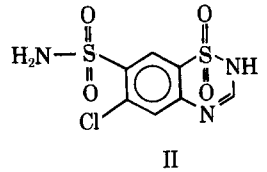

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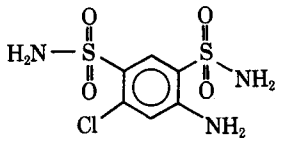

III

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