Determination of Diphenhydramine Hydrochloride in Elixir

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Abstract □ A UV spectrophotometric method for the determination of diphenhydramine hydrochloride in the presence of its postulated decomposition products and 5-(hydroxymethyl)-2-furaldehyde in elixirs was developed. The method involves simple extractions with cyclohexane and is suitable for routine and stability assays of various pharmaceutical liquid formulations. The technique is a modification of the USP XVIII method.

Keyphrases □ Diphenhydramine hydrochloride elixir—UV analysis in presence of 5-(hydroxymethyl)-2-furaldehyde □ 5-(Hydroxymethyl)-2-furaldehyde as elixir decomposition product—noninterference in UV analysis of diphenhydramine hydrochloride elixir □ UV spectrophotometry—analysis, diphenhydramine hydrochloride elixir

5-(Hydroxymethyl)-2-furaldehyde (1–3) is a well-known reaction product of the Maillard reaction. It can also be formed by the acid–base-catalyzed dehydration of hexose sugars. 5-(Hydroxymethyl)-2-furaldehyde is frequently present in pharmaceutical preparations, particularly in products containing sugar syrups. Its presence can interfere in the chemical analysis for the active ingredients.

USP XVIII (4) describes a UV assay for diphenhydramine hydrochloride elixir. This method was found to be inapplicable to certain samples undergoing stability tests. With increasing storage temperatures, consistently higher results were obtained. The separation of the base was reported (5, 6) on a cation exchanger, followed by quantitative spectrophotometric determination. A UV method was developed (7) to measure the steam-distillable compound after hydrolysis and oxidation of diphenhydramine. Colorimetric methods have also been reported. An addition compound formation between diphenhydramine and tetrabromophenolphthalein ethyl ether in 1,2-dichloroethane was used (8), as has ion-pair formation between the amine and an indicator dye (9). The reineckate was prepared in acetone (10). Nonaqueous titrimetry and salt partition was used in procedures for analysis of organic bases (11, 12). Quantitative TLC also was described (13). However, none of these methods has been suggested for stability-indicating purposes.

The present study describes a modification of the official assay procedure for the determination of the diphenhydramine content in elixirs containing postulated decomposition products and 5-(hydroxymethyl)-2-furaldehyde. The amine is separated by extraction from alkaline medium into cyclohexane, purified by washing and by filtration through anhydrous sodium sulfate before being extracted into dilute aqueous acid, and determined by UV spectrophotometry.

EXPERIMENTAL

Materials—The following were used: cyclohexane, spectrograde; 2 *N* sulfuric acid; 1% sodium hydroxide; 0.1 *N* sulfuric acid; 10% sodium hydroxide; and diphenhydramine hydrochloride USP standard reference solution, 0.5 mg./ml. in 0.1 *N* sulfuric acid. The following materials were obtained commercially[1] and used without additional purification: 5-(hydroxymethyl)-2-furaldehyde, diphenylcarbinol, and *N,N*-dimethylethanolamine.

Apparatus—A spectrophotometer[2] was employed.

Procedure—Transfer quantitatively 20 ml. of the elixir, equivalent to 50 mg. of diphenhydramine hydrochloride, into a separator. Add 30 ml. of distilled water and 1 ml. of 2 *N* sulfuric acid and extract with two 25-ml. portions of cyclohexane, discarding the cyclohexane extracts.

To the aqueous phase, add 10 ml. of 10% sodium hydroxide; then extract with three 30-ml. portions of cyclohexane and combine. Wash the combined cyclohexane extracts with two 10-ml. portions of 1% sodium hydroxide, discarding the washings. Extract the cyclohexane with three 25-ml. portions of 0.1 *N* sulfuric acid, collecting the extracts in a 100-ml. volumetric flask. Dilute to the mark with 0.1 *N* sulfuric acid and mix well.

Measure the absorbance difference between the maximum at 258 nm. and the baseline at 290 nm. in 1-cm. cells using 0.1 *N* sulfuric acid as blank. The diphenhydramine hydrochloride content of the sample is calculated from a relative absorptivity value derived by dissolving appropriate amounts of standard reference material in 0.1 *N* sulfuric acid and measuring spectrophotometrically under the same operational conditions as described for the assay procedure.

RESULTS AND DISCUSSION

The browning of the elixirs and a spectral change (Fig. 1) of

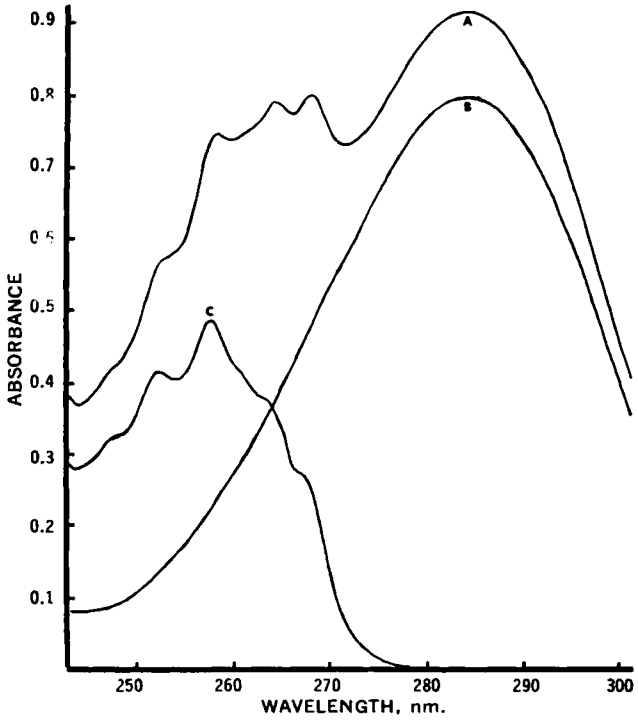

Figure 1—*UV spectra of mixture of diphenhydramine hydrochloride and 5-(hydroxymethyl)-2-furaldehyde (A), 5-(hydroxymethyl)-2-furaldehyde (B), and diphenhydramine hydrochloride (C). All solutions were prepared in 0.1* N H_2SO_4.

[1] Aldrich Chemical Co.
[2] Cary model 15.

Table I—Analysis of Synthetic Mixtures

Number of Assay	Diphenhydramine, mg. Added	Recovery, % Modified Method	Recovery, % USP Method
1	49.92	98.9	97.8
2	49.56	99.1	97.7
3	50.13	99.3	98.3
4	50.09	99.3	98.5
5	50.09	99.4	98.5
6	50.09	99.6	98.8
Percent recovered ± *SD*		99.3 ± 0.2	98.3 ± 0.4

Table II—Analysis of Synthetic Mixtures in the Presence of 5-(Hydroxymethyl)-2-furaldehyde

Number of Assay	Diphenhydramine, mg. Added	5-(Hydroxymethyl)-2-furaldehyde, mg. Added	Recovery, % Modified Method	Recovery, % USP Method
1	50.18	1.0	99.1	113.6
2	50.18	3.0	100.7	141.3
3	50.14	5.0	100.6	162.5
4	50.30	10.0	101.1	230.6
5	50.01	30.0	99.9	508.7
6	49.99	60.0	100.2	957.9

diphenhydramine, in which the absorption maximum shifted from 258 to 283 nm., led to an investigation of 5-(hydroxymethyl)-2-furaldehyde (I). Compound I had been isolated from the elixirs through thick-layer chromatography and identified by UV and IR absorption spectra, TLC, and the color reaction (14) with 2-thiobarbituric acid.

The postulated decomposition pathways for diphenhydramine would be hydrolysis of the ether linkage with formation of diphenylcarbinol and *N,N*-dimethylethanolamine. A study of the alkaline and acid hydrolysis of diphenhydramine was made, but only one of the postulated degradation products was isolated. The melting point, IR absorption spectrum, thin-layer chromatogram, and molar absorptivity data on this product coincide with those described for diphenylcarbinol. However, the presence of *N,N*-dimethylethanolamine was not positively confirmed.

Nevertheless, both postulated decomposition products and I have been taken into consideration as possible interferences. Diphenylcarbinol is practically insoluble in weak sulfuric acid, but it is soluble in cyclohexane and is removed by the initial cyclohexane extractions of the aqueous phase. On the other hand, I is very soluble in aqueous alkaline medium but is insoluble in cyclohexane; therefore, it remains in the aqueous phase throughout the procedure. The possible basic decomposition product, *N,N*-dimethylethanolamine, does not absorb UV radiation in the range employed.

To determine the validity of the method, a synthetic elixir was prepared by mixing a known quantity of diphenhydramine (50 mg. of pure drug) with excipients. Diphenhydramine was then assayed by the modified and USP methods. From the six determinations, the average percent recoveries were 99.3 ± 0.2 *SD* for the modified method and 98.3 ± 0.4 *SD* for the USP method. Both methods are in excellent agreement with each other, as shown in Table I.

The modified and the USP methods are both capable of eliminating the postulated decomposition products. To verify this fact, 1.7×10^{-4} mole each of diphenylcarbinol and *N,N*-dimethylethanolamine were added to the synthetic mixture and then carried through both procedures. No interfering absorbance between 300 and 235 nm. was observed. The specified amount of postulated decomposition products was used on the assumption that 100% hydrolysis of diphenhydramine would have taken place.

Synthetic mixtures in the presence of 1, 3, 5, 10, 30, and 60 mg. of I were assayed by both methods. The modified method gives results near the true values for the diphenhydramine concentration, whereas the method described by USP XVIII gives results that are far too high. The data in Table II indicate that the extraction of diphenhydramine by the USP method from an elixir containing a small amount of I results in a considerable error. This is due to the much greater absorption sensitivity of I.

Table III—Percent Recovery of Diphenhydramine Hydrochloride from Different Stability Samples

Sample	Storage Condition: Period	Storage Condition: Temperature	Recovery, % Modified Method	Recovery, % USP Method
Experimental elixir	Initial	Room temperature	100.0	98.5
	2 weeks	60°	98.7	97.9
	3 weeks	60°	99.2	101.1
	4 weeks	60°	99.6	98.7
Commercial elixir A	Initial	Room temperature	100.2	98.7
	2 weeks	60°	101.0	100.9
	3 weeks	60°	100.3	103.4
	4 weeks	60°	98.3	107.6
Commercial elixir B	Initial	Room temperature	100.6	100.8
	1 day	60°	100.3	102.0
	2 days	60°	100.0	103.1
	3 days	60°	100.3	103.8
	4 days	60°	99.9	104.6
	7 days	60°	100.1	111.6

The percent recoveries (Table III) obtained by using both the modified and USP methods for the stability samples of the experimental elixir are very similar. This similarity is expected, since the experimental elixir does not contain sucrose. The results for the stability samples of commercial Elixirs A and B (Table III) show that the percent recovery obtained by the USP method increases with storage time, while that obtained by the modified method remains constant. This could be explained simply on the basis that the commercial elixirs contained sucrose and that the I formed therefrom was removed by the modified method prior to determination. The results presented in Table III indicate the applicability and accuracy of the modified method for the assay of stability samples.

Based on our experience, the modified method provides definite improvement over the USP method. It is, therefore, suggested that the modified procedure may be considered as a stability-indicating method for the determination of diphenhydramine in various pharmaceutical liquid formulations.

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