Spectrophotometric Determination of Dimenhydrinate with Reinecke Salt

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Received August 9, 1979, from the *Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria.* Accepted for publication November 13, 1980.

Abstract □ A convenient spectrophotometric method was developed for the determination of dimenhydrinate in bulk drug and dosage forms and in 1:1 combinations with aspirin, acetaminophen, meprobamate, phenylephrine, and tolbutamide. The method consisted of reacting dimenhydrinate with reinecke salt in an acidic medium at 27 ± 2°. The purple precipitate was filtered and dissolved in acetone, and the maximum color absorption attained in 15 min was measured at 540 nm. Evidence is provided to establish the optimal experimental parameters. The stoichiometric balance of the precipitate was determined. Reasonably ideal adherence of the color absorption pattern to the Beer–Lambert law permitted microdetermination of dimenhydrinate in pure form, commercial formulations, laboratory-made combinations, and recovery experiments with good accuracy and repeatability. No interference was observed with any of the drugs or tablet adjuvants.

Keyphrases □ Dimenhydrinate—spectrophotometric determination with reinecke salt □ Spectrophotometry—determination of dimenhydrinate with reinecke salt □ Reinecke salt—determination of dimenhydrinate, spectrophotometry

Dimenhydrinate is assayed by official methods (1–3) by estimating diphenhydramine and 8-chlorotheophylline individually. It also has been determined in pharmaceuticals by gas-phase chromatography (4), an argentometrical method (5), UV absorption (6), complexation with phosphomolybdic acid followed by reduction with ascorbic acid in acetone to molybdenum blue (7), and a silicotungstic acid method followed by gravimetry (7).

The present study investigated reinecke salt as a useful precipitant (8) for the spectrophotometric estimation of dimenhydrinate in pure forms, dosage formulations, and laboratory-made combinations. The study investigated color stability, effect of temperature on the colored precipitate, influence of pH on absorbance of the precipitate in acetone solution, determination of the stoichiometric balance, establishment of an absorbance–wavelength relationship, and recovery with various combinations. Adherence to Beer's law was found within a range of 200–1000 μg/ml.

EXPERIMENTAL

Instruments and Materials—A single-beam spectrophotometer[1], a pH meter[2] fitted with a sealed calomel electrode, a shielded glass electrode, and a suitable thermostated[3] water bath were used.

Pharmaceutical grade dimenhydrinate, aspirin, acetaminophen, meprobamate, phenylephrine, and tolbutamide were employed as the working standards.

The commercial preparation analyzed was dimenhydrinate tablets[4]. For drug combinations, aspirin, acetaminophen, meprobamate, phenylephrine, and tolbutamide were mixed with dimenhydrinate in a 1:1 ratio.

The following reagents were used: ammonium nitrate solution[5] (10% w/v). Saturated reinecke salt solution[6] (3×10^{-3} *M*), ammonium thiocyanate[6] (0.01 *M*), ferric ammonium sulfate solution indicator[5], hydrochloric acid[5] (0.1 and 0.01 *M*), methylene blue solution indicator[6], silver nitrate solution[5] (0.01 *M*), and sodium hydroxide solution[6] (0.1 and 0.01 *M*, 20% w/v).

For the standard solution, dimenhydrinate (0.5 g) was dissolved in 100 ml of methanol[6] (analytical reagent).

Sample Preparation—An equivalent weight of a single-powdered tablet from a composite of 20 tablets was placed in a 50-ml volumetric flask and dissolved in 20 ml of methanol; then 0.5 ml of concentrated hydrochloric acid was added. The mixture was allowed to stand for 20 min with intermittent shaking. It was filtered through filter paper[7] into a dry 50-ml volumetric flask and brought to volume by rinsing with methanol.

Procedure—Twenty milliliters of the standard (or of the appropriately prepared sample) solution was transferred to a 100-ml volumetric flask. To it was added 0.5 ml of hydrochloric acid followed by 50 ml of saturated reinecke salt solution. The contents were shaken vigorously for 5 min. The precipitate was filtered through a sintered-glass crucible (G_4) and washed with 10 ml of chilled 0.02% (w/v) aqueous solution of reinecke salt. Then the precipitate was dried in a vacuum desiccator, dissolved in acetone, and transferred quantitatively to a 50-ml volumetric flask. It was brought to volume with acetone (stock). Appropriate dilutions were made, and the solution was transferred into a cell. Absorbance was determined at 540 nm *versus* a blank prepared from 20 ml of methanol and treated identically.

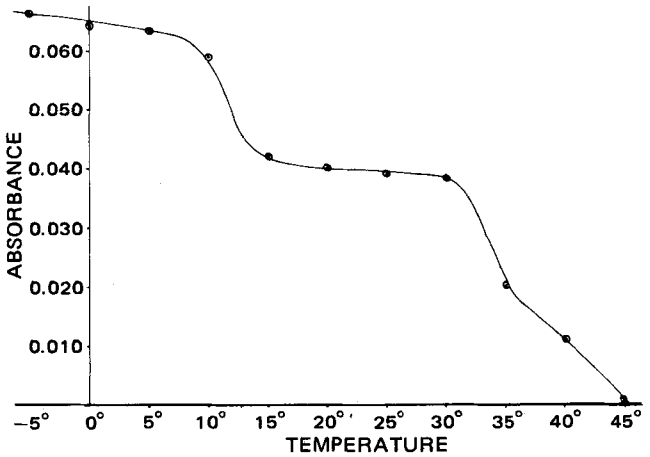

Figure 1—*Plot showing the absorbance* versus *temperature of dimenhydrinate with reinecke salt at 540 nm between −5 and +45°.*

RESULTS AND DISCUSSION

Dimenhydrinate purity was ascertained by BP methods (1) and found to be 97.5 ± 0.5%. The absorbances of the colored precipitate were measured at various wavelengths ranging from 400 to 650 nm. The maximum absorbance was at 540 nm. The stability of the dimenhydrinate–reinecke salt precipitate determined at 27 ± 2° was >2 hr.

The effect of temperature on the formation of the colored precipitate was investigated using a constant-temperature water bath ranging from −5 to +5°; a 1.5×10^{-3} *M* methanolic solution of dimenhydrinate and a 1.5×10^{-3} *M* aqueous solution of reinecke salt (Fig. 1) were employed. Figure 1 shows two near-plateau regions, one from −5 to 7.5° and the other from 15 to 30°. The experiments were carried out at room temperature (27 ± 2°).

[1] Spectronic 20, Bausch & Lomb.
[2] H. Jurgen & Co., Bremen, West Germany.
[3] Gallenkamp.
[4] Contained 50 mg of dimenhydrinate.
[5] B.D.H. Chemicals, Poole, England.
[6] E. Merck, Darmstadt, West Germany.
[7] Whatman No. 1.

0022-3549/81/0600-0690$01.00/0

Table I—Average Percentage of Dimenhydrinate in Laboratory-Made Mixtures and in Commercial Samples by Proposed Method and BP Method

Mixture (M) (1:1)	Proposed Method Mean, %[a]	±SD	BP Method Mean, %[a]	±SD
Dimenhydrinate + aspirin (M_1)	99.32	0.82	98.48	1.06
Dimenhydrinate + acetaminophen (M_2)	99.76	0.36	98.93	0.31
Dimenhydrinate + meprobamate (M_3)	98.88	0.39	98.70	0.65
Dimenhydrinate + phenylephrine (M_4)	99.76	0.37	98.82	0.08
Dimenhydrinate + tolbutamide (M_5)	99.32	0.31	99.71	0.19
Commercial tablet[b] T_1	101.86	0.64	101.16	0.80
Commercial tablet[b] T_2	100.53	0.47	100.44	0.48

[a] Average of four determinations. [b] Each tablet contained 50 mg of dimenhydrinate.

The effect of pH (1.60–11.20) on the absorbance of the colored precipitate (in acetone) was studied. Hydrochloric acid was used to vary the pH from 4.10 to 1.60, and dilute ammonia solution was used to vary it from 4.10 to 11.20. However, absorbance was not affected within a pH range of 2.85–8.30.

The stoichiometric balance was determined by Job's method of continuous variation (9) and a slope-ratio method (10). In Job's method, the maximum absorbance was obtained when $V_1/(V_1 + V_2) = 0.33$, which indicated the formation of the dimenhydrinate–reinecke salt precipitate in a 1:2 molar ratio. In the slope-ratio method, the $slope_1$ and $slope_2$ values were 0.0027586 and 0.0014210 ml^{-1}, respectively. Hence, $slope_1/slope_2$ for the precipitate was nearly equal to 2, thereby suggesting a 1:2 molar ratio.

Reinecke salt had a solubility in water of 1 in 52. Therefore, 50 ml of a saturated aqueous solution of reinecke salt was added to a 20-ml aliquot of a methanolic solution of dimenhydrinate to establish the 1:2 molar ratio requirement for maximum precipitation of dimenhydrinate.

Table II—Recovery Experiments by Proposed Method

Mixture or Tablet	Quantity of Dimenhydrinate Added, g	Corresponding Concentration of Dilution Measured, g %	Mean, %[a]	±SD
M_1	0.600	0.096	99.36	0.40
M_2	0.025	0.075	99.12	0.66
M_3	0.020	0.072	99.01	0.76
M_4	0.055	0.093	99.36	0.12
M_5	0.035	0.081	98.69	0.52
T_1	0.005	0.033	99.93	1.17
T_2	0.010	0.036	99.41	0.64

[a] Average for four determinations.

After the optimal experimental conditions for the maximal precipitation of dimenhydrinate–reinecke salt were established, the Beer's plot was obtained by employing the stock solution of the dimenhydrinate–reinecke salt precipitate in acetone. It obeyed Beer's law in the concentration range of 200–1000 μg/ml. With the least-squares method, the calibration curve from the data obtained can be described by the following regression equation: $A = 0.0045 + 1.905C$, where the regression coefficient is 0.999.

Five laboratory-made mixtures and two commercial tablet samples containing dimenhydrinate were subjected to analysis by the proposed method and the BP method (1) (Table I).

The activity of phenylephrine was checked directly with the reagent under identical experimental conditions and was found not to react.

To justify the repeatability of the proposed method, known amounts of pure dimenhydrinate were added to preanalyzed samples of mixtures and dosage forms and reassayed by the proposed method (Table II).

The presence of either pure drugs, *i.e.*, aspirin, acetaminophen, meprobamate, phenylephrine, and tolbutamide, or tablet adjuncts like starch, lactose, talc, and magnesium stearate in the quantities used caused no detectable interference in the proposed method. The analyses of two commercial products and the efficient percentage recoveries and significant reproducibility obtained suggest the feasibility of utilizing the proposed method for the quantitation of dimenhydrinate.

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ACKNOWLEDGMENTS

The authors thank Professor P. Iwe. Akubue, Dean, Faculty of Pharmaceutical Sciences, for interest and encouragement and M/S Searle (India) Ltd., Bombay, for the reference sample of dimenhydrinate.

Characteristics of Equilibrium Reaction of Zolazepam

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Received September 18, 1980, from **Analytical Research and ‡Product Development, Warner-Lambert Pharmaceutical Research Division, Warner-Lambert Company, Morris Plains, NJ 07950.* Accepted for publication November 17, 1980.

Abstract □ The equilibrium reaction of zolazepam, a pyrazolodiazepinone, was studied and analyzed using the approach used previously for other pyrazolodiazepinone derivatives. The intrinsic ring closure equilibrium constant for this reaction was ~100 times larger than that observed for pyrazolodiazepinones studied previously. This study illustrates that the diazepinone ring can dominate in equilibrium mixtures formed at pH values far below the pKa of the corresponding open form.

Keyphrases □ Zolazepam—analysis of equilibrium reaction □ Structure–activity relationships—equilibrium reaction of zolazepam □ Pyrazolodiazepinones—equilibrium reaction of zolazepam □ Equilibrium—analysis of zolazepam in reaction

The characteristics of the equilibrium reaction of certain pyrazolodiazepinones were reported previously (1). This study was an extension of that work and concerned the equilibrium behavior of zolazepam, 4-(*o*-fluorophen-

0022-3549/81/0600-0691$01.00/0