Spectrophotometric Determination of two Antihistamines by Charge-Transfer Complex Formation with Chloranilic Acid

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A rapid and sensitive spectrophotometric method has been developed for the determination of two antihistamines, mebrophenhydramine hydrochloride and hydroxyzine hydrochloride in pure form and in different dosage forms. The method is based on the formation of stable donor-acceptor complex between the studied antihistamines and chloranilic acid in acetonitrile. The resulting intensely coloured purple chloranilic acid radical anion possesses a characteristic maximum at 535 nm. Beer's law is obeyed over the concentration range 25-150 μg/ml in respect of both drugs. The stoichiometric ratio and stability constant of each charge-transfer complex are determined and the mechanism of the reaction is discussed. The molar absorptivity and Sandell sensitivity of the charge-transfer complexes formed are reported. Statistical treatment of the experimental results indicates that the method is precise and accurate. Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedure. The procedure described was successfully applied to the determination of the bulk drugs and their pharmaceutical formulations.

Mebrophenhydramine hydrochloride (MPH) is a potent antihistaminic drug used in all allergies. Literature survey revealed that little attention has been paid to develop analytical methods for the assay of MPH. Sastry *et al.*[1] have described an extractive spectrophotometric method using cobalt thiocyanate as a reagent, but this method lacks sensitivity. Capillary electrophoretic determination[2] though sensitive is expensive. The other method reported for its determination is potentiometry[3]. Hydroxyzine hydrochloride (HDH) primarily has skeletal muscle relaxation, antihistaminic and antiallergic effects[4]. The reported techniques for the determination of HDH include titrimetry[5-8], gravimetry[9], visible spectrophotometry[10,11], uv-spectrophotometry[12], coulometry[13], gas-chromatography[14], liquid chromatography[15] and high performance liquid chromatography[16]. The chromatographic methods deal mainly with the separation and determination of the drug in the presence of its metabolites and in human urine and serum and involve experimental set up which is not always easily available. This paper describes a simple and sensitive spectrophotometric method based on the formation of charge-transfer complex with chloranilic acid.

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A Systronics model 106 digital spectrophotometer with 10 mm matched glass cells was used for all spectral measurements. All chemicals used were of analytical reagent grade and distilled water was used to prepare aqueous solutions and solvents used were of spectroscopic grade. Chloranilic acid (CAA, 0.1%) was prepared by dissolving 100 mg of CAA (S. D. Fine Chem. Ltd., Mumbai) in 100 ml acetonitrile, and aqueous ammonia solution (6 M) was prepared by diluting 42 ml of concentrated ammonia (S. D. Fine Chem. Ltd., Mumbai) to 100 ml with distilled water.

For the preparation of the standard drug solutions, an accurately weighed amount of MPH or HDH equivalent to 100 mg of the free base was dissolved in about 25 ml of water in a beaker. The solution was quantitatively transferred into a separating funnel, made alkaline with ammonia solution and shaken with four 20 ml portions of chloroform for 2 min each time. The chloroform extracts were pooled in a 100 ml calibrated flask after passing through a

filter paper containing anhydrous sodium sulphate, the paper was washed with chloroform and the solution was diluted to the mark with chloroform to provide a standard drug base equivalent to 1000 μg/ml.

Accurately measured volumes (0.1-0.75 ml) of the solution of both antihistamine free bases in chloroform equivalent to 100-750 μg were transferred into a series of 5 ml calibrated flasks to give a final concentration of 25-150 μg/ml. Enough chloroform was added to bring the volume to 1 ml. Then, 1.0 ml (for MPH) or 1.5 ml (for HDH) of CAA solution was added to each flask. The volume was made up to mark with acetonitrile, mixed well and the absorbance of each solution was measured at 535 nm against a reagent blank. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

To determine the drug in the tablets, twenty tablets of MPH or HDH were weighed and powdered. An amount of the tablet powder equivalent to 50 mg of base was accurately weighed and transferred into a separating funnel containing about 20 ml of water. The mixture was shaken for 15 min, then made alkaline with ammonia solution and the base was extracted with chloroform, dried over anhydrous sodium sulphate and made up to 50 ml to give a solution of 1000 μg/ml of free base. A suitable aliquot was taken and determined by the procedure described above.

Solution of CAA in acetonitrile displayed an absorption peak at 430 nm while the drugs showed negligible absorbance in the region 400-700 nm. When mixed with the chloroform solution of both drugs, an intense purple colour with an absorption band at 535 nm resulted due to the charge-transfer complexation reaction between the n-donor drugs and the π-acceptor CAA followed by the formation of radical anion[17,18]. CAA in acetonitrile reacted stoichiometrically with both the antihistamines forming single purple CAA radical anion. The reaction between the drugs and CAA was instantaneous and the product remained stable for at least 20 h.

The optical characteristics such as Beer's law limits, detection limits, molar absorptivities and Sandell sensitivities are presented in Table 1. The molar-ratio of the reactants in the complexes as found by Job's method of continu-

TABLE 1: QUANTITATIVE PARAMETERS AND PRECISION OF THE PROPOSED METHOD.

Parameter	MPH	HDH
Beer's law limits (μg/ml)	25 – 150	25 – 150
Molar absorptivity, ε (l/mol/cm)	1.2360×10^{3}*	1.3722×10^{3}*
	1.2120×10^{3}**	1.3330×10^{3}**
Sandell sensitivity (ng/cm^2)	310.27	326.11
Detection limit (μg/ml)	1.3197	1.2480
Regression equation, y$^{\psi}$		
Intercept, a	- 0.0089	0.0024
Slope, b	0.0033	0.0030
Confidence interval of the intercept, α	-0.0089±0.1812	0.0025±0.0197
Confidence interval of the slope, β	0.0034±0.0019	0.0030±0.0002
Correlation coefficient, r	0.9998	0.9991
Molar-ratio (Drug : CAA)	1:1	1:1
Formation constant, K	2.64×10^{3}**	1.07×10^{3}**
Relative standard deviation (%) (n=7)	1.76	1.28
Range of error (%) (P=0.05)	1.75	1.28

*Indicates from Beer's law data, **indicates from Benesi – Hildebrand plot. ψ y = a+bx, where, y is the absorbance for concentration x in μg/ml. MPH stands for mebrophenhydramine hydrochloride and HDH for hydroxyzine hydrochloride.

TABLE 2: RESULTS OF ASSAY OF MPH AND HDH IN PHARMACEUTICAL FORMULATIONS.

Antihistamine studied	Dosage form	Lable claim, mg/tablet	Mean[$] ± SD
MPH	Mebryl tablets,	25	25.53±0.40
HDH	Atarax tablets,	25	24.50±0.39

[$] Average of five determinations. MPH stands for mebrophenhydramine hydrochloride and HDH for hydroxyzine hydrochloride. Mebryl are MPH tablets of strength 25 mg marketed by Smith Kline Beechem and Atarax are HDH tablets of strength 25 mg marked by UNI-UCB Ltd.

ous variations[19] and the formation constants calculated using Benesi-Hildebrand equation[20] are also compiled in Table 1. The precision of the method was tested by performing seven replicate analyses at a concentration of 100 μg/ml of each drug. The relative standard deviation (%) and percent range of error at 95% confidence level for the method are given in Table 1.

The effect of a wide range of excipients and additives which often accompany the drugs in tablets was examined. Starch, talc, gum acacia, lactose, sodium alginate and magnesium stearate did not interfere. The method was applied to the assay of drugs in tablets and the results are summarised in Table 2. To further evaluate the validity and accuracy of the method, recovery experiments were performed using standard-addition method. To a known fixed amount of MPH or HDH in pre analyzed tablet powder, pure drug at three levels was added, and the total was determined by the proposed method. Each such determination was repeated three times. From knowledge of the total found, the percent recovery of the pure drug added is calculated. To conclude, the proposed method has the advantages of speed, simplicity, sensitivity and fair degrees of accuracy and precision, and employs a coloured species which is highly stable.

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