RESEARCH PAPER

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Spectrophotometric Determination of Ketamine Hydrochloride by Charge-Transfer Complexation with p-Chloranilic Acid

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A spectrophotometric method is described to illustrate the utility of charge transfer-complexation in a non-aqueous medium for the assay of ketamine hydrochloride. Conformity to Beer's Law enabled the assay of dosage forms of the drug. Employing Job's method of continuous variation, chloranilic acid was found to form a charge-transfer complex in a stoichiometry with maximum absorption band at 528 nm for ketamine hydrochloride. The method has been successfully applied to the analysis of commercially available ketamine hydrochloride dosage forms without interference from their excipient.

KETAMINE hydrochloride, (cyclohexanone2-)(2-chloropheny)-2-(methylamine hydrochloride) is a rapidly-acting non-barbiturate general anaesthetic that produces anaesthesia characterized by profound analgesia, normal to hyperactive pharyngeal reflexes, normal or slightly enhanced skeletal muscle tone, and cardiovascular stimulation[1]. It is a white colourless solid with a characteristic odour, which is acid to litmus, melts with decomposition 262-263°, pH of a 1 in 10 solution was found to be between 3.5 and 4.1.

The method is based on the molecular interaction between the drug and chloranilic acid to form charge-transfer complex in which the drug acts as an n-donors and chloranilic acid as π-acceptor in non-aqueous media. An investigation of the complex was made with respect to composition, association constant, molar absorptivity, degree of dissociation and free energy changes.

MATERIALS AND METHODS

The following reagents were obtained form commercial sources and used as supplied : *p*-chloranilic acid (Reidel de hean, Germany), chloroform and Dioxan (May and Baker, Germany). Other solvents and reagents uses were of analytical grade. The drug, ketamine hydrochloride (Rotexmedic GMBH, Germany) was obtained from a local pharmacy. A solution of p-chloranilic acid of the strength 5.0×10^{-3}M was prepared in dioxan.

Determination of Absorption Spectrum of Chloranilic Acid

Two ml of chloranilic acid solution was introduced into a 5 ml flask and dioxan added to make up to the mark. Measurement of the absorbance (under standard conditions) of the solution between 400 nm and 500 nm wavelength using dioxan as blank was carried out in a spectronic 20 spectrophotometer.

Determination of Absorption Spectrum of Ketamine Hydrochloride-Chloranilic Acid Complex

Two ml of chloranilic acid solution and 2 ml of drug solutions were pipetted into a 5 ml graduated test tube separately and made up to mark with dioxan. The reaction mixtures were scanned between 430-580 nm for ketamine hydrochloride using dioxan as the blank.

Preparation of Assay Solution

Five hundred mg equivalent to 10 ml of the ketamine hydrochloride was dissolved in 15 ml of water in a 250 ml separatory funnel, alkalinized and extracted with 15 ml and three 10 ml portions of chloroform. The extracted base was

washed with 10 ml of water in another separatory funnel. The washed extracts were then passed through anhydrous sodium sulphate supported on a filter paper in a funnel and collected in a 50 ml calibrated flask and made up to mark with chloroform.

Determination of Job's Plot for the Complex

Five aliquots of ketamine hydrochloride between 0.5-4.5 ml in multiples of 1.0 ml were pipetted into different test tubes. The volumes were made up to 5 ml with dioxan which was used as a blank. Each flask was allowed to stand at room temp for 30 min.

Study of Time-Absorbance Relationship for the Complex at Room Temperature

Similar solutions of the drug were introduced into different volumes of chloranilic acid in 5 ml volumetric flasks or test tubes. Chloranilic acid solution between 0.5-2.5 ml in multiples of 0.5 ml were used. The volumes were made up to the mark depending on the time for full complexation, after which the absorbance measurements were taken using Dioxan as a blank.

Determination of the Association Constant and Molar Absortivity of the Complex (Benesi-Hildebrand Plot)

The drug solution between 0.8-2.4 ml in multiples of 0.4 ml were used. 1 ml chloranilic acid solution was added to each test tube and the volume made up to 4 ml mark with dioxan. All the test tubes were allowed to stand at room temperature for 30 min. Absorbance was measured at 528 nm against a dioxan blank.

Evaluation of the Assay Solution of the Drug

Varying volumes of the drug extract were pipetted into five different test tubes, from 0.5-2.5 ml in multiples of 0.5 ml. Equal volumes of chloranilic acid solution was added to each test-tube and shaken to allow proper mixing. Dioxan was then added to each test tube to make up the volume to 7.0 ml. Absorbance readings were taken at 528 nm.

RESULTS AND DISCUSSION

Chloranilic acid in dioxan gave a golden yellow colouration with maximum absorption at 435 nm as shown in fig 1. The reaction product (complex) in non-aqueous solvent gave a purple colour upon addition of excess of the drug. It shows that the colour generated is

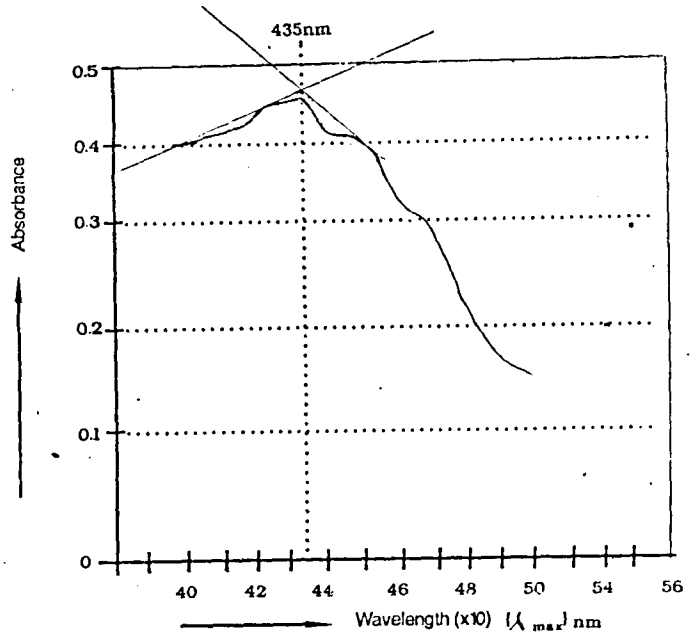

Fig. 1: Absorption spectrum of chloranilic acid in dioxan

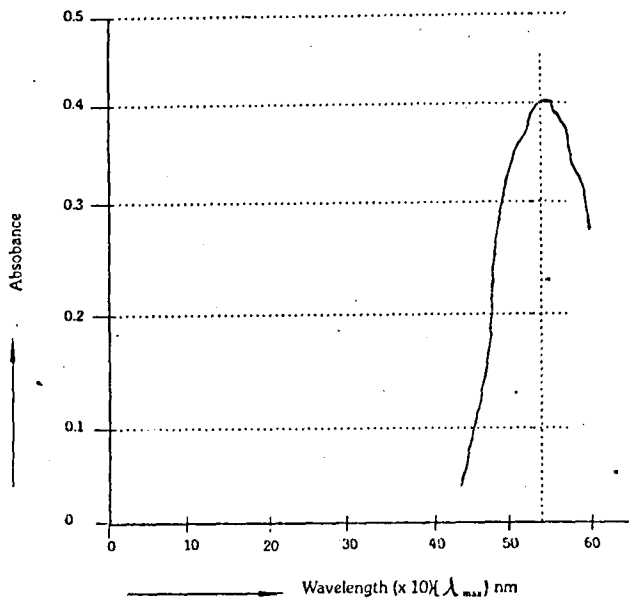

Fig. 2: Absorption spectrum of cholranilic acid-ketamine hydrochloride complex

concentration-dependent. The colour of the complex is stable for at least 24 hours when stored in the dark. The wavelength of the complex was at 528 nm (Fig. 2). Dioxan was chosen as the solvent because of it's low dielectric constant and it appears not to compete or shield the charge-transfer process from donor to acceptor which is invariable

Table 1 : Results of the Assay of Ketamine Hydrochloride Solution.

Flask No.	Ketamine hydrochloride (ml)	Chloranilic acid (ml)	Calculated Conc. (Mg/ml x10-5M)	Extrapolated conc. (Mg/ml x10-5M)	% Recovery
1	0.2	2.0	2.81	2.70	96.08
2	0.3	2.0	4.22	4.01	99.53
3	0.4	2.0	5.63	5.20	92.36
4	0.5	2.0	7.04	6.91	98.01

necessary for instant and stable colour formation at room temperature.

The absorption bands shown by this drug can be attributed to the formation of charge-transfer complex between the drug acting as n-donors (D) or lewis base and chloranilic acid as the π acceptor (A) or lewis acid, with the subsequent formation of a coloured anion radical of chloranilic acid, according to the following equation[2].

$$R_3N + CA \underline{\text{fast}} (R_3N\text{——}CA)\text{———}R_3N+CA \quad .....(1)$$

For determination of composition of the complex of the drug, Job's method[3] of continuous variation was employed. The method assumes the presence of only one single product in solution in this reaction.

$$aD+bA = DaAb \quad ....(2)$$

a is the concentration of donor and b mole of acceptor if the concentration CD and CA are varied but when total combined analytical concentration is constant then :

$$CD+CA = \text{constant.}$$

The molar absorptivity and association constant for the complex were evaluated by using Benesi-Heldebrand equation[4]. Whereby the concentration of the donor is higher than that of the acceptor. From the Fig. 3, the intercept of the formed straight line with the ordinate is molar absorptivity (ε)-1 and the slope equals the association constant.

Table 1 shows the Results of the assay of ketamine hydrochloride solution. The result indicate that the method is fairly accurate since high percent recovery was achieved.

The experiment was performed in order to validate the accuracy of the proposed assay method.

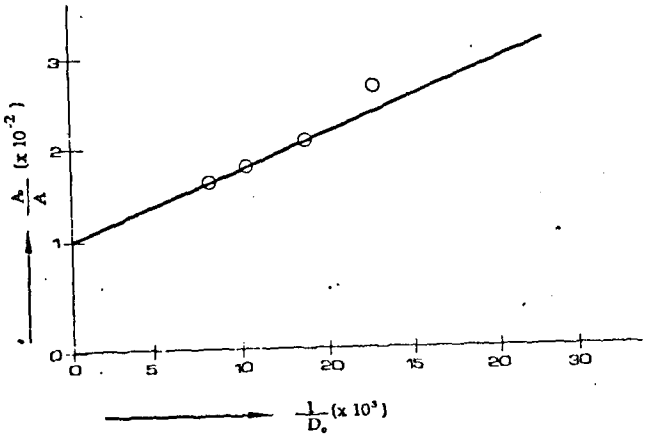

Fig. 3: Benesi-Hildebrand Plot for ketamine Hydrochloride-Chloranilic Acid Complex

Percentage Recovery (%R)=C1/C x 100, where C1 is the extrapolated concentration and C represents the concentration obtained through calculation.

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