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TITRIMETRIC AND SPECTROPHOTOMETRIC ASSAY OF BUPROPION HYDROCHLORIDE IN PHARMACEUTICALS USING MERCURY(II) NITRATE
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are found in the literature for the determination of BUP in pure form and in tablets.

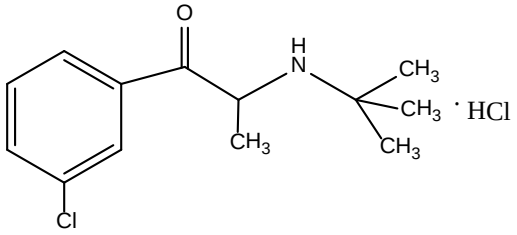

Figure 1. Structure of bupropion hydrochloride

There is only one report on the titrimetric [20] determination of BUP, which involves neutralization of the drug with perchloric acid in non aqueous medium. As per our literature survey, no visible spectrophotometric method has ever been reported for the determination of BUP in pharmaceuticals.

The purpose of this investigation was to develop simple, rapid, accurate and inexpensive procedures for the quantitation of BUP in pure form and in pharmaceutical formulations. The titrimetric procedure involves the titration of the chloride content of the hydrochloride of the drug in acidic condition with mercury(II) nitrate while the spectrophotometric method uses an indirect procedure based on the measurement of the decrease in absorbance of mercury(II)–diphenylcarbazone complex at 515 nm in acidic condition.

Experimental details

Apparatus

A Systronics model 106 digital spectrophotometer provided with 1-cm matched quartz cells was used for all absorbance measurements.

Materials

Pharmaceutical grade bupropion hydrochloride (BUP) pure was received from GlaxoSmithKline Pharmaceuticals, Mumbai, India. The following pharmaceutical preparations were purchased from commercial sources in the local market and subjected to analysis: Bupron-SR-150 from Sun pharmaceutical industries, jammu, India, and Ession-ER-150 from psycoremedies, ludhiana, Punjab, India.

Reagents

All the reagents used were of analytical-reagent grade and double distilled water was used throughout the investigation.

Mercury(II) nitrate (0.01 mol L^{-1}). Prepared by dissolving 1.713 g of the chemical (S.d fine-chem. Ltd., Mumbai, India) in distilled water and diluting to 500 mL. The solution was standardized using pure potassium chloride [24]. The stock solution was diluted to 0.005 mol L^{-1} for the titrimetric work and diluted stepwise to obtain 50 µg mL^{-1} Hg(II) for the spectrophotometric work.

Diphenylcarbazone–bromophenol blue mixed indicator for titrimetry. The mixed indicator was prepared by dissolving 0.25 g of diphenylcarbazone (The British Drug Houses LTD, Poole, England) and 0.025 g of bromophenol blue (LOBA Chemie PVT LTD, Mumbai, India) in 50 mL of ethanol.

Diphenylcarbazone for spectrophotometry (0.02 %). Prepared by dissolving 20 mg of the reagent in 15 mL of ethanol and diluting to 100 mL with distilled water.

Formate buffer. It was prepared by dissolving 0.52 g sodium formate (LOBA Chemie PVT LTD, Mumbai, India, assay 99.0 %) in 70 mL of distilled water, pH adjusted to 3.4 with 0.5 mol L^{-1} nitric acid and finally diluted to 100 mL with water.

Nitric acid (0.05 mol L^{-1}). Concentrated nitric acid (Merck, Mumbai, India; sp. gr. 1.41) was diluted appropriately with water to get 0.05 mol L^{-1}.

Gum Arabic (2 %). Prepared by dissolving 2 g of acacia (LOBA Chemie PVT LTD, Mumbai, India) in 100 mL of hot water and the solution was filtered when it is turbid.

Standard solution of bupropion hydrochloride. A stock standard solution equivalent to 2.0 mg mL^{-1} of BUP was prepared by dissolving accurately weighed 200 mg of pure drug in water and diluting to the mark in a 100 mL calibrated flask with water. This solution was used in titrimetric work. The stock solution equivalent to 2000 µg

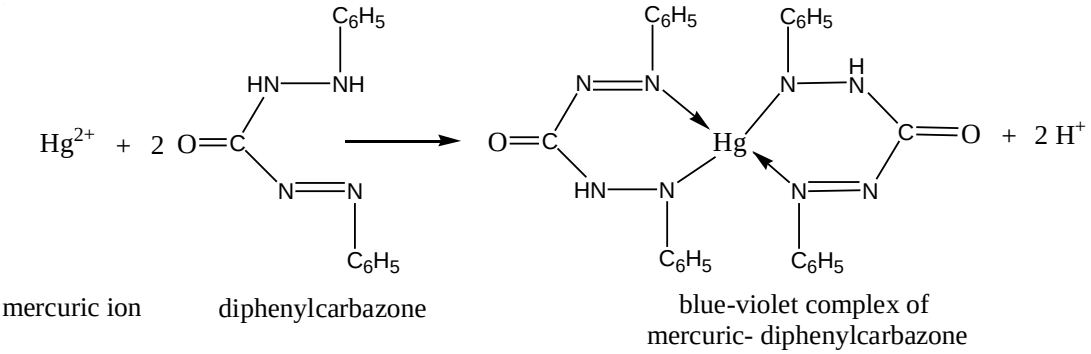

Figure 2. Formation of mercury(II)-diphenylcarbazone complex

Although diphenylcarbazone is a suitable indicator for the titration of chloride with Hg^{2+} [30] diphenylcarbazone– bromophenol blue mixed indicator was found to give better results as reported by Clarke [31]. Best results were obtained at pH 3.2–3.4 which was adjusted by adding a requisite amount of 0.05 mol L^{-1} nitric acid. Bromophenol blue indicator covers the same pH range (3.0 to 3.6) and makes the first detectable change from its alkaline blue to acid yellow at approximately pH 3.6. It therefore can serve the dual purpose of masking premature colour and adjusting pH [31]. The reaction stoichiometry was calculated to be 2:1 (BUP: Hg^{2+}) in the 2-20 mg range investigated and the quantitative calculations were based on this ratio.

Spectrophotometric method. The spectrophotometric method is based on the reaction of the chloride ion of the drug by a known excess of mercury(II) to form soluble mercuric chloride, and the subsequent determination of the unreacted mercury(II) by interacting with diphenylcarbazone under acidic pH conditions (Fig. 3), and measuring the absorbance at 515 nm (Fig. 4).

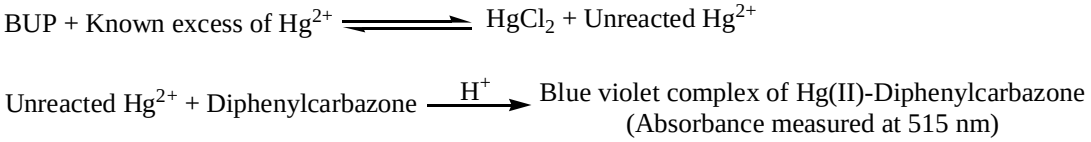

Figure 3. Reaction scheme for spectrophotometric method

Method Validation

Analytical parameters. A linear relation is found between absorbance and concentration of BUP in 1-15 μg mL^{-1} range, and Beer's law is obeyed in the reverse manner; the equation of the line being

$$Y = 0.6588 + (- 0.0331) X$$

where Y is the absorbance and X is concentration in μg mL^{-1}. The correlation coefficient (r) of the calibration plot is calculated to be (-0.9996) confirming a linear decrease in absorbance with increasing the concentration. The molar absorptivity is calculated to be 8.6×10^3 L $mol^{-1}cm^{-1}$, and Sandell sensitivity being 0.0321 μg cm^{-2}. The limits of detection (LOD) and quantification (LOQ) are calculated to be 0.33 and 1.00 μg mL^{-1}, respectively.

Accuracy and precision. The accuracy of an analytical method expresses the closeness between the reference value and the found value [32]. Accuracy was evaluated as percentage relative error between the measured concentrations and taken concentrations for BUP (Bias %). The results obtained are compiled in Table 1 and showed that the accuracy is good for both methods. The precision of the methods was calculated in terms of intermediate precision (intra-day and inter-day) [33]. Three different concentration of BUP (within the working limits) were analysed in seven replicates during the same day (intra-day precision) and five consecutive days (inter-day precision). The RSD (%) values of intra-day and inter-day studies showed that the precision was good for both methods (Table 1).

Table 1. Evaluation of intra-day and inter-day precision and accuracy

Method*	BUP taken	Intra-day (n=7)			Inter-day Inter-day (n=5)		
		BUP founda	Precisionb	Accuracyc	BUP founda	Precisionb	Accuracyc
Titrimetric method	5.00	4.95	1.54	1.00	5.06	2.24	1.20
	10.0	9.91	0.63	0.90	10.11	1.68	1.10
	15.0	14.89	0.66	0.73	15.20	1.39	1.33
Spectrophotometric method	4.0	3.94	2.74	1.50	4.09	3.15	2.25
	8.0	7.75	2.25	3.12	8.14	2.86	1.75
	12.0	11.91	1.24	0.75	12.26	2.32	2.17

* BUP taken / found in titrimetric method is in mg and the same in spectrophotometric method is in μg mL^{-1}, a. Mean ± standard error, b. Relative standard deviation (%), c. Relative Error (%)

Selectivity. To determine the selectivity of the methods, the analytical placebo was prepared and subjected to analysis by the proposed methods. It was confirmed that the change in the titrant value and absorbance with respect to the water blank was caused only by the analyte. To identify the interference by common tablet excipients, a synthetic mixture with the composition: BUP (200 mg), talc (80 mg), starch (160 mg), calcium gluconate (80 mg), lactose (80 mg), sodium alginate (40 mg) and magnesium stearate (40 mg), was prepared and subjected to analysis by the proposed methods after solution preparation using the procedure described for tablets. The percent recoveries of BUP were 101.20 ± 0.83 (n =5) and 103.50 ± 1.49 (n =5) by titrimetry and spectrophotometry, respectively, suggesting no interference by the excipients in the assay of BUP under the described optimum conditions.

Application to formulations. The proposed methods were successfully applied to the determination of BUP in two representative tablets bupron-SR-150 and ession-ER-150. The results obtained are shown in Table 2 and were compared with those obtained by the official method [20] by means of student's t- and F-tests at 95 % confidence level. The official method involves the visual titration of the

Conclusions

Two useful methods for the determination of BUP have been developed and validated. The assay results demonstrate that it is possible to use mercury(II) nitrate, which is stable enough and need no special precautions during storage or use, as a reagent for determination of BUP in authentic samples. The only titrimetric method currently available [20] uses non aqueous medium. The proposed titrimetric method is simple, rapid, free from critical experimental variables, uses aqueous medium and applicable over a wide range (2-20 mg). The spectrophotometric method is the first visible spectrophotometric method for determination of BUP and it is free from the usual analytical complications like heating and extraction. Moreover, the methods are accurate, reproducible, adequately sensitive and free from interference by common additives and excipients. The wide applicability of the new procedures for routine quality control is well established by the assay of BUP in pure form and in pharmaceutical preparations.

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