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AAS and spectrophotometric determination of propranolol HCl and metoprolol tartrate

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Abstract

Two simple and accurate spectrophotometric methods are described for the determination of propranolol hydrochloride (I) and metoprolol tartrate (II). The methods are based on the reaction of each drug as a secondary amine: (a) with carbon disulphide, the formed complex extracted into iso-butyl methyl ketone (IBMK) after chelation with Cu(II) ions at pH 7.5, followed by measuring the absorbance at 435.4 nm or indirectly for the drug by flame atomic absorption spectrophotometry (AAS). The calibration graph is linear up to 40 and 60 μg ml^{-1} with apparent molar absorptivities of 6.89×10^3 and 1.08×104 l mol^{-1} cm^{-1} and correlation coefficients of 0.9994 and 0.9995 for propranolol and metoprolol, respectively; (b) with π-acceptors, tetracyanoethylene (TCNE), or chloranilic acid (CLA) to give highly coloured complex species. The coloured products are quantitated spectrophotometrically at 415 or 510 nm for the two drugs with TCNE and CLA, respectively, and obey Beer's Law with RSD less than 2.0. The methods were applied to the determination of these drugs in pharmaceutical preparation without interferences. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Propranolol hydrochloride; Metoprolol tartrate; CS_2; Tetracyanoethylene (TCNE); Chloranilic acid (CLA); Spectrophotometer

1. Introduction

Propranolol hydrochloride (I), and metoprolol tartrate (II) are β-adrenergic blocking drugs. These drugs are amongst the most widely prescribed drugs in the world, based on the aryloxypropranololamine backbone, which are of therapeutic value in the treatment of various cardiovascular disorders such as angina pectoris, cardiac arrhythmia and hypertension [1,2]. The assay procedures of these drugs listed in USP 23 NF18 (1995) [3] and BP (1998) [4] describe itrimetric, spectrophotometric and chromatographic methods. Other methods involving spectrophotometric [5–7], chromatographic [8,9] and HPLC [10–12] methods were reported. Colorimetric determination of some β-blocking drugs using carbon disulphide and Cu(I) ions has been reported [5]. Chloroform was used as an extractant for the formed complex. No atomic absorption spec-

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trophotometric (AAS) determination of these drugs was carried out. This paper describes a spectrophotometric and AAS assay for propranolol, and metoprolol based on the interaction of these drugs with CS_2, followed by complexation with Cu(II) ions, using iso-butyl methyl ketone (IBMK) for extraction of copper dithiocarbamate complex. The reaction of secondary amino group and CS_2 in presence of metal ions, and its wide application in pharmaceutical analysis has attracted the interest of researchers [13–15].

Charge transfer (CT) complexation reactions have been extensively used for the determination of electron donating basic nitrogenous compounds using π-acceptor in organic solvents [16–21]; tetracyanoethylene reacts with primary and secondary aliphatic and aromatic amines to give CT-complexes. The present work extends the applications of the π-acceptors tetracyanoethylene (TCNE) and chloranilic acid (CLA) for estimation of I and II in pharmaceutical preparations.

$$[Ar{-}O{-}CH_2{-}CH(OH){-}CH_2{-}NH{-}C(CH_3)_2\ R]_u\ X$$

$$[Ar{-}O{-}CH_2{-}CH(OH){-}CH_2{-}NH{-}C(CH_3)_2\ R]_n\ X$$

(I) Ar =  , R = CH_3 , n = 1, X = HCl

(II) Ar = CH_3-O-$(CH_2)_2$ –  , R = H , n = 2 ,

X = OH - CH - COOH
OH - CH - COOH

2. Experimental

2.1. Apparatus

All spectrophotometric determinations were performed with a Pye-Unicam SP6-400 UV-visible spectrophotometer. Atomic absorption spectrophotometric (AAS) measurements were carried out using a Perkin-Elmer 2380 atomic absorption spectrophotometer.

2.2. Materials and reagents

All solvents and reagents were of analytical reagent grade. TCNE and CLA (Sigma) were freshly prepared as 5×10^{-3} M solutions in acetonitrile.

Propranolol hydrochloride and Inderal tablets (labelled to contain 10 mg of propranolol hydrochloride per tablet) were obtained from Kahira. Metoprolol tartrate and Betaloc tablets (labelled to contain 100 mg per tablet) were obtained from Egyptian Chemical Industries Development (CID).

2.3. Reference drug solution

Solution of the two drugs (0.2 mg ml^{-1}) was prepared in distilled water; 500 μg ml^{-1} was prepared by dilution with distilled water (for CS_2 and AAS assay).

2.4. Standard drug solutions

The drug base, 10^{-3} M solution in acetonitrile, prepared using an accurately weighed amount of the drug salt equivalent to 29.58 and 68.48 mg base of propranolol and metoprolol, respectively, was dissolved in a small volume of distilled water and render alkaline with conc. ammonia solution. The liberated base with five 10-ml portions of ether was extracted by passing the separated organic layers through anhydrous sodium sulphate. The ether was removed in a stream of N_2. The free base was then dissolved in acetonitrile in 100-ml volumetric flask. Whenever required, dilute solutions were obtained by appropriate dilution with acetonitrile (for CT assay).

For sample preparation solution, an aliquot from a composite of the mixed contents of ten tablets, equivalent to 50 mg of the drug salt, was weighed. Then the procedure for reference drug solution (for CS_2 assay) was followed.

An accurately weighed amount of the tablet powder equivalent to 50 mg of the drug base was dissolved. Then the procedure for the stock drug solution of CT assay was followed. All drug solutions were stored in tightly-closed containers protected from light.

A 2×10^{-2} M $CuCl_2$ solution was prepared in water and standardized [22]. Ammonia buffer was prepared as described in Eur. Pharmacopoeia [23] and acetic acid 25% v/v solution was prepared in distilled water (for CS_2 assay).

3. General procedure

3.1. Carbon disulphide method

The following solutions were placed in a separating funnel: 0.5–3.0 ml of reference or sample solution (containing amounts in the range 50–1250 μg propranolol or 50–1500 μg Metoprolol), 1 ml of CS_2, and 1 ml ammonia buffer solution of pH 10. The mixture was shaken for 2 min. Then 1 ml $CuCl_2$ (2×10^{-3} M), and 1 ml of 25% acetic acid solution was added, the mixture was shaken well and 25 ml IBMK was added with repeated shaking for 3 min. The solution was allowed to stand for 10 min to clarify the two phases. Finally, the absorbance of the organic layer was measured at 435.4 nm against a reagent blank prepared and treated similarly.

3.2. Atomic absorption procedure

To a 1-ml sample containing 0.025–0.25 mg of drug the procedure above was followed as far as 'the solution was allowed to stand for 10 min'. The IBMK extract was then aspirated into the flame, using a hollow cathode lamp of copper under the following conditions: wavelength = 324.8 nm, slit width = 0.7 mm, lamp current = 7 mA.

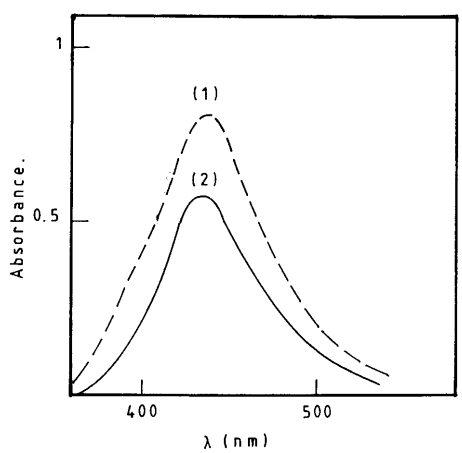


Fig. 1. Absorption spectra of reaction product using 35 μg ml^{-1}. (1) Propranolol hydrochloride; (2) metoprolol tartrate.

3.3. Charge transfer procedure

Into 10-ml calibrated flasks were placed 0.2–3.5-ml aliquots of 500 μg ml^{-1} drug, and 2 ml of TCNE or CLA (5×10^{-3} M) in acetonitrile. The reaction mixture was allowed to stand for 15 min at 25°C. The volume was made up to 10 ml with the same solvent and the absorbance was measured at 415 or 510 nm for TCNE and CLA, respectively, against a reagent blank prepared in the same manner.

4. Results and discussion

4.1. Carbon disulphide method

Propranolol hydrochloride, and metoprolol tartrate drugs possess a secondary amino group which reacts with CS_2 to give dithiocarbamate in the presence of ammonia buffer according to:

$$RR'NH + CS_2 + NH_3 \rightarrow RR'N\underset{\underset{S}{\|}}{C} - SNH_4$$

In the presence of Cu^{2+} ions this forms a stable yellow Cu^{2+} dithiocarbamate complex with a characteristic absorption maximum at 435.4 nm in iso-butyl-methyl ketone (IBMK) (Fig. 1).

The reaction rate and the amount of complex produced and extracted are influenced considerably by the pH of the reaction mixture. Fig. 2 shows the effect of acetic acid concentration on the stability of the extracted copper (II)-dithiocarbamate complex. The complex is most stable by addition of 1 ml (25% v/v) acetic acid which maintains the pH in the range 7.0–7.5. At pH greater than 7.5 the absorbance decreases. A pH of 7.5 was chosen as the working pH. The effect of copper concentration on the determination of the drugs is examined and it is found that 1 ml of

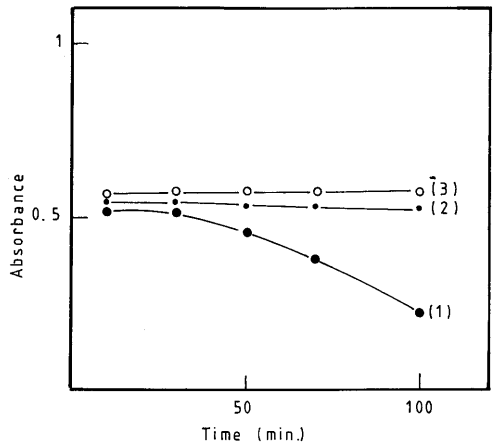


Fig. 2. Effect of time on the reaction product of 35 μg ml^{-1} metoprolol tartrate: (1) without acetic acid; (2) in presence of 0.5 ml 25% acetic acid; (3) in presence of 1 ml 25% acetic acid. $\lambda = 435$ nm.

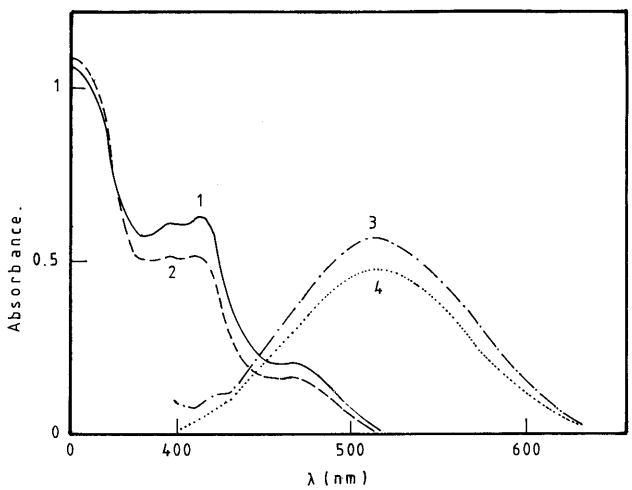
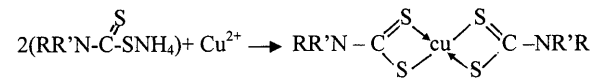


Fig. 3. Absorption spectra of 100 and 160 μg ml^{-1} of I and II, with 5×10^{-4} M TCNE (1,2) and CLA (3,4).

2×10^{-3} M Cu(II) provided the optimum concentration of copper and 1 ml of CS_2 was chosen as optimum volume for colour development.

In order to study the stoichiometry of the coloured products the molar ratio between cupric ions and each drug was determined using the continuous variation method [24]. It is found that the ratio between copper and propranolol or metoprolol is 1:1 or 1:2, respectively.

The 1:2 ratio is according to:



The developed colours are stable for at least 24 h. A linear correlation is found in the ranges 5–40 and 5–60 μg ml^{-1} with relative standard deviations of 0.249 and 0.185 for propranolol and metoprolol, respectively.

The reaction under investigation is suitable for indirect determination of propranolol hydrochloride, and metoprolol tartrate by AAS. The copper content equivalent to reacted drug in IBMK layer is determined by AAS. It is found that Beer's law is obeyed in the range 1–10 μg ml^{-1} and the method is reliable for the determination of the investigated drugs.

The use of IBMK allows for sensitive spectrophotometric and AAS methods for the determination of drugs at the microgram level, whereas chloroform is an unsuitable solvent for AAS determination.

The results obtained for each drug by using the proposed CS_2 procedure show that this method is sensitive, and two instruments can be used for analysis. The reaction is specific for secondary aliphatic amino group.

4.2. Charge-transfer complexation methods

In acetonitrile these drugs exhibit maxima in the UV region. Upon addition of TCNE or CLA, a pronounced bathochromic shift to 415 or 510 nm, respectively, is observed (Fig. 3), due to the charge-transfer complexation of both drugs as n-doner (D) and π-acceptor (A) with the subsequent highly coloured radical anions (A) according to the following equation:

$$\ddot{\mathrm{D}} + \mathrm{A} \rightarrow \left(\ddot{\mathrm{D}} \rightarrow \mathrm{A} \right) \underset{\text{Solvent}}{\overset{\text{Polar}}{\rightarrow}} \dot{\mathrm{D}}^{+} + \dot{\mathrm{A}}^{-} \text{ radical anion}$$

Both drugs exhibit approximately the same absorption maxima but with different intensities (Fig. 3). The dissociation of the DA complex is promoted by acetonitrile which is found to be the

Table 1
Quantitative parameters for the complexation of propranolol and metoprolol with TCNE, and CLA

Parameter	Propranolol hydrochloride		Metoprolol tartrate	
	TCNE	CLA	TCNE	CLA
λ (nm)	417	510	417	510
Beer's law limits (μg ml^{-1})	10–160	20–200	10–170	20–230
Molar absorptivity (l mol^{-1} cm^{-1}) ($\varepsilon \times 10^{-4}$)	0.173	0.098	0.349	0.173
Sandell sensitivity (μg cm^{-2})	0.181	0.281	0.172	0.410
Regression equation				
Slope (b)	0.0064	0.0034	0.0051	0.0026
Intercept (a)	−0.0346	−0.0164	0.0193	−0.0164
Correlation coefficient	0.9980	0.9989	0.9949	0.9976
Relative standard deviation (RSD%)	0.919	1.460	0.263	1.514

best solvent for TCNE and CLA, because it has a high relative permittivity which ensures the maximum yield of TCNE and CLA species [25].

When various concentrations of TCNE or CLA were added to a fixed concentration of drug, 1 ml of a 5×10^{-3} M solution of the π-acceptor was found to be sufficient for maximum and reproducible colour intensity.

The optimum reaction time is determined by following the colour development at ambient temperature (25°C). It is observed that complete colour development is attained after 5 min and that the colour remains stable for at least 24 h. The relative sensitivities of the two π-acceptors are compared using the apparent molar absorptivity values of the chromogens (Table 1).

Application of Job's method of continuous variation indicates a molar ratio of donor to acceptor of 1:1 for propranolol and 1:2 for metoprolol, with respect to drug salt (Figs. 4 and 5). The formation of 1:2 complex in the case of metoprolol is due to the presence of two base molecules in the salt.

A linear correlation is found between absorbance and concentration in the ranges given in Table 1. The correlation coefficients, intercepts and slopes for the calibration data are given also. The mean molar absorptivity (ε) and Sandell sensitivity (S) as calculated from Beer's law are presented in Table 1. The CT-procedure has the advantages of a wider range of determination, and is less time consuming.

4.3. Comparison of the methods

Table 2 shows the mean recoveries and relative standard deviation (RSD) for authentic samples of metoprolol tartrate and propranolol hydrochloride as determined by the proposed spectrophotometric, AAS and B.P. (1998) methods for propranolol and metoprolol. Statistical comparison between the results of the different methods investigated and the official method using Student's t-test and the F-test (Table 2) revealed that the difference between these methods is not significant and the results showed that the calculated t- and F-values did not exceed the theoretical

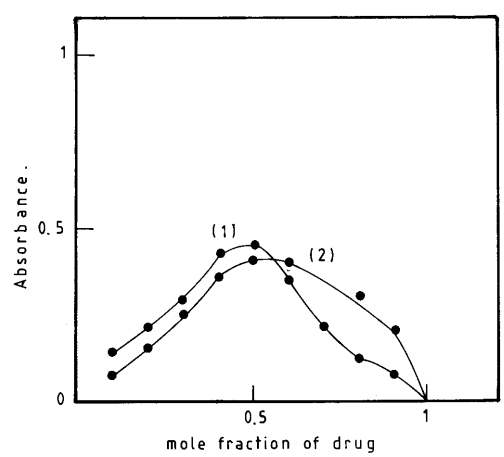


Fig. 4. Job's method for the propranolol complexes. Total molarity = 5×10^{-4}. (1) TCNE, $\lambda = 415$ nm; (2) CLA, $\lambda =$ 510 nm.

Table 2
Statistical comparison between the proposed methods and reference methods.

Parameter	Propranolol hydrochloride					Metoprolol tartrate				
	CS_2 methods		CT methods		Spectrophotometric method [4]	CS_2 methods		CT methods		Spectrophotometric method [4]
	Spectrophotometric	AAS	TCNE	CLA		Spectrophotometric	AAS	TCNE	CLA	
Mean recovery[a] $\pm$ S.D.	100.25 ± 0.66	99.89 ± 0.41	100.13 ± 0.39	100.03 ± 0.50	100.52 ± 0.42	100.62 ± 0.49	99.94 ± 0.69	99.97 ± 0.43	99.95 ± 0.37	100.34 ± 0.53
RSD (%)	0.65	0.41	0.38	0.49	0.41	0.48	0.69	0.43	0.37	0.52
Variance	0.43	0.16	0.15	0.25	0.17	0.24	0.47	0.18	0.13	0.28
Student's t-test	0.79	2.3	1.5	1.68		0.89	1.05	1.22	2.4	
Variance ratio 'F'	2.53	1.04	1.13	1.47		1.17	1.7	1.56	2.15	
Confidence limit	100.25 ± 0.69	99.89 ± 0.43	100.13 ± 0.41	100.03 ± 0.52		100.62 ± 0.51	99.94 ± 0.72	99.97 ± 0.45	99.95 ± 0.38	

[a] There were six experiments. The theoretical t-value ($P = 0.05$) is 2.23. The theoretical F-value (95%) is 5.05.

Table 3
Determination of metoprolol tartrate, and propranolol hydrochloride in pharmaceutical formulations using the proposed method.

Compound	Preparation	Manufacturer	Content/mg per tablet	Found in sample[a] mg/tablet				
				CS_2		CT		Spectrophotometric method [4]
				Sp.	AAS	TCNE	CLA	
Metoprolol tartrate	Betaloc	CID	100	99.7 ± 0.71	$99–5 \pm 0.58$	98.8 ± 0.81	100.2 ± 0.76	100.04 ± 0.63
Propranolol hydrochloride	Inderal	Kahira	10	9.95 ± 0.07	9.89 ± 0.11	10.10 ± 0.09	10.16 ± 0.12	9.75 ± 0.09

[a] Average of five determinations.

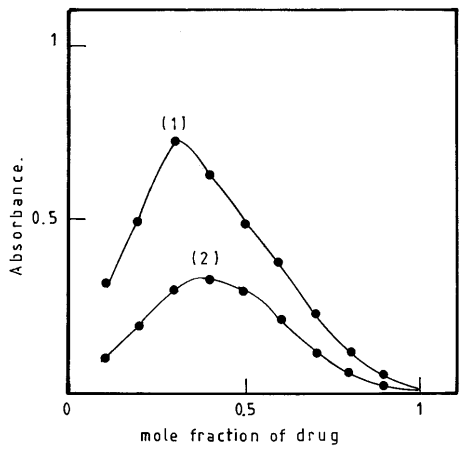


Fig. 5. Job's method for metoprolol complexes. Total molarity $= 5 \times 10^{-4}$ M. (1) TCNE, $\lambda = 415$ nm; (2) CLA, $\lambda = 510$ nm.

values. The confidence limits are given. It can be concluded that these methods are equally accurate and precise.

4.4. Interferences

In the case of CS_2 method, interferents are mainly basic compounds that contain secondary amino group in their aliphatic chain. Thus as far as drugs are concerned, other β-blockers and ephedrine give positive reactions. However, such compounds are not usually present with examined drugs, and hence are not likely to cause analytical problems.

In the case of CT methods, substances having no basic centres are not expected to interfere, since extraction of the drug base preceedes the colour reaction.

On the other hand, tablet fillers such as lactose, starch, and stearic acid which can represent a potential source of interference, do not interfere in the proposed method.

4.5. Analytical application

The proposed methods are applied to some pharmaceuticals containing propranolol hydrochloride or metoprolol tartrate. The results in Table 3 indicate high accuracy. The proposed methods are suitable for determination without interferences from excipients.

5. Conclusion

The proposed methods are sensitive as a small amount can be determined with good accuracy, without interferences from excipients such as starch, and glucose, and hence they can be applied in pharmaceutical analysis. The foregoing data obtained from the described procedures prove good accuracy, and reasonable precision, and they offer other methods for the evaluation of the studied drugs in pharmaceutical preparations without interference from dosage additives.

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