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# PREPARATION AND CHARACTERIZATION OF COPPER(II)-ATENOLOL COMPLEX INDIRECT ATOMIC ABSORPTION SPECTROMETRIC (AAS) DETERMINATION OF ATENOLOL

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*The Cu(II)-atenolol complex was prepared, and characterized by elemental analysis and spectroscopic techniques (via. IR, electronic and EPR spectra). The spectral results obtained indicate tetrahedral geometry around the Cu(II) ion. An indirect atomic absorption spectrometric method was undertaken to estimate atenolol in pharmaceutical preparations, based on its reaction with $Cu^{2+}$ in alkaline medium. The method is simple, rapid, accurate and sensitive.*

## INTRODUCTION

Atenolol, 4-(2-hydroxy-3-isopropylaminopropoxy) phenyl acetamide, is one of a number of drugs collectively known as β-blockers. Its pharmaceutical use is in the management of hypotension, angina pectoris, cardiac dysrhythmias and myocardial infarction, where it acts preferentially upon the B-adrenergic receptors in the heart[1]. A review of atenolol and its dimerization was given[2]. The interest in atenolol complex drew the attention of some workers in solution[6], yet

it seems that the complexes in the solid state drew little attention in respect of their structure and geometry.

The existing methods for determining this drug include spectrophotometric[3,4], chromatographic[5], titrimetric[2] and colorimetric methods[6]. No atomic absorption spectrometric (AAS) determination of atenolol has been carried out. Recently, copper ion, and AAS has been frequently utilized for the estimation of drugs[7-12].

The aim of the present investigation was to prepare the solid Cu-atenolol complex, and to characterize it by elemental analysis, and conductance measurements. The bonding between Cu(II) and atenolol was confirmed by IR spectra. Electronic and ESR spectral studies were conducted to explain the geometry of atentolol molecules around Cu(II) ion.

## EXPERIMENTAL

All chemicals used in the present work were of analytical reagent grade and solvent was of spectroscopic grade. Copper chloride solution was standardized by the recommended method[13]. Atenolol as bulk substance and tablet was obtained from commercial sources, and their purity was determined by UV-spectrophotometry[3] at $\lambda$ max 224 nm. Stock solutions of the reference compound and of extract of the tablets were freshly prepared as 0.5 mg $ml^{-1}$ solutions in 0.1 N HCl.

## Apparatus and Working Procedure

The apparatus and working procedures for investigating the solid complex were as described previously[8,9]. For investigating solutions, the methods were as described in previous work[10].

## Preparation of Copper-atenolol Complex

A solution of the Cu(II) chloride (0.001 mole) in methanol was added dropwise to a solution of atenolol (0.0022 mole) in methanol and the reaction mixture was stirred for 24 h. The green crystals obtained were filtered off, washed several times with distilled water to remove any excess of the metal ions, then with methanol to removed any excess of the ligand, and finally with diethyl ether ( 2 x 25 ml) and dried in vaccum.

## General Procedure

To the sample solution of atenolol (5 ml) in a 20 ml capacity test tube, add 1 ml 1% $CuCl_2.2H_2O$ and 0.5 ml NaOH 10%, to bring the mixture to pH 11, then dilute to 10 ml with $H_2O$ and add 10 ml butanol pre-quilibrate at the same alkalinity with 0.5 g $Na_2SO_4$ anhydrous, then shake gently and centrifuge. Examine the butanol layer with an AA-instrument using a concentration of atenolol up to 300 ug. Calculate the concentration of atenolol from the relevant calibration curve in the range 0-30 ug $ml^{-1}$.

**Determination of Atenolol in Tablets**

Twenty tablets were weighed and powdered. An accurately weighed portion of powder equivalent to 20 mg of drug was placed in a suitable vessel containing 50 ml of 0.1 N HCl solution, and the active ingredients were extracted by continuous stirring for about 10 minutes. The extract was filtered through Whatman No. 42 filter paper then delivered quantitatively into a 100 ml calibrated flask, then washed three times each with 10 ml of solvent. The combined extract was diluted to volume with the same solvent and an accurately measured volume of this solution was assayed as described above under "General procedure".

## RESULTS AND DISCUSSION

On the basis of the analytical data obtained the Cu(II)-atenolol complex can be formulated as [CuLCl]. The calculated (found): % C, 46.15 (46.4); % H 5.74 (5.2); & N 7.65 (7.1); % Cl 9.75 (10.1); % Cu 17.45 (17.8). The molar conductance of the prepared complex in DMF is less than 17.0 $ohm^{-1}$ $cm^2$, indicating that the complex is a nonelectrolyte[14]. Hence atenolol would behave as a monobasic-acid on reaction with Cu(II) ion.

The IR spectrum of the Cu(II)-atenolol complex displays interesting changes in comparison to that of the free ligand.

(i) The two bands observed at 3350, and 3100 $cm^{-1}$ in the free atenolol are due to $\nu NH_2$, and $\nu$ NH respectively. The first band was found at the same position in the spectra of the Cu(II) complex, while the second band was shifted by 100 $cm^{-1}$ to lower wave-number on complex formation and was of lower intensity, suggesting that one NH contributes to chelation.

(ii) The disappearance of the alcohlolic OH group from the spectrum of the complex denotes the participitation of the alcoholic form in chelation through $H^+$ displacement. This is in accordance with the results of conductance measurements which indicate that atenolol behaves as a mono-anionic species on reaction with Cu(II) ion.

(iii) The three new bands observed at 380 , 475 and 334 $cm^{-1}$ in the spectrum of the Cu(II)-complex can be assigned to $\nu$ Cu-O , $\nu$ Cu-N, and $\nu$ Cu-Cl respectively[15].

The electronic absorption spectrum of the Cu(II) atenolol complex in DMF comprises three bands with $\lambda$ max at 280, 379, 675 nm. The first bands are assigned to $\pi$ - $\pi^*$ electronic transition within the aromatic nucleus and charge transfer band. The band at 675 nm can be assigned to the d-d transition with Cu(II) ion. The sharp nature and position of the band suggest tetrahedral geometry of the ligand around the Cu(II) ion.

The X-band EPR spectrum of the Cu(II)-atenolol complex. measured at room temperature exhibits 28 lines with a hyperfine splitting, A ≈ 20 G, as shown in Fig. 1. The $G_{eff}$ value is equal to 1.973.

The intensity ratios of the hyperfine splitting are: 0.22 : 0.221; 0.11 : 0.332 : 0.221 : 0.332 : 0.332 : 0.442 : 5 : 64 : 0.221; 2.43 : 0.44 : 2.32 : 2.54 : 1.77 : 1.10 : 0.332 : 1.7 : 0.221 : 0.553 : 0.553 : 0.332 : 1.10 : 0.11 : 0.11 : 0.221 : 1.66.

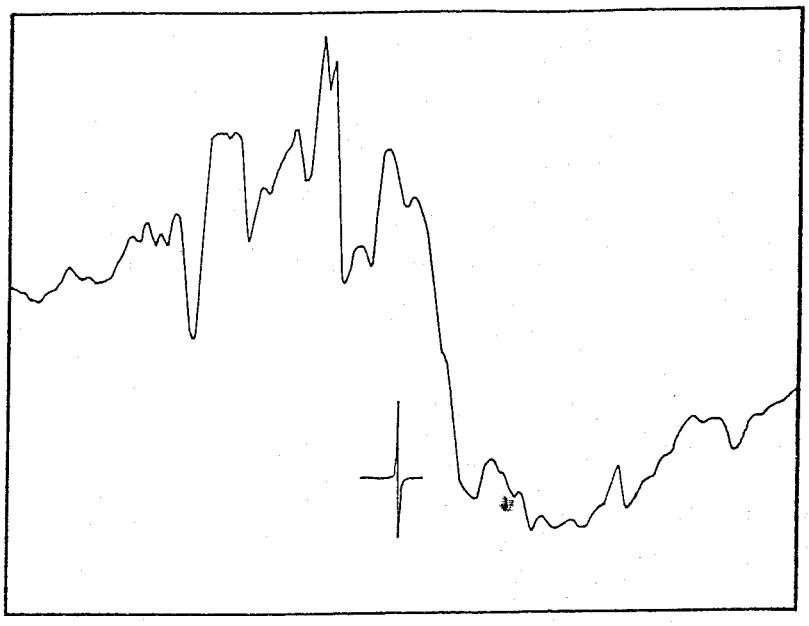
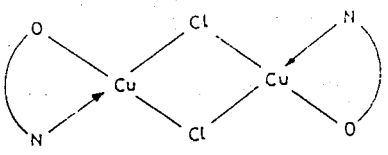


Fig.1 ESR spectrum of the [Cu(Atenolol)Cl] complex at 300 K.

Based on the above results and the previous observation[2], the bonding between atenolol and Cu(II) can be represented.



## Spectrophotometric and Atomic Absorption Spectrometric (AAS) Investigation

The absorption spectra of the Cu(II)-atenolol complex was studied at different pH values (Fig. 2). At pH 7-10, the absorption spectra exhibit a broad band situated at 640 nm, the solution has a blue colour. On increasing the pH of the medium >10 the broad band is shifted to a shorter wavelength at 530 nm, the colour of the solution is changed to purple, and a maximum is observed at pH 11. The increased tendency for complex formation and the shift of the band with increasing pH is probably due to the shift in the equilibrium in favour of the formation of different types of complexes. Thus in acidic and slightly alkaline media, a blue complex is observed whereas at pH >10 a purple complex becomes the perdominant species.

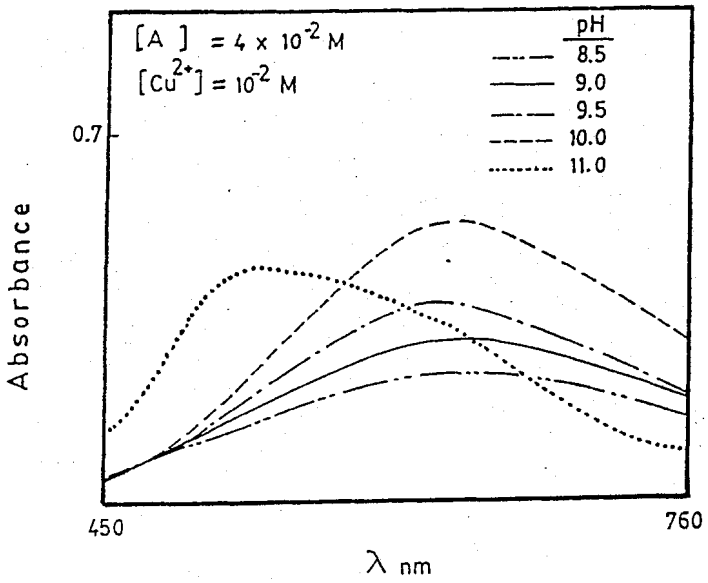



Fig.2. Effect of pH on the absorption spectra of Copper - Atenolol complex .

The determination of atenolol is based on the formation of its copper complex in alkaline medium. The formed complex is extracted with n-butanol, then the analysis is completed by determining the copper content using the atomic absorption method.

In the presence of $Cu^{2+}$, and NaOH, atenolol formed a complex which can be extracted at pH 11 into n-butanol, from a solution containing anhydrous $Na_2SO_4$. The maximum absorption of copper-atenolol complex in organic phase was obtained at 500 nm, Fig. 3. The stoichiometry of the copper-atenolol extract was elucidated by employing the molar ratio method[16] which indicated a 1:2 donor: acceptor ratio. The stoichiometry of copper-atenolol complex is aqueous solution was investigated. It was found that 1:1 and 1:2 complexes are formed at pH 11.

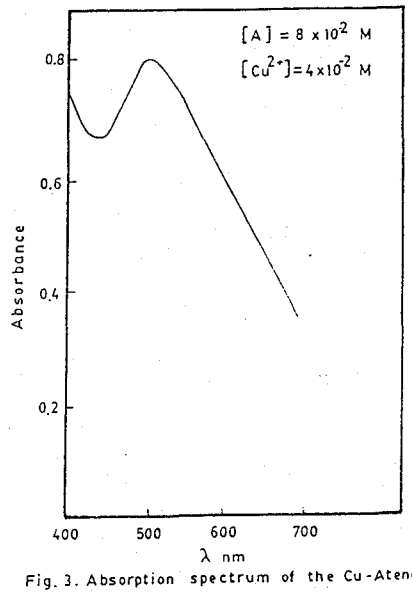



Fig. 3. Absorption spectrum of the Cu-Atenolol complex in n-butanol.

The complex in the organic layer was stable for 72 hours. The effect of temperature on the extraction of the complex was investigated at temperatures ranging from 0 to 100°C and the absorbance values found were not affected by the temperature within that range. The relationship between absorbance and the concentration of atenolol was linear within the range 0-30 ug $ml^{-1}$. The calibration graph was linear and passed through the origin which is represented by the equation.

$$Y = 0.1 \text{ x } -0.0$$

where Y = absorbance, and X = atenolol concentration ug $ml^{-1}$ Sandell's sensitivity[17] for this method is 0.041 ppm $cm^{-2}$ of atenolol.

In order to determine the accuracy and precision of the method, standard solutions containing three different concentrations of atenolol were prepared and five absorbance measurements were performed on each standard atenolol solution. The overall relative standard deviation of 15 determinations was 1.61%. The results are shown in Table (1).

Table (1): Accuracy and precission of the AAS-method

| Solution No. | Atenolol Concn. (ug) | | % Recovery ± S.D. | RSD % |
|---|---|---|---|---|
| | added | Found* | | |
| 1-5 | 10 | 10.0 | 100.0 ± 0.15 | 1.5 |
| 6-10 | 15 | 14.8 | 98.6 ± 0.24 | 1.62 |
| 11-15 | 20 | 19.6 | 98.0 ± 0.34 | 1.73 |
| Mean | | | 98.86 ± 0.243 | 1.61 |

* Average of five measurements.

The proposed AAS method was successfully applied to raw materials and to tablets without any interference from the included excipients. The method was compared with the official method. The results obtained when the two methods were applied to atenolol itself and the two pharmaceutical preparations are shown in Table 2. These results indicate that the proposed method is in good agreement with the official one[3].

Table (2): Determination of atenolol alone and in pharmaceutical preparations by AAS, and official methods.

| Sample | Sample No. | Percentage of labelled content found* | |
|---|---|---|---|
| | | Proposed method | Official method |
| Atenolol | 1 | 99.0 ± 0.25 | 99.92 ± 0.28 |
| | 2 | 99.33 ± 0.34 | 99.25 ± 0.30 |
| | 3 | 100.20 ± 0.52 | 100.25 ± 0.44 |
| Tenormin Tab. | 4 | 100.00 ± 0.53 | 100.01 ± 0.46 |
| (100 mg) | 5 | 100.66 ± 0.42 | 100.59 ± 0.40 |
| (Kahira Co. Egypt) | 6 | 99.60 ± 0.38 | 99.65 ± 0.33 |
| Ateno | 7 | 101.00 ± 0.44 | 100.95 ± 0.36 |
| (100 mg) | 8 | 100.00 ± 0.36 | 100.00 ± 0.32 |
| (EIPICO. Co. Egypt) | 9 | 99.80 ± 0.51 | 99.85 ± 0.45 |

* Results are means of five measurements with standard deviations.

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# تحضير ودراسة خواص متراكب النحاس مع الأتينولول
# تقدير الأتينولول بطريقة غير مباشرة بإستخدام
# طريقة طيف الإمتصاص الذرى

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تم تحضير متراكب النحاس مع الأتينولول ، كما تم دراسة التركيب البنائى للمتراكب بإستخدام التحليل العنصرى الدقيق ، التوصيل الكهربى والطرق الطيفية مثل الأشعة تحت الحمراء وكذلك الطيف الألكترونى البارامغناطيسى وتم إستنتاج التركيب البنائى للمتراكب مع أيون النحاس الثنائى .

كما تم إستحداث طريقة لتعيين الأتينولول بإستخدام طيف الإمتصاص الذرى للنحاس غير المباشر وتم تطبيق الطريقة فى المستحضرات الصيدلية .