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# Micro-determination of angiotensin-converting enzyme inhibitor drugs benazepril, moexipril and quinapril hydrochlorides in pharmaceutical formulations using atomic absorption and atomic emission spectrometry

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## ABSTRACT

Ion - associate complexes of benazepril; (Bp), moexipril;(Mp) and quinapril;(Qp) hydrochlorides with $[Mn(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ were precipitated and the excess unreacted manganese or zinc complex was determined. A new method using atomic emission and atomic absorption spectrometry for the determination of the above drugs in pure solutions and in pharmaceutical preparations is given. The drugs can be determined by the affort method in the ranges 0.73 - 82.89, 085 - 96.39 and 0.75 - 8541 μg $mL^{-1}$ solutions of Bp, Mp and Qp, respectively.



## KEYWORDS

Atomic emission;
Atomic absorption;
Benazepril;
Moexipril and quinapril;
Thiocyanate complexes;
Pharmaceutical analysis.

## INTRODUCTION

Benazepril, moexipril and quinapril hydrochlorides are very important pharmaceutical compounds. Therefore, we found it important to prepare new ion-associates containing these drugs and to study and elucidate the chemical structures. Also the work present a new rapid method for the determination of these drugs after transformation into the ion-associates.

Benazepril hydrochloride, (3-[(1-ethoxycarbonyl-3-phenyl-(1*S*)-propyl) -amino]-2,3,4,5-tetrahydro-2-oxo-1-(3*S*)-benazepine-1-acetic acid hydrochloride)[1], is a prodrug type angiotensin-converting enzyme (ACE) inhibitor[2], which is proved effective in treating congestive heart failure and hypertension[3-5]. Moexipril hydro-chloride, (3*S*)-2-[(2*S*)-2-{[(1*S*)-1-(ethoxycarbonyl)-3-phenyl-propyl]-amino}-1-oxopropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride, is a new potent orally active non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor for the treatment of hypertension and congestive heart failure[6]. Quinapril hydro-chloride,(3-isoquinolinecarboxylic acid, 2-[2-[1-(ethoxycarbo-nyl)-3-phenylpropylamino]-1-oxopropyl]-1,2,3,4-tetrahydro-mono-hydro-chloride, is a non-peptide, non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor belonging to the third class of ACE inhibitors. The role of this kind of drugs is to inhibit the last step of the biosynthesis of angiotensin II, a potent vasoconstrictor, causing general vasodilatation. Quinapril is used for the treatment of mild to moderate hypertension and congestive heart failure, either alone or in conjunction with other drugs[7-10].

Several methods have been published on the de-

termination of Bp; including high performance liquid chromatography (HPLC)[11-19], derivative spectrophotometry[13,20,21], capillary electrophoresis (CE)[22,23], high performance thin layer chromatography-densito-metry (HPTLC)[17], HPLC-electro-spray-mass spectrometry[24], enzy-matic method[25], coated-wire ion-selective electrode with thermal studies[26] and gas chromatography-mass spectrometry (GC-MS)[27]. Only two methods have been reported for the determination of Mp, GC-MS[28] and derivative spectrophoto-metry-HPLC[29] and Qp; HPLC with UV detection[13,30], HPLC with fluorescence[31], radio chemical detection[32], GC-MS[33], electron capture detection[34] and HPLC[35], the use of simpler, faster, less expensive and sensitive method is desirable.

Although, Direct Coupled Plasma-Atomic Emission Spectrometry (DCP-AES) and Atomic Absorption Spectrometry (AAS) are rapid methods and have a very low detection limits which can not be reached by most of other methods, they have so far not been applied yet to the determination of these drugs. The present study includes new DCP-AES and AAS methods for the determination of the investigated drugs. The method is based on the precipitating the ion-associates formed as a result of the combination of these drugs with an excess of $[Mn(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$. The equilibrium concentration of the metal ion present as the soluble inorganic complex ion in the supernatant solution was determined using atomic emission and absorption.

## EXPERIMENTAL

### Reagent and materials

Doubly-distilled water and analytical grade reagents were used in the preparation of all solutions. Bp was obtained from Ciba Company, Egypt, Mp was purchased from Schwarz Pharma, Germany and Qp was purchased from Goedecke, Germany. Manganese chloride, zinc acetate and potassium thiocyanate were from Aldrich. The pharmaceutical preparations of Bp; [Cibacin (10 mg / tablet) and Cibadrex (25 mg / tablet)] tablets were obtained from a local pharmacy, of Mp; was from Schwarz pharma, Germany [Uniretic tablets (7.5 mg / tablet)] and of Qp; was from Servier, France [Accuzide 20 tablets (20 mg / tablets)].

### Apparatus

The pH of the solutions was measured using an Orion Research Model 701A digital pH-meter. Direct coupled plasma atomic emission measurements were carried out using a Beckman spectra span III emission spectrometer and atomic absorption measurements were made on Hitachi atomic absorption Z-6100 polarized Zeeman spectrometer. Conductimetric measurements were carried out using conductivity measuring bridge type M.C.3 model EBB/10 ($K_{cell} = 1$); [Chertsey, Surry, England]. The IR absorption spectra were obtained by applying the KBr disk technique using a PYE UNICAM SP – 300 infrared spectrometer.

### Preparation of the standard solutions

The standard solutions of Mn (II) and Zn (II) were prepared by weighing 1.0 g of high purity manganese chloride or zinc metal and transferring to a 1-liter volumetric flask and then adding 50 ml of concentrated $HNO_3$. After complete dissolution, the solution was filled to the mark with distilled water. The 1000 $\mu g\ mL^{-1}$ Mn or Zn solutions were stored in plastic bottles which had been presoaked in dilute $HNO_3$. The solutions were stable for approximately one year.

### Emission and absorption measurements

Using AES the manganese was measured at wavelength 257.61 nm, order 87, plasma position 0.0, detection limit 0.003 $\mu g\ mL^{-1}$, linear dynamic ranges 0.03-100 $\mu g\ mL^{-1}$, background equivalent concen-tration 0.1 mg, entrance slits 50 x 300 $\mu m$ and exit slits 100 x 300 $\mu m$. Using AAS the Zn (II) was measured at wavelength 213.9 nm, slit 0.7 nm, relative noise 1.0, sensitivity 0.018 $\mu g\ mL^{-1}$ and linear range 1.0 $\mu g\ mL^{-1}$. The instruments were equally adequate for present purposes and were used according to availability. The atomic spectrometry was calibrated as in the previously reported work[36].

### Determination of solubility of the ion - associates

The solid ion-associate was added in excess to a solution of the optimum pH and ionic strength. The solution was shaken for 4-6 h and left to stand for a weak to attain equilibrium. Then the saturated solution was filtered into a dry-beaker (rejecting the first few ml of filtrate). The equilibrium concentration of

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the metal ion present in the form of a soluble inorganic complex was measured using atomic spectrometry. Hence the solubility (S) of the precipitate was evaluated, from which the solubility product of the ion-associate was calculated.

### Conductometric measurements

The stoichiometry of the ion-associates was elucidated also by conductometric titrations[37] of the drugs with $[Mn(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ solutions.

### Analytical determination of the drugs in aqueous solutions

Aliquots (0.04 - 4.5 mL) of 0.001 mol $L^{-1}$ drug solutions were quantitatively transferred to 25 mL volumetric flasks. To each flask 1.0 mL of 0.01 mol $L^{-1}$ standard solution of $[Mn(SCN)_4]^{2-}$ or $[Zn(SCN)_4]^{2-}$ was added and the volume was completed to the mark with the aqueous solutions of the optimum pH and ionic strength (prepared from HCl and NaOH). The solutions were shaken well and left to stand for 15 min then filtered through Whatman P/S paper (12.5 cm). The equilibrium metal ion concentration in the filtrate was determined using AES or AAS. The consumed metal ion (Mn or Zn) in the formation of ion-associates was calculated, and the drug concentration was determined indirectly.

### Analytical determination of drugs in pharmaceutical preparations

For analysis of Bp, sampling was made by griding up 10 tablets of both Cibacin and Cibadrex tablets then taking 1.50-78.35 and 2.50-80.65 μg of Cibacin and Cibadrex, respectively. For analysis of Mp, sampling was mad by grinding up 20 tablets of Uniretic tablets then taking 1.25-85.50 μg. In case of analysis Qp, sampling was made by grinding up 12 tablets of Accuzide 20 tablets then taking 2.25-82.25μg of the tablets. In all cases the tablets were analyzed applying the above described procedure.

## RESULTS AND DISCUSSION

The results of the elemental analysis (TABLE 1) of the produced solid ion-associates revealed that in all cases two drug cations form ion-ssociates with one $[Mn(SCN)_4]^{2-}$ or $[Zn(SCN)_4]^{2-}$ ion. These results are comparable to the previously reported results[38-40].

**TABLE 1 : Elemental analysis, composition and some physical properties of the drug ion - associates**

| Drug | Ion-associate composition | m. p. $^0$c | Molar ratio | Color | % Found (calculated) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Metal (Mn or Zn) |
| Benazepril | $(C_{24}H_{28}N_2O_5)_2[Mn(SCN)_4]$ | 365 | 2 : 1 | white | 54.88 (54.91) | 4.95 (4.93) | 9.88 (9.86) | 4.87 (4.84) |
| | $(C_{24}H_{28}N_2O_5)_2[Zn(SCN)_4]$ | 324 | 2 : 1 | white | 54.46 (54.42) | 4.90 (4.88) | 9.79 (9.76) | 5.72 (5.69) |
| Moexipril | $(C_{27}H_{35}N_2O_7)_2[Mn(SCN)_4]$ | 320 | 2 : 1 | white | 54.13 (54.10) | 5.47 (5.44) | 8.74 (8.70) | 4.30 (4.27) |
| | $(C_{27}H_{35}N_2O_7)_2[Zn(SCN)_4]$ | 288 | 2 : 1 | white | 53.69 (53.66) | 5.42 (5.39) | 8.66 (8.63) | 5.06 (5.03) |
| Quinapril | $(C_{25}H_{30}N_2O_5)_2[Mn(SCN)_4]$ | 265 | 2 : 1 | white | 56.56 (56.53) | 5.27 (5.23) | 9.81 (9.77) | 4.82 (4.79) |
| | $(C_{25}H_{30}N_2O_5)_2[Zn(SCN)_4]$ | 250 | 2 : 1 | white | 55.18 (55.16) | 5.14 (5.11) | 9.57 (9.53) | 5.59 (5.56) |

Conductometric titrations of the investigated drugs with $[Mn(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ were performed to provide insight into the stoichiometric compositions of the ion-associates formed in solution. With all ion-associates, the characteristics curve-breaks are observed at a cation / anion mol ratio of about 2, confirming the formation of 2 : 1 (drug : $X^{2-}$) ion-associates. The results obtained coincide with the elemental analysis of the precipitated ion-associates. The optimum pH and ionic strength values (TABLE 2) have been elucidated by determining the solubility of the ion-associates in HCl-NaOH solutions of different pH values and ionic strengths. The best were those exhibiting lowest solubility values.

### Analytical determination of drugs in aqueous solutions and pharmaceutical preparations

Benazepril HCl, moexipril HCl and quinapril HCl were determined precisely and accurately in aqueous solutions at their optimum conditions of pH and ionic strength (TABLE 2) and in pharmaceutical preparations using the present method. The results given in TABLE 3 reveal that recoveries were in the range 99.89 - 101.32 % and 98.76 - 101.26 %, reflecting the high

accuracy in addition to the high precision indicated by the very low values of the relative standard deviation.

**TABLE 2 : Solubility and solubility product of the ion-associates at their optimum conditions of pH and ionic strength (μ) values ate 25 °C**

| Ion - associate | pH | μ | $p^s$ | $Pk_{sp}$ |
|---|---|---|---|---|
| Benazepril Mn - thiocyanate | 5.0 | 0.2 | 6.43 | 18.68 |
| Moexipril Mn - thiocyanate | 4.0 | 0.4 | 6.33 | 18.41 |
| Quinapril Mn - thiocyanate | 7.0 | 0.3 | 6.36 | 18.49 |
| Benazepril Zn - thiocyanate | 6.0 | 0.5 | 6.01 | 17.43 |
| Moexipril Zn - thiocyanate | 5.0 | 0.3 | 6.03 | 17.48 |
| Quinapril Zn - thiocyanate | 8.0 | 0.4 | 6.07 | 17.62 |

**$p^s$: -log solubility; $p^k_{sp}$: -log solubility product**

**TABLE 3 : Determination of the investigated drugs in aqueous solutions and in pharmaceutical preparations by AES and AAS**

| Sample | Taken (μg) | Mean recovery (%) | Mean RSD (%) |
|---|---|---|---|
| **Using $[Mn(SCN)_4]^{2-}$*** | | | |
| Benazepril solution | 0.73 - 82.89 | 99.89 | 1.2 |
| Cibacin tablets[a] | 1.50 - 78.35 | 101.03 | 1.1 |
| Cibadrex tablets[b] | 2.50 - 80.65 | 101.09 | 1.3 |
| Moexipril solution | 0.85 - 96.39 | 101.16 | 0.7 |
| Uniretic tablets[c] | 1.25 - 85.50 | 101.06 | 1.5 |
| Quinapril solution | 0.75 - 85.41 | 101.32 | 0.6 |
| Accuzide 20 tablets[f] | 2.25 - 82.25 | 101.16 | 0.8 |
| **Using $[Zn(SCN)_4]^{2-}$**** | | | |
| Benazepril solution | 0.73 - 82.89 | 98.76 | 1.3 |
| Cibacin tablets[a] | 1.50 - 78.35 | 100.08 | 1.2 |
| Cibadrex tablets[b] | 2.50 - 80.65 | 100.12 | 1.0 |
| Moexipril solution | 0.85 - 96.39 | 101.06 | 0.7 |
| Uniretic tablets[c] | 1.25 - 85.50 | 100.04 | 1.2 |
| Quinapril solution | 0.75 - 85.41 | 101.26 | 0.5 |
| Accuzide 20 tablets[d] | 2.25 - 82.25 | 101.12 | 0.7 |

**RSD : Relative Standard Deviation (six determinations); *By AES; **By AAS; [a]Ciba, Egypt; [b]Ciba, Switzerland; [c]Schwarz pharm, Germany; [d]Servier, France**

Generally, the present method is as good as those reported before where,0.73- 82.89,0.85- 96.39 and 0.75-85.41 μg $mL^{-1}$ solutions of Bp, Mp and Qp using $[Mn(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ were determined, respectively, which means that this method is applicable over wider concentration ranges than previously published methods for Bp[14,17,20] in which Bp was determined using micro-bore liquid chromatography by Panderi and Poulou, derivative spectro-photometry by El-Gindy et al. and ratio spectra derivative spectrophotometry by Nevin Erk in the ranges 5-20, 4-20 and 8-36 μg $mL^{-1}$, respectively. For Mp[29] in which Mp was determined using HPLC by Erturk et al. in the range 1.0 – 11 μg $mL^{-1}$. In case of Qp[35] in which Qp was determined using HPLC by Gumieniczek and Hopkala in the range 0.1 – 0.5 mg $mL^{-1}$.

In pharmaceutical analysis it is important to test the selectivity toward the excipiences and the fillers added to the pharmaceutical preparations. Fortunately, such materials mostly do not interfere. It is clear from the results obtained for the pharmaceutical preparations (TABLE 3) that these excipiences do not interfere.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression[41] of observed drug concentration against the theoretical values (five points) was calculated. The student's *t-test*[41] (at 95% confidence level) was applied to the slope of the regression line (TABLE 4), which showed that it did not differ significantly from the ideal value of unity. Hence, it can be concluded that there are no systematic differences between the determination and the true concentration over a wide range. The standard deviations (SD) can be considered satisfactory at least for the level of concentrations examined.

Although the present method is more time consuming than some other methods, it exhibits fair sensitivity and accuracy. Moreover, the reproducibility of the results is superior to those obtained with other methods.

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