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Developing Metal Complexes for Captopril Quantification in Tablets Using Potentiometric and Conductometric Methods

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ABSTRACT: Potentiometric and conductometric methods were successfully applied to elucidate the interaction of 10 ions, viz., Cr^{3+}, Fe^{3+}, La^{2+}, Th^{4+}, Co^{2+}, Mn^{2+}, Pd^{2+}, Sr^{2+}, Ti^{2+}, and Zr^{2+}, with the antihypertensive drug captopril (CAP) and its role to determine CAP in pure powder and tablet forms. The ionization constant of CAP and the generated complexes' stability constants (log K) were evaluated using potentiometric and conductometric methods at 25 ± 0.1 °C and 0.05 M ionic strength (I) of $NaNO_3$ aqueous solution, and CAP was then determined in pure powder and tablet forms. Complexes having metal:ligand ratios of 1:1, 1:2, and/or 1:3 were produced, regardless of the type of the ligand or metal ions. Both the suggested potentiometric and conductometric procedures were utilized to confirm the stoichiometry of the M−CAP binary complexes formed. These two different techniques were utilized successfully to determine CAP in pure powder and tablet forms. Using the standard addition method (SAM) based on the Gran plot, CAP was satisfactorily determined throughout the concentration range of 0.83−13.04 mg/mL (SD = 0.20, $R = 0.9986$ ($n = 5$)), with a detection limit of 0.64 mg/mL (SD = 0.20, $R = 0.9986$ ($n = 5$)). In the presence of common tablet excipients, no interferences were observed. The percentage of CAP recovered from various dosage formulations (tablets) varied from 95.88 to 99.92%.
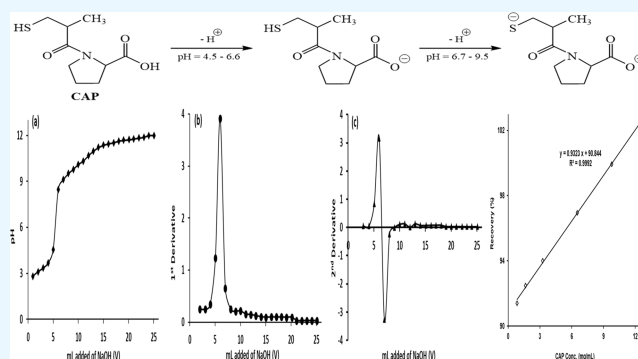
1. INTRODUCTION

Captopril (CAP), also known chemically as [2S]-N-[3-mercapto-2-methylpropionyl]-L-proline, is a broadly utilized drug for the treatment of high blood pressure, diabetic nephropathy, congestive heart seizure, and the preservation of kidney damage.[1,2] In order to investigate the presence of CAP in pharmaceuticals, numerous analytical procedures have been postulated. CAP was determined using chromatography,[3−6] fluorometry,[7−9] UV−visible spectroscopy,[10,11] chemiluminescence,[12] and voltammetric techniques.[13−17] Although these analytical strategies are highly sensitive and accurate, they are costly, time-consuming, and require complex procedures for sample preparation and analysis protocols.

The use of potentiometric and coductometric methods to analyze the binary and trinary complexes formed between metals and biological and pharmacological compounds has attracted a lot of interest as electrochemical methods.[18−24] CAP was previously determined using potentiometric[25−28] and conductometric[29−32] methods. The potentiometric assessment of complex formation among both stimulants and metal ions gives a clear overview of how interactions between drugs and metals may affect medication delivery to target areas.[33,34] In biological fluids, the presence of certain ions is thought to have

a major impact on the pharmacological actions of some chemical substances.[35]

As an analytical application of potentiometric studies, the equivalence point of the produced titration curves was identified using the Gran plot.[36] Sundry Gran plot applications have been published in the literature.[37−44] The goal of this work was to create a potentiometric process for assessing CAP in tablets directly using a Gran plot which was designed using data from a potentiometric investigation of the complexation equilibrium of CAP with various metal ions, especially Cr^{3+}, Fe^{3+}, La^{2+}, Th^{4+}, Co^{2+}, Mn^{2+}, Pd^{2+}, Sr^{2+}, Ti^{2+}, and Zr^{2+}.

2. EXPERIMENTAL SECTION

2.1. Reagents and Instruments. Sigma (St Louis, MO, USA) provided captopril (CAP), and NaOH (BDH) was used as earned. Most other ionic species solutions (NO_3^- and Cl^-

salts) were of highest purity, and they were used exactly as acquired from the manufacturer (BDH, UK, Geneva, or India).

Pharmaceutical formulations: captopril tablets (25 and 50 mg) manufactured by Sedico Pharmaceutical Co., 6th of October City, Egypt. Deptopril was bought from Micro Labs Ltd., India. Epsitron was purchased from Remedica Ltd., Limassol, Cyprus, Europe. Captohexal was manufactured by HEXALAG83607, Holzkirchen, Germany. Capritin was obtained from Laboratorios Atral, S.A. Lisbon, Portugal. All these pharmaceutical samples were used for CAP determination.

VWR Scientific Products Model 2000, USA, was used to gather all the pH readings. Standard buffer pH values of 4.01, 7.00, and 9.00 were used to calibrate the combined glass electrode. A conductivity meter model 4320 Jenway with an immersion cell was used to conductometrically titrate the samples. In both pH and conductometric titration curves, the solution was kept under constant agitation at a temperature of 25 ± 0.1 °C.

2.2. Methods. *2.2.1. Metal Complexes of CAP.* The dissociation constant of CAP as well as the formation constant of its various complexes with the studied ions in aqueous solution was calculated using the Calvin−Bjerrum approach, as described by Irving and Rossoti.[37] At 25 ± 0.1 °C, the following solutions were potentiometrically titrated with 0.1 M standard CO_2-free NaOH solution (which was standardized against potassium hydrogen phthalate):

(a) 0.005 M HNO_3 + 0.045 M $NaNO_3$ (for cell calibration).
(b) Solution (a) + 0.001 M CAP (for the purpose of determining the CAP protonation constants).
(c) Solution (b) + 0.001 M metal ions solutions (for the log K determination of metal ion−CAP binary complexes (M−CAP))

With the addition of dual-distilled water, the entire volume was maintained at a constant level at 50 mL. Titrations were carried out in aqueous solution at 25 ± 0.1 °C with various values of $I = 0.05$, 0.15, and 0.25 M $NaNO_3$.

Conductometric titrations were carried out at 25 ± 0.1 °C by combining 25 mL of 1×10^{-3} M of each ion with 1×10^{-2} M of CAP (in 0.5 mL increments). By multiplying the specific conductance values by $((25 + V))/25$, where V is the volume of the titrant delivered, the dilution effect is corrected.

2.2.2. Determination of CAP. 2.2.2.1. Pure Form. A stock solution (25 mL) of CAP (1×10^{-2} M) (I is adapted to 0.5 M with $NaNO_3$) was provided by diluting the actual stock solution with double-distilled water. Regarding this, 15 mL of CAP solution was potentiometrically and conductometrically treated with few drops of NaOH solution ($I = 0.1$ M) in a thermostated glass cell (25 ± 0.1 °C).

2.2.2.2. Tablet Form. Ten tablets were weighed and then finely pulverized and homogenized to obtain the average tablet weight. A portion of the powder that contains about 21.7 mg of CAP was accurately weighed and added in 10 mL of double-distilled water. The derived samples were filtered, and their ionic strength was reduced to 0.5 M using $NaNO_3$. Finally, in a 25 mL flask, a portion of this solution was diluted in double-distilled water and analyzed for the pure form of CAP, as previously stated. Using a standard calibration curve, the quantity of CAP per tablet was calculated.

2.2.3. Statistical Analysis. All statistics, stoichiometry constant, and log K were illustrated and calculated using Microsoft Excel. For CAP determination, the Gran plot was

constructed, and LOD, LOQ, and SD were calculated using SAM. Previously, Microsoft Excel and SAM were successfully applied for the same purpose.[18,39−41]

3. RESULTS

3.1. Formation Constants of CAP Complexes. *3.1.1. Proton−Ligand Stability Constants of CAP.* CAP was potentiometrically titrated in the presence of 0.01 M HNO_3. At $I = 0.05$, 0.15, and 0.25 M $NaNO_3$ at 25 ± 0.1 °C, using CO_2-free NaOH as a titrant, the protonation constant of CAP and log K of CAP complexes formed with some metal ions were tabulated (Figure 1).
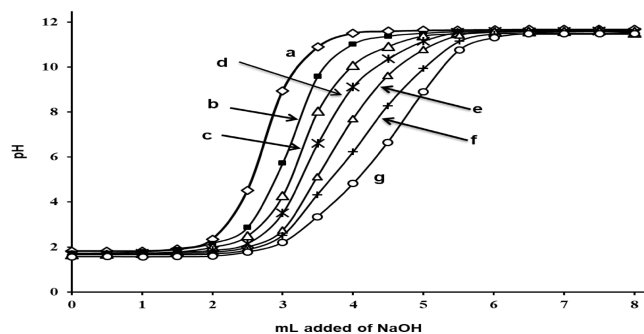

Figure 1. Potentiometric titration curves of CAP at 0.05 M $NaNO_3$ and 25 ± 0.1 °C: (a) 0.01 M HNO_3, (b) a + 0.001 M CAP, (c) b + 0.001 M Th^{4+}, (d) b + 0.001 M Co^{2+}, (e) b + 0.001 M Zr^{2+}, (f) b + 0.001 M Ti^{2+}, and (g) b + 0.001 M Sr^{2+}.

The proton−ligand formation constants will be determined by charting $\bar{n}A$ against pH, according to Irving and Rossotti[45] (for the potentiometric titration curves a and b). As shown in eq 1, the average number of attached protons per ligand, $\bar{n}A$, was calculated at various pH values:

$$\bar{n}A = Y + \frac{(V_1 - V_2)(N° + E°)}{(V° + V_1)T_cL°} \quad (1)$$

where V_1 and V_2 are the alkali portions required to achieve the same pH in inorganic acid (HNO_3) and (HNO_3 + CAP) solutions, respectively. $T_cL°$ represents the total concentration of CAP, $N°$ represents the concentration of NaOH solution (0.1 M), and $E°$ represents the preliminary concentration of free HNO_3 in the titrated solution. The following diagram depicts the reaction mechanism:
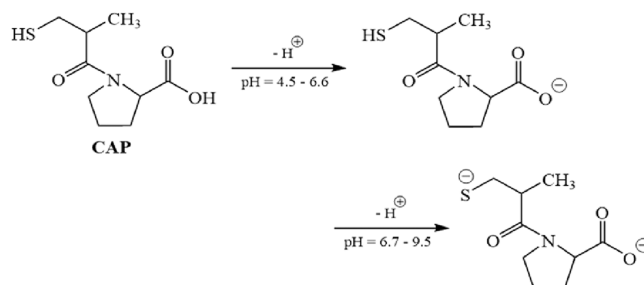

3.1.2. Determination of Formation Constants of Metal−CAP Complexes. The pH-metric titration of 10 metal salts, Fe^{3+}, Cr^{3+}, La^{2+}, Th^{4+}, Co^{2+}, Mn^{2+}, Pd^{2+}, Ti^{2+}, Sr^{2+}, and Zr^{2+}, was performed and researched using a potentiometric method to explicate their interaction with CAP. The titration curves of the M−CAP solutions (from c to g) differ and are well separated from curve b, which is related to free CAP (Figure

1). Complexation is responsible for the replacement of the H^+ ion. The Irving and Rossotti equations[45] were utilized to calculate the $\bar{n}$ (the average number of CAP molecules for every metal ion) and pL (free-ligand exponent) values from these titration curves.

$$\bar{n} = \frac{(V_3 - V_2)(N^\circ + E^\circ)}{(V^\circ + V_2)\bar{n}HT_cM^\circ} \quad (3)$$

$$pL = \log\left[\frac{1 + \beta_1[H^+] + \beta_2[H^+]^2}{(T_cL^\circ - \bar{n}T_cM^\circ)} \times \frac{V^\circ + V_3}{V^\circ}\right] \quad (4)$$

where V_2 and V_3 are the alkali quantities necessary to achieve the very same pH for free acid and free acid + CAP + metal solutions, in both. V° denotes the original volume of the mixtures (50 mL), and T_cM° indicates the total metal content in the solution. Metal complexation equilibiria formation curves were derived from charting the $\bar{n}$ values versus the relevant pL values (Figure 2).
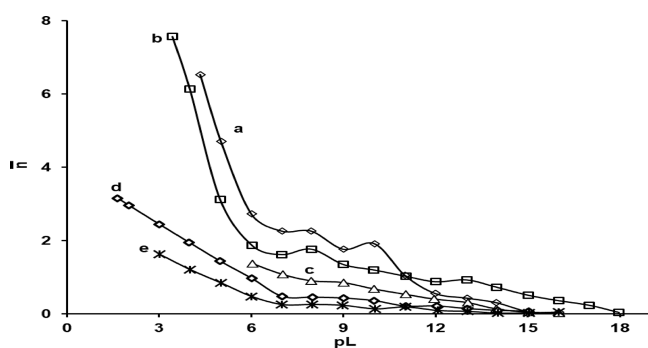
Figure 2. Illustrative formation curves of binary metal ion complexes with CAP at 0.05 M $NaNO_3$ and 25 ± 0.1 °C: (a) Ti^{2+}, (b) Zr^{2+}, (c) Sr^{2+}, (d) Mn^{2+}, and (e) La^{2+}.

Table 1 shows the log K values of metal ion complexes which were calculated in 0.05 M $NaNO_3$ using the half-integral

Table 1. Protonation Constants of CAP and log K of Metal Ion Complexes at 0.05 M $NaNO_3$ and 25 ± 0.1 °C

central ion	log K_1 (M:L)^a	log K_2 (M:L)^a	log K_3 (M:L)^a
H^+	9.7 (1:1)	3.7 (1:2)	
Fe^{3+}	7.9 (1:1)	5.55 (1:2)	
Pb^{2+}	6.39 (1:1)	5.54 (1:2)	4.22 (1:3)
Co^{2+}	7.73 (1:1)		
Cr^{3+}	7.94 (1:1)	5.94 (1:2)	
Th^{4+}	6.96 (1:1)	5.7 (1:2)	4.38 (1:3)
Zr^{2+}	7.97 (1:1)		
Mn^{2+}	6.99 (1:1)	5.06 (1:2)	
La^{2+}	6.5 (1:1)		
Ti^{2+}	6.76 (1:1)		
Sr^{2+}	6.16 (1:1)	5.065 (1:2)	

^{a}Potentiometric and conductometric methods were used to calculate these ratios.

method.[45] From the tabulated formation constant data, over the studied pH range, we can ensure the presence of the M−CAP complex (1:1) (metal:CAP) with some metal ions, viz., Co^{2+}, Zr^{2+}, La^{2+}, and Ti^{2+}, while the formation of other M−CAP complexes is disrupted by metal ion precipitation and hydrolysis. As a result, the newly discovered pH data would be

useless in computing values. Furthermore, because the pH observations at this stage displayed an unsteady drift, these data cannot be considered to be in equilibrium. Moreover, some ions, such as Sr^{2+}, Mn^{2+}, Fe^{3+}, and Cr^{3+}, create two forms of M−CAP complexes (1:1) and (1:2) (metal:CAP), whereas other ions, such as Pb^{2+} and Th^{4+}, produce three types of M−CAP complexes (1:1), (1:2), and (1:3) at the investigated I values. It could also be owing to the CAP concentration, I, or the metal ion nature.

As expected, log K of the various complexes produced between CAP and the inspected metal ions in this research follows the Irving−Williams order[46] for (1:1) (metal:CAP) at I = 0.05 M $NaNO_3$:

$$Fe^{3+} > Zr^{2+} > Cr^{3+} > Co^{2+} > Mn^{2+} > Th^{4+} > Ti^{2+}$$
$$> La^{2+} > Pb^{2+} > Sr^{2+}$$
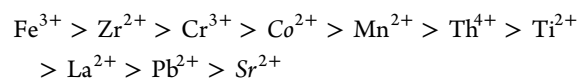
The effect of I alteration on log K of M−CAP complexes using various metal ions, Cr^{3+}, Fe^{3+}, Co^{2+}, Th^{4+}, and Pb^{2+}, was investigated at 25 ± 0.1 °C using $NaNO_3$ at I = 0.05, 0.15, and 0.25 M. We can conclude that a diminish occurred in log K of the M−CAP complexes (1:1) by plotting the correlation between the investigated I and log K_1^H.

3.2. Conductometric Results for the Metal Complexes of CAP. The many forms of chelate complexes produced between Sr^{2+}, Ti^{2+}, La^{2+}, Fe^{3+}, and Th^{4+} and CAP were traced using the conductivity data in this investigation. The recorded values of specific conductance were plotted as a function of the added volumes of CAP in a conductometric titration. The relationships have breaks that are clearly defined which correspond to the stoichiometric (M−CAP) complex ratios (1:1), (1:2), and/or (1:3). These findings are comparable with those acquired using the potentiometric process (Table 1).

3.3. Species Distribution Diagrams of CAP Complexes. Figure 3 shows that the main varieties of CAP in the
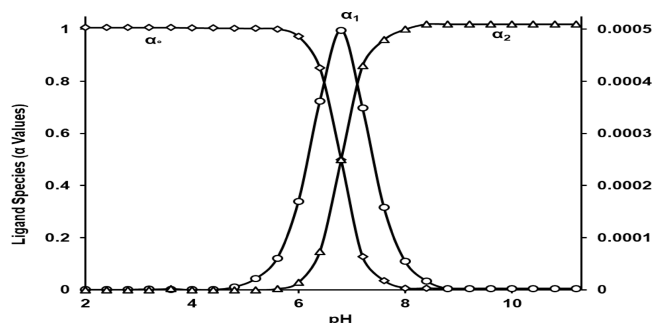
Figure 3. Ionic equilibria of CAP in diverse values of pH's.

pH range of 2.0−5.8 are the α° = H_2L species, whereas the main species in the pH range of 6.0−7.4 are the α_1 = HL^- species. Furthermore, the α_2 = L^{-2} are the dominant species in the pH levels of 7.8−11.2. Mole fractions of α_{ML} and α_{ML2} can be determined from the potentiometric data using the obtained log K for ML complexes and the initial concentrations of metal ions and ligands.[47] Figure 3 depicts the species distribution curves as a function of pH. Plotting α (α = mole fraction of the species) versus pH values under consideration can produce all of these curves.

The distribution curves of the M−CAP complexes formed can be represented in Figure 4. These curves show that complexation begins at pH = 4.6 for Co^{2+}, Zr^{2+}, and Th^{4+}; 4.2,
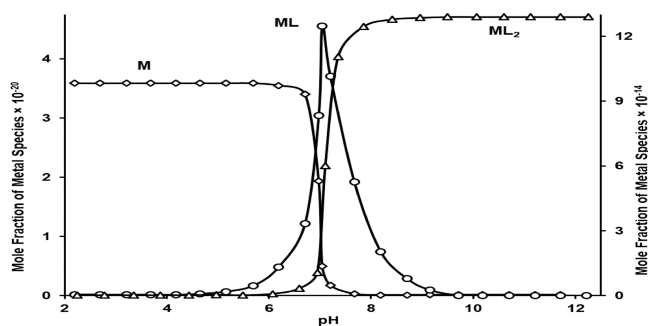
Figure 4. Ionic equilibria of La−CAP complexes in diverse values of pH's.

Figure 5. Linearity range of pure CAP at I = 0.5 M NaNO$_3$.

4.4, 4.45, 4.5, 4.62, 4.47, and 4.64 for Pb^{2+}, La^{2+}, Sr^{2+}, Mn^{2+}, Ti^{2+}, Fe^{3+}, and Cr^{3+} complexes, respectively.

The most significant difference between pH 7.2 and 11.8 is the rise in ML$_2$ concentration accompanied by a decline in ML. Beyond this pH range, a significant amount of M^{2+} ions persist as ML and ML$_2$ species, which grow in concentration when the pH of the solution rises. This illustrates that the ML species have a much more sustainable solution than ML$_2$. This attitude is aware of the values of the chelates' log K (Table 1). It is worthy to note that the ML varieties are prominent in Sr^{2+} over the pH range of 7.0−9.2, with no significant ML$_2$ species of Co^{2+}, Fe^{3+}, and Th^{4+}, however, at high pH values.

3.4. Effect of Ionic Strength on Pure CAP Determination. In the presence of 1×10^{-2} M CAP, the effect of I alteration on the proposed potentiometric and conductometric procedures for CAP determination was studied under optimized conditions. This study was accomplished over a concentration range of 0.05−1.5 M NaNO$_3$. The obtained results show that the calculated percentage recovery was close to 100% at I = 0.5 M NaNO$_3$.

3.5. Determination of CAP in Pure Form. The suggested methods for determining pure CAP in NaNO$_3$ were successfully implemented (I = 0.5 M) at 25 ± 0.1 °C. Recovery percentages ranging from 95.69 to 99.92% of CAP were obtained, with standard deviations (SD) of 0.56−0.78% (n = 5) at 95% confidence level, respectively. The accuracy and precision of the procedures are evidenced by these outcomes.

The detection and quantification limits were computed as $3\sigma/b$ and $10\sigma/b$, respectively, where b is the slope, and σ is the intercept SD.[18] It can be seen that CAP can be detected at 0.64 mg/mL (SD = 0.20, R = 0.9992 (n = 5)). The calculated correlation coefficients are quite similar to those obtained earlier using various approaches for determining CAP like chromatography,[3−6] fluorometry,[7−9] UV−visible spectroscopy,[10,11] chemiluminescence,[12] voltammetry,[13−17] potentiometry,[25−28] and conductometry[29−32] methods. Using the proposed methods, CAP was determined successfully over a concentration range from 0.83 to 13.04 mg/mL (Figure 5).

3.6. Interferences. The impact of some additives used as excipients, such as D(+) lactose monohydrate and NaCl, was explored at least 100 times in a concentration range greater than that of pure CAP to assess the potential analytical applications of the explored methods to drug quality assurance.

3.7. Analytical Applications. Figure 6a depicts the curve for a typical potentiometric titration of capritin (50 mg) as an example. Variations at the titration end point were evident enough in the suggested technique to yield potentiometric titration curves of adequate shape for highly repeatable end
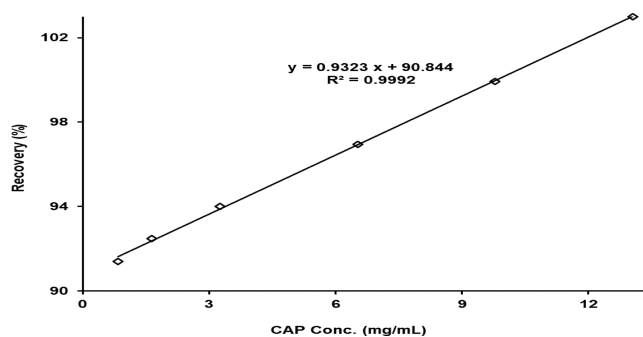
sensing. Figure 6b,c represents the first and second derivatives of the potentiometric curve for calculating CAP, including both.

The conductometric titration method has the advantages of being simple, accurate, and reproducible for pure and dosage forms. The methods were used to test various brands of CAP-containing tablets.

The recovery (%) and standard deviation (SD) for both the proposed potentiometric and conductometric methods were calculated and tabulated in Table 2 under optimal conditions and using SAM for five repetitive readings.

4. DISCUSSION

In accordance with the previously published literature,[48,49] our studies prove that CAP has two sites where the ligand has a great tendency to form M−CAP complexes: the first site is the deprotonation of the carboxyl group (COOH) and the second one is the proton dissociation in the thiol group (SH). These sites are displayed in Figure 7.

It is important to note that using potentiometric approaches to predict the formation composition of binuclear complex species is exceptionally hard. This is because the complexes formed at high pH levels, which are over the precipitation point for such systems. The electron-withdrawing nature of the six−membered chelate ring formed, on the other hand, may explain CAP's weak tendency to form binuclear complexes. Also, this phenomenon could be explained by the steric effect, which is induced by electrostatic dissonance among the protonated metal complex and the metal ion.

The calculation of the first and second proton dissociation constants of CAP (log K_1^H and log K_2^H, repectively) was completed by plotting $\overline{n}$H against pH at 0.05 M NaNO$_3$. Table 1 shows the titration results using solutions a and b. The values of log K_1^H and log K_2^H are the pH values corresponding to $\overline{n}$H = 0.5 and 1.5, respectively.

In order to track the compounds in solution, conductometric experiments can be used. This method can be used to track the digits' fluctuation in the transition metal ions' ionic radii. Conductometric study, in general, is attributed to the difference in the electrical conductivities of a solution as a result of complexes. The ion concentration present, as well as their agility, assess these variations. The perceived increase in conductivity throughout the metal ion titration with CAP, which resulted in the formation of CAP complexes, clearly indicates the deliverance of high mobile H$^+$ ions. Thus, modification can occur through the emergence of a covalent bond among a metal ion and a sulfur atom in a thiol group (SH), followed by hydrogen ion liberation.
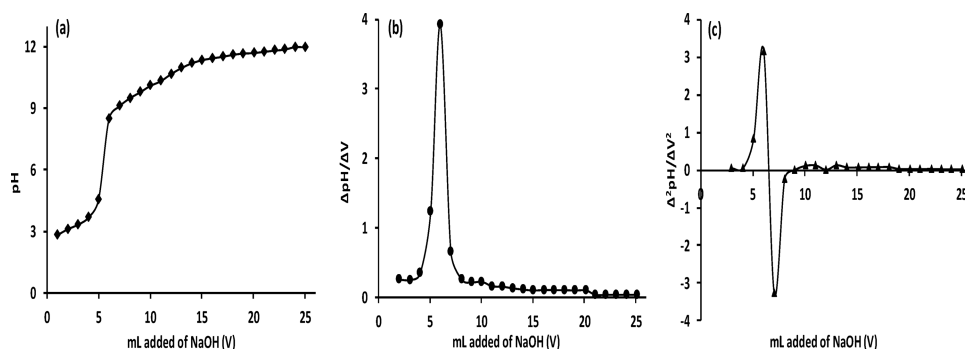
Figure 6. Exemplary potentiometric titration curves of capritin (50 mg): (a) titration curve with only one inflection point, (b) first derivative of curve (a), and (c) second derivative of curve (a).

Table 2. Recovery Data for CAP Determination in Different Dosage Forms by the Proposed Potentiometric and Conductometric Methods[a]

dosage forms	drug dose added (mg)	found (mg)	recovery (%) ($n = 5$)	SD ($n = 5$)	confidence ($n = 5$) $\alpha = 0.05$
captopril (USP)	25	24.98 (23.89)	99.92 (98.92)	0.40 (0.38)	0.35 (0.33)
deptopril	25	24.92 (23.94)	99.68 (97.92)	0.39 (0.35)	0.34 (0.30)
epsitron	25	24.88 (23.95)	99.52 (98.97)	0.46 (0.43)	0.40 (0.38)
captohexal	50	48.89 (47.98)	97.78 (95.98)	0.53 (0.51)	0.46 (0.43)
capritin	50	48.08 (47.98)	96.16 (95.96)	0.70 (0.65)	0.61 (0.57)
captopril (E.I.P.I.CO)	50	48.90 (47.95)	97.80 (95.88)	0.62 (0.57)	0.54 (0.50)

[a]Data in brackets () are from the conductometric method.
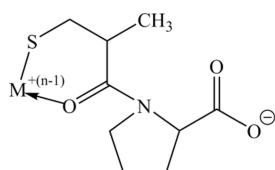
Figure 7. CAP sites as ligands to form M−CAP complexes (ratio of 1:1 (M:CAP)).

In the case of species distribution curves, increasing the pH value decreases the metal ion concentration, whereas ML species tend to develop in the medium with a mildly acidic pH (pH 4.6−7.0). The values of α_M, α_{ML}, and α_{ML2} in solution are primarily determined by the medium's pH. Complex hydrolysis could explain the decreases in the concentration of the Co^{2+}, Fe^{3+}, and Th^{4+} complexes in alkaline media.

The absolute and relative values of the respective stepwise ionization constants[45] determine the growth of polyprotic acid titration curves. In theory, each labile hydrogen will have one inflection. However, for an inflection to be associated with an adequate variation in pH, the following conditions must be met: (i) the relationship between the respective ionization constants must be greater than 10^4, and (ii) the corresponding ionization constant must not be that of a very weak acid.[47] CAP is a dibasic acid having $pK_{a1} = 3.7$ (COOH group) and $pK_{a2} = 9.8$ (SH group); the titration curve shows a noticeable inflection for the first equivalence point where the relationship of the first and second dissociation constants is $pK_1 - pK_2 = 6.1$. However, CAP is a very weak acid with regard to its second hydrogen. Therefore, its titration curve does not present an obvious inflection and can be used to determine the second equivalence point.

The normal potentiometric titration curve for CAP has only one inflection point. Adjustments at the titration end point were capable of creating potentiometric titration curves with sufficient configuration for a reliable and repeatable end detection in the proposed method. Although CAP has previously been defined using various analytical techniques, the proposed technique for CAP detection is indeed described as easy, cost next to nothing, and sample preparation does not necessitate lengthy and laborious procedures. The time needed for the potentiometric analysis of pure CAP (after sample preparation) was 10 min/specimen.

For CAP determination using the proposed method, no interference was observed from the studied chemical excipients over the studied CAP concentration range. Good recoveries ($n = 5$) were obtained for all pharmaceutical preparations, from 96.16 to 99.92% for the potentiometric method (SD = 0.39−0.70) and from 95.88 to 99.52% for the conductometric method (SD = 0.35−0.65), respectively. Both potentiometric and conductometric approaches produce results that are in good accord with those seen in the literature. Results for recovery studies for both methods are shown in Table 2.

5. CONCLUSIONS

The complexation reaction between CAP and several ions, viz, Cr^{3+}, Fe^{3+}, La^{2+}, Th^{4+}, Co^{2+}, Mn^{2+}, Pd^{2+}, Sr^{2+}, Ti^{2+}, and Zr^{2+}, followed either the potentiometric method or the conductometric method. The use of these methods allows for the identification of the formed complexes, determination of their log K, and distribution of species for CAP and its metal complexes at different pH values. Furthermore, as far as we are aware, we were the first to offer potentiometric and conductometric methods for determining CAP in pharmaceutical formulations, with recovery values ranging from 95.88 to 99.92%.

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Notes

The authors declare no competing financial interest.

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