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Metal complexes developing for ramipril determination in tablet by potentiometric technique

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Abstract: Three trivalent metallic ions viz; chromium, iron and aluminum were nominated to clarify the relations of these metallic elements with ramipril (RAM) by means of potentiometric technique. The protonation constant of RAM and formation constants of complexes constructed at ionic strength (I = 0.1 M sodium nitrate) have been tabularized in aquatic medium at room temperature. The ratios of complexes 1:1, 1:2 and/or 1:3 metallic ions towards RAM relations are developed dependent on the nature of RAM or metallic ions. The order of formation constants of the two complexes was investigated. The potentiometric method was employed to approve the ratios of M-RAM binary complexes formed. This method was used successfully to detect RAM in tablets. The standard addition process built on Gran plot, RAM was acceptably estimated at ionic strength I= 0.4 M $NaNO_3$, through a concentration variety of 0.753–12.05 mg/mL (standard deviation SD = 0.11, correlation coefficient R = 0.9992 (n = 5)) by a lower detection limit (LOD) equals 0.55 milligram/milliliters (standard deviation SD = 0.15, R = 0.9992 (n = 5)). In the presence of noted tablet excipients, no interfering was detected. The percentage of RAM obtained from tablet dosage forms diverse from 99.5 to 100.6 % with SD ranging from (0.39 – 0.7).

Keywords: Ramipril; complexes; potentiometry; Gran plot; tablets.

1. INTRODUCTION

Ramipril (RAM), which is known chemically as: 2[N–(S)–1–ethoxycabonyl–3–phenylpropyl]–L–alanyl]–(1S,3S,1S)–2–azabicyclo[3,3,0]octane–3–carboxylic acid, is an orally effective inhibitor of angiotensin. Transforming enzyme (ACE) by antihypertensive drug action. Also, ramipril is employed in the medication of entirely models of hypertension, heart disaster and tracking myocardial violation towards advanced persistence in patients by experimental indication of heart disaster [1]. Despite the importance of RAM, insignificant studies have been issued about its assessment, viz; atomic adsorption spectroscopy [2], gas chromatography (GC) [3,4], radioimmunoassay [5], HPLC (high performance liquid chromatography) [6,7], ion selective electrode derivative potentiometry [8,9], enzymatic analyze by GC/HPLC [10], derivative spectroscopic analysis [11]. The voltametric determination of RAM in tablets and in biological fluids at carbon paste electrode has been examined [1,12]. These techniques are difficult, time-consuming, and involve the use of complicated equipment.

The potentiometric technique is utilized widely in many types of aqueous chemistry. It is by far the greatest precise and broadly appropriate procedure presently available for the investigation of ionic equilibria [13].

Also, it has been proposed that the existence of metallic element in biological fluids might exhibit an important influence on the biological activity of drugs [1].

Newly, more consideration has been given toward the investigation of second complexes of metallic element with particles of biotic and medicinal activity [14].

The strength of RAM in aquatic buffers has been investigated as a utility of hydrogen ion concentration. The rate of RAM loss and the type of degradation are relatively associated with the hydrogen ion concentration of the medium.

The application of potentiometric and conductometric procedures to investigate binary and ternary complexes of metallic elements with biotic and pharmacologic substances have been given a lot of attention as electrochemical techniques [15-21]. Potentiometric estimation of complex formation between both stimulating substance and metallic elements, present a clear impression of how relations among drugs and metallic element may influence medicine approach to objective areas [22]. In biological fluids, the existence of specific ions is assumed to permit a main influence on pharmacological behavior of certain chemical materials [23].

Generally during the potentiometric analyses, the equivalent point of the generated titration curves was recognized by means of Gran plot [24]. Also, the use of Sundry Gran plot was issued in many surveys [25-32].

In this study, the metal ion chelation of RAM as M^{+n}–RAM with iron, aluminum, and chromium metallic ions, acting as nitrate. RAM dissociation constants and its stability constants were computed. Similarly, the objective of the proposed work was extended towards creating a potentiometric method designed for measuring RAM directly in tablets by means of a Gran plot. Also, the Gran plot data generated from the potentiometric analyses gave more insight about the chelation of RAM with several metallic elements, especially trivalent metal ions viz, chromium, iron, and aluminum.

2. EXPERIMENTAL

2.1 Apparatus

Calvin–Bjerrum method which also approved by Irving and Rossoti [14] were applied to determine the deformation constants of RAM and the association constants of its metal complexes by RAM at room temperature in aquatic liquids. All potentiometric experiments included VWR scientific products Version 2000, USA.

2.2 Chemicals and Materials

0.1 M of trivalent metal ions viz, chromium, iron, and aluminum metallic ions solutions (BDH and Merck) as nitrate ions are fixed and standardized by ethylenediaminetetraacetic acid (EDTA) [14]. NaOH (0.1 M) and RAM (0.01 M) solutions (Merck) were prepared as fresh solution in double distilled water.

Dosage forms: Tritace® tablets (Pharmas of Aventis. A. E, Aventis Pharma–Germany) categorized to include 1.25, 2.5, 5 and 10 mg RAM for each tablet.

2.3 General Analytical method

2.3.1 Metallic complexes of RAM

The subsequent solutions were prepared and standardized potentiometrically including 0.1 M NaOH solution titrated via standard solution of potassium hydrogen phthalate,

A) 0.005 M nitric acid + 0.095 M sodium nitrate (for medium).

(B) Solution (A) + 0.001 M RAM (for determiningRAM association constants).

(C) Solution (B) (for estimation of metallic ions-RAM complexes (M-RAM)).

The entire volume was adapted to 50 cm^3 via adding double distilled H_2O in every assignment. The titrations were done at room temperature and with ionic strength equal to 0.1 M $NaNO_3$.

2.3.2 RAM determination

2.3.2.1 Pure RAM Form

25 mL of RAM Solution (0.02 M) (Ionic strength is adjusted to 0.4 M by $NaNO_3$) was prepared with diluting the standard solution with double distilled water. After that, 25 mL of RAM solution was potentiometrically standardized by NaOH solution (I = 0.4 M) in 50 mL conical flask at room temperature.

2.3.2.2 Tablets Forms

10 tablets of RAM were crushed into fine powder and mixed well. A part equal to approximately 0.279 mL was liquified with 100 mL of methanol, mixed well and filtered, then moved into a 100 mL measuring flask and brought to volume by double distilled water. Then 25 mL of the prepared RAM solution was taken to a beaker and the ionic strength was adapted to 0.4 M using sodium nitrate. The resulting solution is considered a pure RAM solution. Via the use of a standard calibration plot, the amount of RAM for each RAM tablet was computed.

2.4 Statistical Assessment

All statistical parameters, stability constant and ratio constant were explained and computed by Excel software. For RAM estimation, Gran plot was created and lower detection limit, lower quantitation limit and standard deviation were estimated by SAM. Previously, SAM, and Excel software were successfully employed for a similar investigation [16].

3. RESULTS AND DISCUSSION

3.1 Potentiometric Studies

According to the titration curves as appear in Fig.1. the mean number of protons connected by RAM, $\bar{n}H$, was computed.

$$\bar{n}H = Y + \frac{(V_1 - V_2)(N^0 + E^0)}{(V_0 - V_1)(Tcl^0)} \quad (1)$$

Wherever Y equals 2 (number of associable hydrogen protons in the RAM), V_o is the original volume, V_1 and V_2 are the volume of NaOH to get the equal pH in nitric acid and (nitric acid +RAM), respectively. Tcl^o is the entire concentration of RAM, N^o is the normality of the NaOH and E^o is the original concentration of HNO_3.

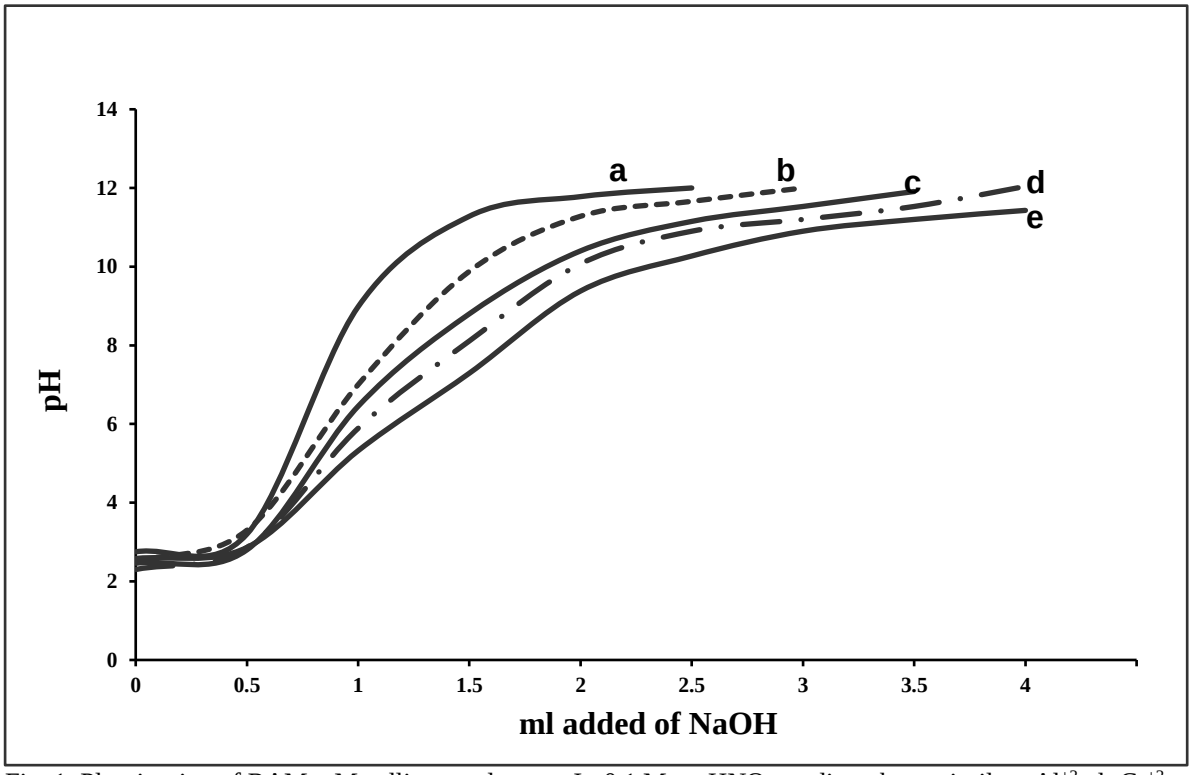


Fig. 1: Plot titration of RAM – Metallic complexes at I= 0.1 M: a- HNO_3 medium, b- ramipril, c- Al^{+3}, d- Cr^{+3} and e- Fe^{+3}

Computation of hydrogen proton RAM formation constants were performed via drawing $\bar{n}H$ opposed to pH in 0.1 M NaOH is displayed in Fig.2. log K_1^H and log K_2^H values (first and second association constants of RAM) are the values of pH related to 1.5 and 2.5, respectively. Excel software system [16] was operated to refine the overall association or formation constants. Table 1 shows that the value of log K_1^H agrees well with those previously stated [1], in aquatic solution medium and at room temperature.

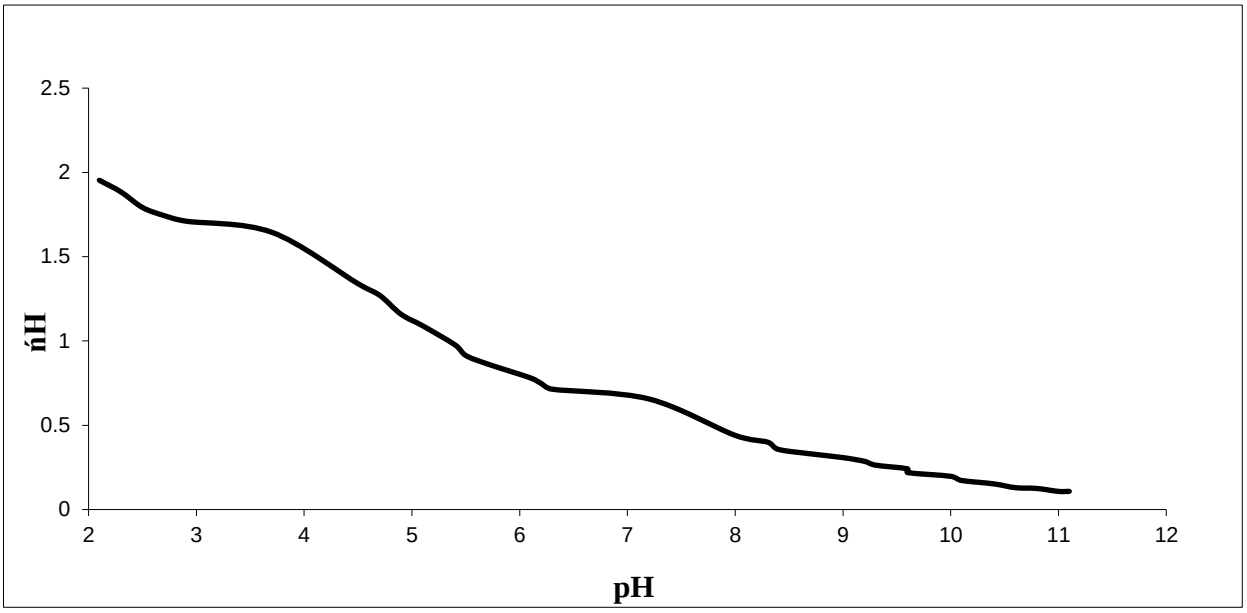


Fig. 2: Association constant plot of RAM at I = 0.1 M HNO_3 and at room temperature

It is worth stating that RAM does not hydrolysis in the ideal experimental conditions. This has been illustrated via the fast ability of equilibria through the titration process. The titration plots of the metallic ion–RAM solutions (C) are good split from that of the RAM solution (B) (Fig.1). Therefore, substitution of H ion is owing to complex formation. From these titration plots, $\bar{n}$ (mean number of RAM involved for each metallic ion) and pL (freed RAM exponent) quantities were computed by Irving and Rossoti calculation [14].

$$\bar{n} = \frac{(V_3 - V_2)(N^0 + E^0)}{(V_0 + V_2)\bar{n}HTcM^o} \quad (2)$$

$$pL = Log\left[\frac{(1 + K_1^H[H^+] + K_2^H[H^+]^2 + K_3^H[H^+]^3 + ----)}{(Tcl^0 - \bar{n}TcM^0)} \times \frac{V_0 + V_3}{V_0}\right] \quad (3)$$

Wherever, V_1, V_2 and V_3 are the quantities of NaOH attain similar pH at the free nitric acid, free HNO_3 + RAM and free HNO_3 + RAM + metallic ions, respectively. T_cM^o represents the overall intensity of metallic ion exist in the mixture.

The values of $\bar{n}$ were drawn versus corresponding values of pL to find the formation plots of the metallic element complex formation equilibrium. The formation plots are displayed in Fig.3. After these formation plots, the formation constants values at I = 0.1 M (Table 1) were governed by half–integral method [14].

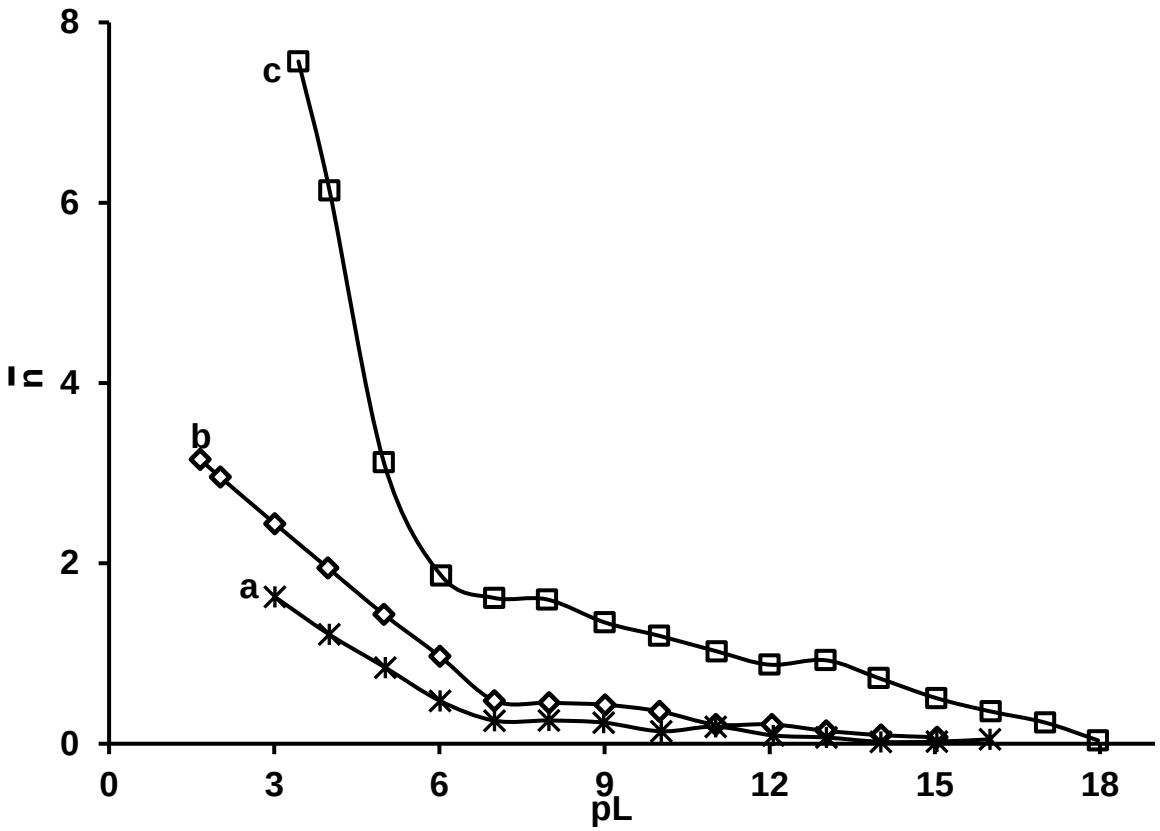


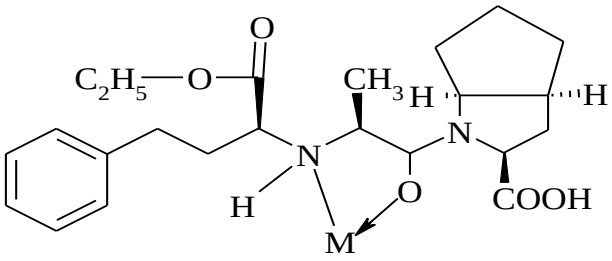
Fig. 3: complex formation plots of binary metallic element complexes by RAM at I = 0.1 M $NaNO_3$ and at 25 °C: a- Cr (III) b- Al (III), c- Fe (III)

Table 1: Association constants of RAM and formation constants of metallic elements at I equal to 0.1M $NaNO_3$ and at room temperature

Metallic ions	$LogK_1$ 1:1	$LogK_2$ 1:2	$LogK_3$ 1:3
H^+	9.3 (9.2) *	4.2(4.0)*	----------
Fe (III)	9.876 (9.704)*	7.475 (7.42)*	7.23 (7.13)*
Al (III)	----------	9.676 (9.585)*	8.475 (8.374)*
Cr (III)	9.616 (9. 504)*	7.952 (7. 822)*	----------

** The data between brackets ( ) is from reference [1].*

RAM has 2 sites; the 1st site is association proton of NH group and the 2nd one is the separation of hydrogen ion from COOH group these positions are explained as the following:



Metal ion–RAM complex

The order of formation constants of the diverse binary complexes designed among RAM and transition metallic element studied at this investigation is as the predictable Irving–Williams order [14] for (1:1) metallic ions to RAM in I = 0.1 M $NaNO_3$: Fe (III) > Cr (III).

It is essential to state that calculating the structure configuration of binuclear complex species by pH methods is difficult. This is due to the complexes produced at extreme pH degrees, which are after the precipitation statement for such structures. While the formation of other M–RAM complexes is disrupted by metal ion precipitation and hydrolysis. The abandoning electron nature of the five–membered chelated ring constructed can further clarify RAM's weak tendency to produce binuclear complexes. Furthermore, this fact might be clarified by the steric effect, which is brought by static dissonance between the protonation metallic complex and the metallic element.

3.2 Distribution graphs of RAM complexes

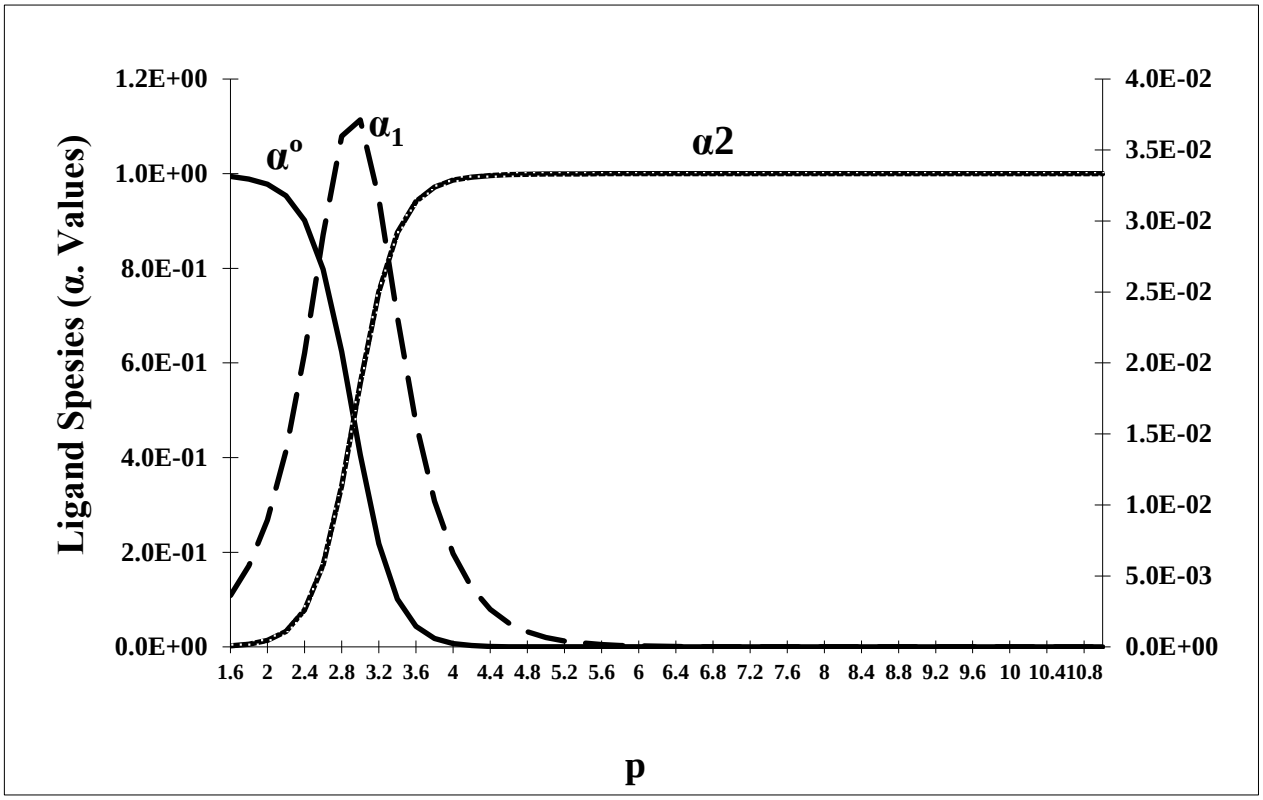


Fig. 4: Ionic species of RAM in different values of pH`s

Viewing at Fig. (4), in the pH variety after 2.1 to 4.8, the main type of RAM is α0= H2L types, but in the pH after 2.2 - 4.6, the α1= HL- types is the main one, as well as the α2= L— kinds are the main in the pH range of 4.8 - 10.8.

The mole fraction α_{ML} and α_{ML2} was estimated from pH-metric data via the attained formation constant of ML, and ML_2 complexes and the original concentrations of metallic elements and ligand [14]. The distribution plots can be obtained by plotting α (α= mole fraction of the species) versus pH. For example, curves for Fe metal ion distribution through the pH are shown in Fig (5). Same behavior was noticed for the other metallic elements-ligand complexes.

By increasing the pH of the solution, the metallic ion concentration tends to reduce, whereas the ML species tends to develop at reasonably basic media (pH≈7.8-10.2). The distribution plots show that complexation starts at pH values ~ 7, 7.3 and 7.4, for the trivalent Cr, Fe and Al metal ion complexes, respectively.

After pH 7.1 to 11.8 the main changeover is the rise in the ML concentration with a reduction in M species. Over this point approximately the entirety of M(III) ions remain in the ML species and their concentration grows on rising the pH of the medium. This obviously reveals that ML types are greatly further established than ML_2 in its solutions. It is worth stating that Fe (III) curve shows, the ML types are governing over the 7.8-10.2 pH range, with no significant αML_2 species of trivalent Cr, Fe and Al metal ions even at high values of pH.

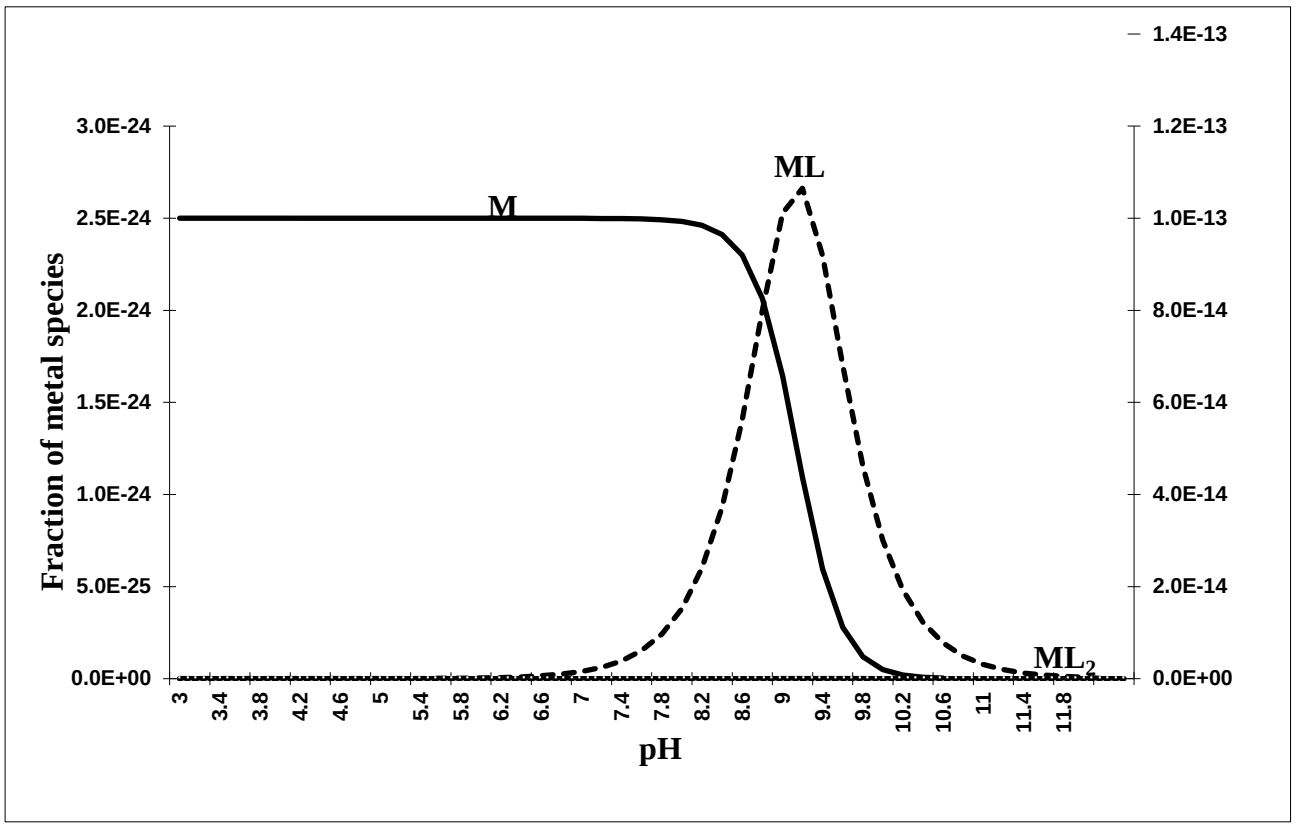


Fig. 5: Metallic equilibria of Fe-RAM complexes in different pH's ranges

3.3 influence of ionic strength on estimation of RAM

In the existence of 0.02 M RAM, the influence of ionic strength on the suggested potentiometric method of RAM determination was planned under adjusted conditions. This investigation establishes a concentration limit of 0.1-1.5 M of $NaNO_3$. The data shows that the evaluated percentage recoveries were around 100 % at I = 0.4 M $NaNO_3$.

3.4 RAM estimation in pure form

The recommended method for pure RAM estimation in $NaNO_3$ was well fulfilled (I = 0.4M) at room temperature. Recovery percentages vary between 91.41 to 102.99 % for RAM were achieved with SD of 0.1-0.4 % (n = 5) at 95 % confidence point, respectively. The precision and accuracy of the methods are verified via these results.

The ordinary pH-metric titration plot of RAM has only one variation site. Modifications at the titration equivalent point could create potentiometric titration plots using sufficient configuration for repeatable and reliable end detection in this promising technique. While RAM has previously been investigated by different analytical techniques [1, 14, 33], this promising method for RAM evaluations is labelled as easy, cost effective, simple to prepare and does not demand extensive laboratories trials. The time required for pH- metric study of RAM after the sample is prepared was ten minutes for each sample.

The LOD and QL were calculated as $3\sigma/b$ and $10\sigma/b$, respectively, wherever b = slope and σ = intercept SD [18]. RAM can be found at 0.55mg/mL (SD = 0.15, R = 0.9993 (n = 5)). The evaluated correlation coefficients are very like those taken previously by different methods for estimating RAM such as voltammetry method [1]. Via the suggested technique, RAM was found successfully above the detection limit from 0.753 to 12.05 mg/mL (Figure 6 and table 2).

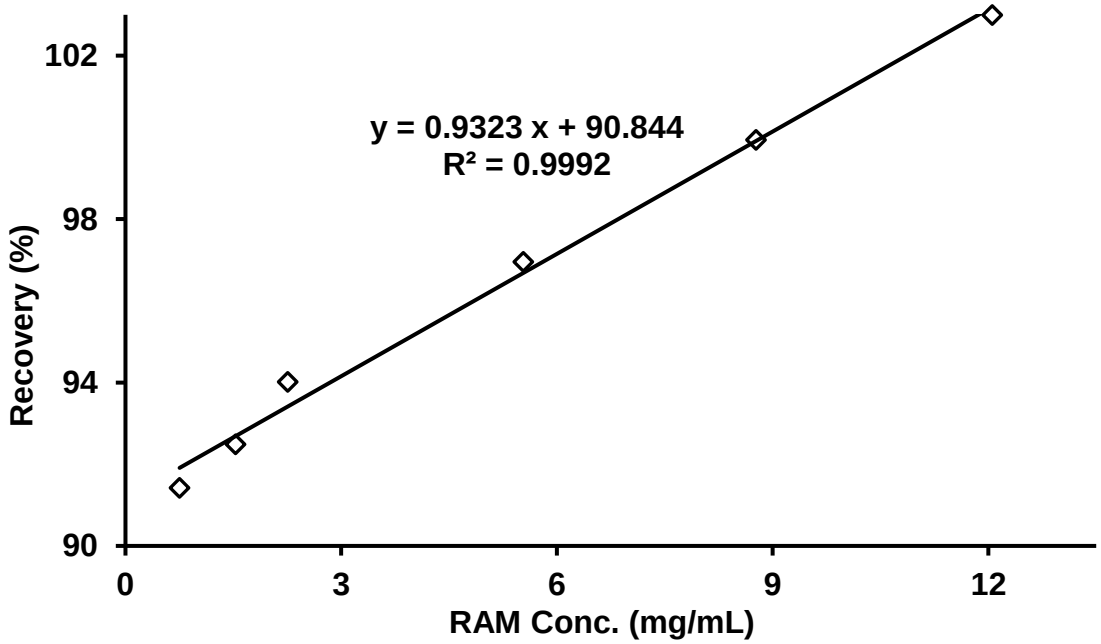


Fig. 6: Linearity limit of pure RAM at ionic strength I = 0.4 M NaNO3.

Table 2. Recovery data for spiked pure RAM by potentiometric method

Add pure (milligram)	Found (milligram)	Percentage recovery (%)	Standard deviation (n=5)	Confidence(n=5) α =0.05
0.753	0.688	91.41	0.4	0.63
1.532	1.416	92.48	0.1	0.12
2.25	2.115	94.01	0.22	0.25
5.53	5.361	96.95	0.35	0.51
8.77	8.765	99.94	0.32	0.2
12.05	12.410	102.99	0.31	0.48

3.5 Interfering:

The influence of some spices used as excipients, like D (+) lactose monohydrate and sodium chloride, were performed at a minimum of hundred times in a concentration variety larger than that of RAM. This technique shows its ability to be used in quality control of drugs. However, for RAM estimation by this simple technique, no interfering was noticed from the chemical excipients through the investigation of RAM concentration variaty.

3.6 Methodical application:

Figure 7 (*a*) shows a plot for a representative potentiometric titration of Tritace® (1.25, 2.5, 5 and 10 milligram), for example. The titration equivalence point was sufficient in this method to produce pH-metric titration plots with high quality and reproducibility. Fig. 7 (*b*) and Fig. 7 (*c*) represent the 1st and 2nd derivatives of the pH-metric plot for computing RAM are combined.

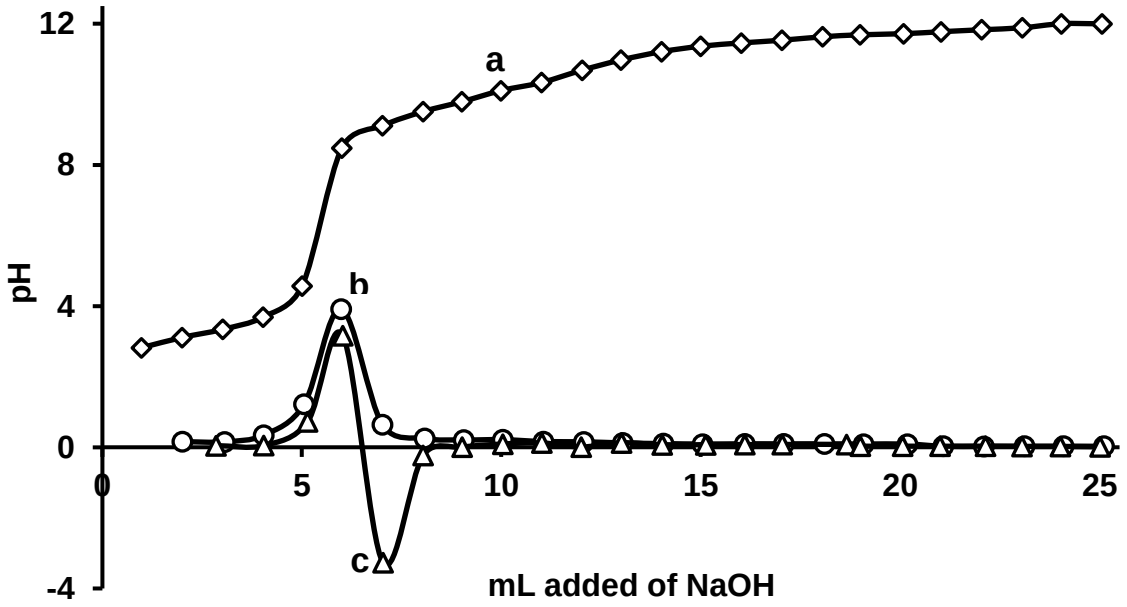


Fig. 7: Potentiometric titration plots for Tritace® (10 milligram): (a) titration plot with one variation point, (b) 1st derivative of plot (a) and (c) 2nd derivative of plot (a)

The recovery (%) and standard deviation (SD) for the suggested pH-metric techniques were estimated and formulated in Table 3 in optimum conditions and by using SAM for 5 replicates readings.

Table 3. Recovery results for ramipril estimation in differs dosage forms

Tablets Forms	Tablet dose added. (mg)	Found (mg)	Recovery %	Standard deviation (SD)
Tritace® tablet	1.25	1.245	99.6	0.39
Tritace® tablet	2.5	2.515	100.6	0.65
Tritace® tablet	5	5.02	100.4	0.7
Tritace® tablet	10	9.95	99.5	0.5

For RAM estimation by this technique, no interfering was noticed from the investigated chemical excipients through the RAM concentration variaty. Very good recoveries (n = 5) were gained for entire dosage forms, from 99.5 - 100.6 % (SD = 0.39–0.70). The potentiometric data produced are in very good agreement with that found in the literature[1].

3.7 Precision and repeatability:

This technique used for the investigation of RAM in tablets formula, exhibit a correlation coefficient of 0.9937, recovery value 95.5 % with the standard deviation of 0.39 %, revealing acceptable precision and accuracy of this advance technique

4. Conclusion

The complex formation reaction among RAM and some trivalent metal ions *viz;* Cr, Fe and Al using potentiometric technique were successfully investigated. This method permits the detection of constructed complex formation, to determine their stability constant and species distribution for RAM and its metallic complex at various pH ranges. The novelty of this analytical technique was successfully approved by the generated data obtained in this study. Additionally, for the first time the advance pH-metric method for finding RAM concentrations in tablets was confirmed by recovery data varying from 99.5 - 100.6 (SD= 0.39 – 0.7 %).

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الملخص باللغة العربية

معقدات معدنية تتطور لتحديد عقار راميبريل في الأقراص باستخدام تقنية القياس الجهدي

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تم ترشيح ثلاثة أيونات معدنية ثلاثية التكافؤ وهي؛ الكروم والحديد والألمنيوم لتوضيح علاقات هذه العناصر المعدنية مع راميبرل (RAM) عن طريق تقنية قياس الجهد. تم جدولة ثابت بروتونات RAM وثوابت تكوين المعقدات المبنية بقوة أيونية (I = 0.1 M نترات الصوديوم) في وسط مائي في درجة حرارة الغرفة. تم تطوير نسب المعقدات 1:1 و1:2 و/أو 1:3 أيونات معدنية تجاه علاقات RAM اعتمادًا على طبيعة RAM أو الأيونات المعدنية. تم التحقيق في ترتيب ثوابت تكوين المركبين. تم استخدام طريقة قياس الجهد للموافقة على نسب المعقدات الثنائية M-RAM المتكونة. تم استخدام هذه الطريقة بنجاح للكشف عن RAM في الأقراص. تم تقدير عملية الإضافة القياسية المبنية على مخطط جران، RAM بشكل مقبول عند القوة الأيونية I = 0.4 M NaNO3، من خلال مجموعة تركيز تتراوح من 0.753- 12.05 مجم / مل (الانحراف المعياري SD = 0.11، معامل الارتباط (n = 5) R = 0.9992) من خلال حد اكتشاف أدنى (LOD) يساوي 0.55 مليجرام / مل (الانحراف المعياري SD = 0.15، R = 0.9992 (n = 5). في وجود سواغات أقراص ملحوظة، لم يتم الكشف عن أي تداخل. تباينت نسبة RAM المستحصل عليها من أشكال جرعات الأقراص من 99.5 إلى 100.6٪ مع انحراف معياري يتراوح من (0.39 - 0.7).

الكلمات المفتاحية: راميبريل؛ معقدات؛ قياس الجهد؛ مخطط جران؛ أقراص.