



Conductometric determination of sibutramine HCl, sumatriptan succinate and lomefloxacin HCl and the solubility products of their ion associates with molybdophosphoric acid

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ABSTRACT

Conductometric determination of sibutramine HCl, sumatriptan succinate and lomefloxacin HCl with molybdophosphoric acid as a precipitating reagent was investigated. Various experimental conditions were evaluated and results obtained showed good recoveries, (mean recovery values of 100.51, 99.68, 99.41 and relative standard deviation of 0.332, 0.404, 0.509 for sibutramine HCl, sumatriptan succinate and lomefloxacin HCl, respectively). Numerical derivatization (first and second derivative) of the data was also applied, showing more accurate results compared to classical ones. The described procedures allowed the determination of equilibrium constants those indicated high degree of completeness of the precipitation reaction. Other parameters related to ion pair complex such as solubility and solubility product were also calculated. The described procedures allowed the determination of the studied drugs in the range of 5-15 mg. The precipitate obtained by ion pairing of lomefloxacin HCl with molybdophosphoric acid was spectroscopically characterized using IR. The method was further applied successively to pharmaceutical formulations, the proposed method offering a high degree of accuracy and precision when compared to reference methods.

1. Introduction

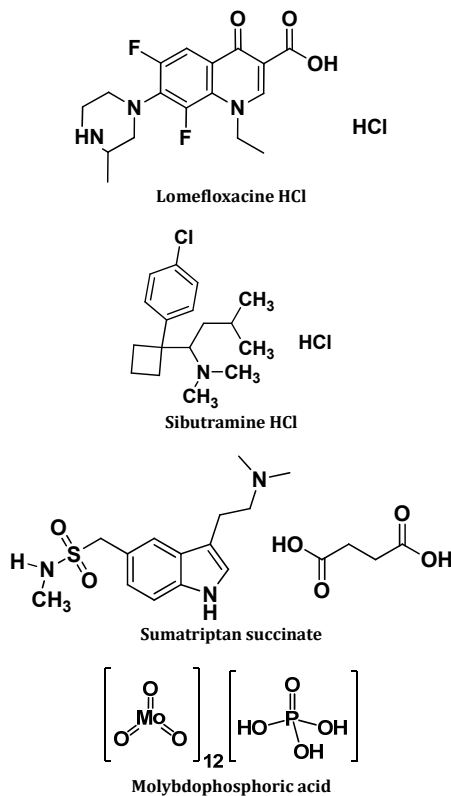
Sibutramine HCl, sumatriptan succinate and lomefloxacin HCl are three pharmaceuticals of different pharmacological actions and similar chemical properties that enable them to react with molybdophosphoric acid. Sibutramine HCl is used in the management of obesity, sumatriptan succinate is an antimigraine drug and lomefloxacin HCl is an antibacterial fluoroquinolone [1] (Scheme 1). Several methods are reported in literature for the determination of the drugs either in pure form or in pharmaceutical formulations. Literature survey of sibutramine HCl revealed that chromatographic methods [2,3], potentiometric methods [4], other spectroscopic methods using folin-ciocalteu reagent or UV-Vis spectrophotometry [5,6] were reported for its assay. On the other hand for sumatriptan succinate in United States Pharmacopoeia (USP), suggests a chromatographic method for its determination in bulk and tablet formulations [7]. LC-Tandem MS [8], HPTLC [9], RP-HPLC [10], voltammetric [11] methods were reported for its determination. Also Different spectroscopic methods were used for its analysis such as condensation reaction with aromatic aldehyde like (vanillin or para dimethyl- amino cinnamaldehyde (PDAC) [12], nucleophilic substitution reaction using (folin reagent) [13], ion pair formation with (tropaeolin OOO) [14] and formation of purple red coloured product using (sod-nitroprusside-acetaldehyde reagent) [15]. Also, the drug was quantitated bromometrically using bromate-bromide as the bromination reagent in acid medium and methyl orange or indigo carmine as subsidiary reagents [16] or

by using charge transfer complexation reactions with different acceptors [17]. Several techniques were adopted for the determination of Lomefloxacin HCl. Among these were chromatography [18], capillary electrophoresis [19], voltammetry [20] and spectroscopic methods [21-32].

An inspection of the performance characteristics of the reported methods for the studied drugs revealed that some of them suffer a few drawbacks such as extraction, using of organic solvents, too many steps and expensive chromatographic methods.

Because of the widespread usage of the cited drugs in Egypt and many countries in the area, there was a need to have a simple, sensitive, cost-effective, rapid technique for the determination of these drugs either in pure forms or in formulations. To the best of our knowledge, despite the advantages of the conductometric analysis, there were no previous reports for the conductometric determination of the cited drugs using molybdophosphoric acid. For this reason, the purpose of this work was to develop a conductometric method for the determination of the drugs in their dosage formulations. The proposed method is very simple and the reagents are of low expenses in comparison to the other techniques but at the same time it offers a high degree of accuracy and precision when compared to reference methods. The proposed procedure is very simple, accurate and can be readily adopted for routine analysis in quality control laboratories. Reaction between the three studied drugs and molybdophosphoric acid (MPA) was investigated by conductometric technique. The titrant was used for quantitative determination of some

pharmaceutical compounds applying conductometric, spectrophotometric and potentiometric procedure [33-35]. The sharpness of the endpoint is greatly dependent on the solubility of the formed ion-pairs [36]; the conductance data were employed to calculate the solubility products of the considered precipitation reaction. The endpoint was established via an experiential graphical process where the intersection of two straight lines represents the equivalence point. Numerical derivatization (first and second derivative) of the data showed more accurate results compared to classical ones. Additionally, structural elucidation of lomefloxacin HCl-Molybdophosphoric acid ion associate as an example of the reaction was performed using IR.



Scheme 1

2. Experimental

2.1. Apparatus

JENWAY model 470 Conductivity / TDS Meter (470 201), with Conductivity/Temperature Probe (027 298) (England) was used. FT-IR measurements were recorded as KBr disks using Mattson 1000 spectrophotometer, Micro analytical Center, Cairo University, Giza, Egypt.

2.2. Reagents and chemicals

Bi-distilled water and analytical grade reagents were used to prepare all solutions Sibutramine HCl (99.7%), sumatriptan succinate (99.7%) and lomefloxacin HCl (89.61%) were kindly provided by SIGMA Pharmaceutical Industries -Egypt-S.A.E. Molybdophosphoric acid (99%), was obtained from Aldrich (Germany). 3×10^{-2} M of sumatriptan succinate and 6×10^{-2} M of both sibutramine HCl and lomefloxacin HCl. were prepared in doubly distilled water. Acetone (99%), ethanol (98%) and methanol (98%) (El-Nasr Pharm. Chem. Co., Egypt) were also used.

2.3. Standard drug solutions

Standard solutions of 1 mg/mL of the cited drugs were, prepared by dissolving 100 mg of pure drug in 100 mL distilled water.

2.4. Pharmaceutical formulations

The following commercial formulations are subjected to analytical procedure:

Smartan[®] tablet from (Memphis Pharmaceutical Industries-EL Amiryra, Cairo, Egypt) containing 10 mg of Sibutramine HCl monohydrate/tablet.

Sibotrim[®] capsule from (EvaPharma Pharmaceutical Industries Egypt-S.A.E) containing 15 mg of Sibutramine HCl monohydrate/capsule.

Slimax[®] capsule from (Multi-Apex Pharmaceutical Industries Badr city-Cairo-Egypt) containing 15 mg of Sibutramine HCl/capsule.

Sumigran[®] tablet from (SIGMA Pharmaceutical Industries -Egypt-S.A.E) containing 25 mg of sumatriptan Succinate/tablet.

Lomex[®] tablet from (SIGMA Pharmaceutical Industries -Egypt-S.A.E) containing 400 mg of Lomefloxacin HCl/tablet.

Orchcin[®] eye drops (Orchidia pharmaceutical Industries) containing 3 mg of lomefloxacin/mL.

2.5. General procedures

Aliquots of standard drug solution (5-15 mL) containing 5-15 mg of each drug were transferred into the titration cell and the volume was made with doubly distilled water up to 50 mL. The conductivity cell was immersed in and the solution was titrated with 3×10^{-2} M molybdophosphoric acid for sumatriptan succinate and 6×10^{-2} M titrant for both sibutramine HCl and lomefloxacin HCl. using a microburette. The conductance was measured 2 minutes subsequent to each addition of the titrant after thorough stirring. Conductivity corrected for dilution effect [37] vs volume plot for a particular titrant was constructed and the end point was determined. The nominal content of the drug was calculated using the following equations:

$$\Omega^{-1}_{\text{correct}} = \Omega^{-1}_{\text{obs}} [v_1 + v_2 / v_1] \quad (1)$$

where $\Omega^{-1}_{\text{correct}}$ is the corrected electrolytic conductivity, Ω^{-1}_{obs} is the observed electrolytic conductivity, v_1 is the initial volume and v_2 is the volume of reagent added. A graph of corrected conductivity versus the volume of added titrant was constructed and end-point was determined. The nominal content of the compound under study was calculated from the following equation:

$$\text{Amount of the drug (mg)} = V.M.R / N \quad (2)$$

where V = volume (mL) of the titrant, M = molecular weight of the drug, R = molarity of the titrant and N= number of moles of the titrant consumed per mole of the drug.

2.6. Assay of the pharmaceutical formulations

Tablets or capsules: the contents of 10 tablets were pulverized, the content of 10 capsules were emptied, an accurately weighed amounts equivalent to 100 mg of the studied drugs were extracted by shaking with 50 mL distilled water, filtered, transferred to a 100 mL volumetric flask, completed to the mark using distilled water.

Eye drops: accurate volume of Orchcin[®] eye drop equivalent to 50 mg of Lomefloxacin HCl was measured; completed to 50 mL with double distilled water, Then Standard addition technique was used for the determination of the cited drugs in their formulations in which the end point of authentic

= End point of (authentic + End point of tablets)- End point of tablets).

2.7. Conductometric determination of the solubility products

The conductivities of solutions of different concentrations (C) were measured at 25 °C for the studied drugs and MPA. The specific conductivities (K_s), corrected for the effect of dilution, were calculated and used to get the equivalent conductivities (Λ) of these solutions. Plots of Λ vs. \sqrt{C} were constructed and Λ_0 , $\Lambda_{0\text{ sib}}$, $\Lambda_{0\text{ sum}}$, $\Lambda_{0\text{ lome}}$, $\Lambda_{0\text{ PMA}}$ were obtained from the intercept of the respective straight lines with the Λ axis. The activity coefficients of the ions employed were taken as unity because all the solutions were sufficiently dilute. The values of Λ_0 ion associate were calculated using Kohlrausch's law of independent migration of ions [38]. The solubility (S) and solubility product (K_{sp}) values of a particular ion associate were calculated using the following equations;

$$S = K_s / \Lambda_0 \text{ "ion-associate"} \quad (3)$$

$$K_{sp} = S^2 \text{ (for 1:1 Ion Associates)} \quad (4)$$

$$K = 1 / K_{sp} \quad (5)$$

where, " K_s " are the specific conductivity of the saturated solution of the ion associate and Λ_0 is the intercept of the Λ vs. \sqrt{C} curve.

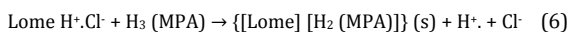
Numerical derivatization of data was used Mathematical differentiation of the obtained conductivity data against the corresponding reagent volume was applied using first and second derivatives (Using the version number of Excel 2007).

2.8. Preparation of ion-associates

IR spectrum of ion pair of molybdophosphoric acid and lomefloxacin HCl was investigated as an example of the reaction. The ion associate was prepared by mixing solutions containing 10^{-2} M of molybdophosphoric acid, and the requisite amount of the drug. The obtained precipitate was filtered, thoroughly washed with water, and dried at room temperature. Then the precipitate was subjected to IR spectroscopy

3. Results and discussion

Conductance measurements were used successfully in quantitative titration of systems in which the conductance of the solution varies before and after the equivalence point. In these cases, the titration curve could be represented by two intersecting lines at the end point. The conductometric technique was used for the determination of many drugs [33,36,39] on using MPA as a titrant; the ion- associates are formed between the studied drugs and MPA as shown in the following equation:



The investigated system showed a steady increase in conductance values up to the equivalence point where a sudden change in the slope occurs. This divergence from linearity can be attributed to the formation of an ion-associate, presumably, by replacing the drug cation (lomeH^+) with the highly mobile H^+ ions, so the conductivity increases. After the endpoint, more acid reagent is added and the conductivity changes more rapidly [33,40]. Titration curves (Figure 1) had weak curvature around end point that may affect its value. Numerical derivatization of data was used to overcome this problem. Mathematical differentiation of the obtained conductivity data against the corresponding reagent volume was applied using first and second derivatives. Figure 2 represents the conductometric titration of 6mg sibutramine HCl applying the

numerical first derivative plot ($\Delta k/\Delta V$) and numerical second derivative plot ($\Delta^2 k/\Delta V^2$) as an example.

A curve break is noted at a drug-reagent molar ratio of 1:1. This molar ratio was ascertained through spectrophotometric method [41]. Investigations were carried out to establish the most favorable conditions to attain end point. The optimum conditions for performing the titration in a quantitative manner were elucidated as described below.

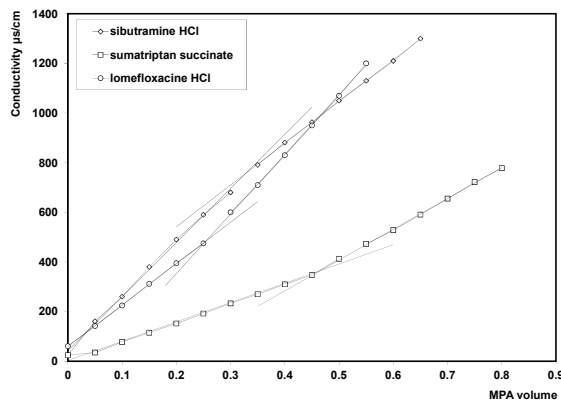


Figure 1. Conductometric titration of 6 mg sibutramine HCl, sumatriptan succinate and lomefloxacin HCl against MPA.

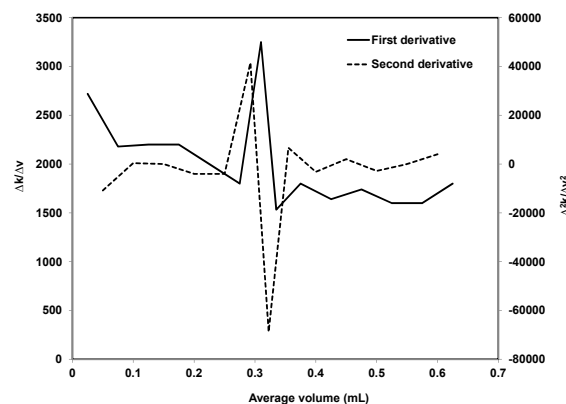


Figure 2. Conductometric titration of 6mg sibutramine HCl applying the numerical first derivative plot ($\Delta k/\Delta V$) and numerical second derivative plot ($\Delta^2 k/\Delta V^2$).

3.1. Effect of solvent

Different solvents were tried to obtain the best results as distilled water, ethanol, methanol, acetone, ethanol-water (50%, v:v) mixture, methanol-water (50%, v:v) mixture and acetone-water (50%, v:v) mixture. Preliminary experiments showed that aqueous media was the most suitable for successful results.

3.2. Reagent's concentration

The reagent concentration in each titration must be not less than ten times that of the drug solution in order to minimize the dilution effect on the conductivity through the titration. Different concentrations of molybdophosphoric acid solution were tried ranging from 1.25×10^{-2} to 6×10^{-2} molar solution. The optimum concentration of the reagent was 3×10^{-2} M for sumatriptan succinate and 6×10^{-2} M for both sibutramine HCl and lomefloxacin HCl.

Table 1. Solubility product constants and other functions related to precipitation of the cited drugs using MPA.

Ion associate	Solubility (S) mol/L	Ksp	K = 1/Ksp
Sibutramine HCl-MPA	4.18×10^{-11}	1.75×10^{-21}	5.71×10^{20}
Sumatriptan succinate-MPA	1.5×10^{-11}	2.33×10^{-22}	4.30×10^{21}
Lomefloxacin HCl-MPA	9.5×10^{-12}	9.02×10^{-23}	1.11×10^{22}

Table 2. Determination of the studied drugs using MPA in pure form *.

Items	Sibutramine HCl		Sumatriptan succinate		Lomefloxacin HCl	
	Taken (mg)	Recovery % *	Taken (mg)	Recovery % *	Taken (mg)	Recovery %*
5	100.38	100.38	5	99.26	5	99.07
6	100.63	100.63	6	100.00	6	98.84
7	100.81	100.81	7	100.00	7	99.67
8	100.95	100.95	8	99.22	8	100.00
9	100.21	100.21	9	100.00	9	99.48
10	100.57	100.57	10	99.26	10	98.84
15	100.00	100.00	15	100.00	15	100.00
Mean	100.51		99.68		99.41	
N	7		7		7	
S.D.	0.334		0.403		0.506	
R.S.D.	0.332		0.404		0.509	
S.E.	0.118		0.142		0.179	
V	0.111		0.162		0.256	

* Mean: the mean of three different experimental; N: number of samples; S.D.: the standard deviation; R.S.D.: the relative standard deviation; S.E.: the standard error; V.: the variance.

Table 3. Statistical data for the determination of the studied drugs using conductometric method compared with reference spectrophotometric methods.

Items	Sibutramine HCl		Sumatriptan succinate		Lomefloxacin HCl	
	Reference method	Proposed method	Reference method	Proposed method	Reference method	Proposed method
Mean \pm S.D.	101.01 \pm 0.663	100.51 \pm 0.334	100.13 \pm 0.254	99.68 \pm 0.403	99.81 \pm 0.326	99.41 \pm 0.506
N	5	7	4	7	8	7
V	0.44	0.111	0.064	0.162	0.107	0.256
t		1.734 (2.228) *		1.993 (2.262) *		1.757 (2.170) *
F		3.96 (4.53) *		2.531 (4.76) *		2.39 (4.28) *

* Theoretical values of t and F at $p = 0.05$.

3.3. Solubility products of ion-associates

Ion-associates formation is the main controlling factor in many chemical reactions, such as precipitation reactions, where the degree of feasibility of titration depends on the degree of completeness of the precipitation reaction. The equilibrium constant of the precipitation reaction is inversely proportional to the solubility product whereas the smaller the solubility product of the formed ion-associate, the sharper the end point. The solubility product together with the parameter related to ion associates of the investigated drugs were listed in (Table 1).

The equilibrium constant values were very high, indicating the high degree of completeness of the ion-associate formation reactions. At equilibrium, the solubility of the undissociated ion-associates in water (the intrinsic solubility) was omitted as this term makes a negligible contribution to the total solubility because the ion-associates are sparingly soluble in water and their saturated solutions are therefore very dilute.

3.4. Validation of the studied method

The results of drug determination presented in (Table 2) showed good recoveries and low standard deviation. This means that the proposed method is satisfactorily accurate, precise and reproducible. The optimum concentration ranges were 100-300 $\mu\text{g/mL}$ for the three drugs indicating wide linear range.

Student's t-test and variance ratio F-test, were applied to the results obtained compared with that obtained from reference one [6,16,27]. The results showed that there is no significant difference between the proposed and reference method. The results of different statistical data are shown in Table 3.

3.5. For application (standard addition technique)

Standard addition technique was used for the determination of the cited drugs in their formulations in which the end point of authentic = End point of (authentic + End point of tablets) - End point of tablets). Satisfactory results (Table 4) were obtained for the recoveries of the drugs and were in good agreement with the label claimed, indicating high selectivity of the methods towards the studied drugs. Thus, other excipients and binders in the formulations didn't interfere in the determination.

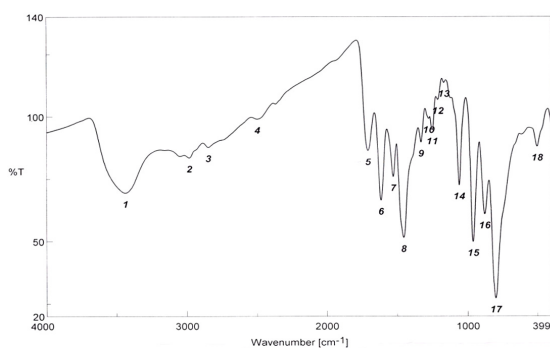
3.6. IR Spectrum

IR spectrum of ion pair of molybdophosphoric acid and some drugs were done [33], ion pairing of lomefloxacin HCl was investigated as an example of the reaction by comparing IR, spectrum of the formed ion associate with those of the free ligand. The IR spectrum of lomefloxacin HCl displays characteristic bands at 3428, 3054, 2933, 1724, 1617 and 1532 cm^{-1} assigned to νOH , νCH (aromatic), νCH (aliphatic), $\nu\text{C}=\text{O}$ (acid), $\nu\text{C}=\text{O}$ (pyridone) and $\nu\text{C}=\text{C}$, respectively. On the other hand, the IR spectrum of MPA had two characteristic bands at 1622 and 1065 cm^{-1} due to ν_{sym} ($\text{P}=\text{O}$) and ν_{as} ($\text{P}=\text{O}$) and a strong, broad peak at 3396 cm^{-1} due to ν (OH) vibration; respectively. The IR spectra of the formed ion associate shows both bands corresponding to drug and MPA as νCH (aliphatic) at nearly (2983 cm^{-1}), $\nu\text{C}=\text{O}$ (pyridone) at nearly 1615 cm^{-1} and also stretching vibrations of $\text{C}=\text{O}$ that shifted to a lower frequency by ~ 17 cm^{-1} . In addition, the peak due to ν_{sym} ($\text{P}=\text{O}$) at nearly 1059 cm^{-1} . The above arguments indicate that an ion associate was formed (Figure 3).

Table 4. Application of the proposed method for the analysis of the studied drugs in their formulations.

Formulation	Taken (mg)	Added (mg)	Recovery % *
Smartan® tablet	5	-	100.76
Sibutramine HCl monohydrate		5	100.76
10 mg/tablet		6	101.27
		7	101.63
		8	100.95
		9	100.21
		10	101.52
Mean * ± S.D.			101.06±0.530
Sibotrim®capsule	5	-	99.24
Sibutramine HCl monohydrate		5	98.48
15 mg/capsule		6	100.95
		7	100.00
		8	99.52
		9	100.27
		10	100.00
Mean * ± S.D.			99.87±0.826
Slimax®capsule	5	-	101.52
Sibutramine HCl monohydrate		5	100.00
15 mg/capsule		6	99.05
		7	98.37
		8	98.10
		9	99.79
		10	99.24
Mean * ± S.D.			99.09±0.754
SUMIGRAN® tablet	5	-	99.26
Sumatriptan Succinate,		5	99.26
25 mg/tablet		6	101.24
		7	99.12
		8	99.22
		9	99.17
		10	99.26
Mean * ± S.D.			99.55±0.832
LOMEX®tablet	5	-	97.67
Lomefloxacin HCl		5	100.00
400 mg/tablet		6	98.84
		7	101.33
		8	101.74
		9	99.48
		10	100.00
Mean * ± S.D.			100.23±1.104
ORCHACIN® eyedrop	5	-	99.07
Lomefloxacin HCl (3 mg/mL)		5	100.93
		6	101.55
		7	100.33
		8	100.87
		9	100.00
		10	101.63
Mean * ± S.D.			100.89±0.647

*Average of three different experiments.

**Figure 3.** IR spectra of Lomefloxacin HCl, PMA ion associate.

4. Conclusion

The simple and rapid procedures described in this manuscript can be considered as an alternative to the more complex and expensive methods for assay of the cited drugs. There is no need for complicated devices, expensive chemicals or complicated steps like extraction, heating or using buffer system. Numerical derivatization (first and second derivative) of the data shows more accurate results compared to classical

one. The proposed procedure is very simple, accurate and can be readily adopted for routine analysis in quality control laboratories. Additionally, the proposed method can be easily applied for the determination of the cited drugs in pharmaceutical formulations.

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References

- [1]. Sweetman, S. C. Martindale-The Complete Drug Reference, 36th edition, The Pharmaceutical Press, London, 2009.
- [2]. Ariburnu, E.; Uludag, M.; Yalcinkaya, H.; Yesilada, E. *J. Pharmaceut. Biomed.* **2012**, *64*-65, 77-81.
- [3]. Chorilli, M.; Bonfilio, R.; Chicarelli, R. S.; Salgado, H. R. N. *Anal. Method.* **2011**, *3*, 985-990.
- [4]. El-Gohary, N. A.; El-Nashar, R. M.; Aboul-Enien, H. Y. *Anal. Lett.* **2011**, *44*, 241-257.
- [5]. Valarmathi, R.; Karpagam, K. S. S.; Revanthi, R. *The Indian Pharm.* **2004**, *3*, 71-72.
- [6]. Maluf, D. F.; Farago, P. V.; Barreira, S. M. W.; Pedrosa, C. F.; Pontarolo, R. *Lat. Am. J. Pharm.* **2007**, *26*, 909-912.
- [7]. The United States Pharmacopoeia 30, National Formulary 25, US Pharmacopoeial Convention, Rockville, MD, 2007.

- [8]. Cheng, K. N.; Redrup, M. J.; Barrow, A.; Williams, P. N. *J. Pharm. Biomed. Anal.* **1998**, *17*, 399-408.
- [9]. Tipre, D. N.; Vavia, P. R. *Indian Drugs*. **1999**, *36*, 501-505.
- [10]. Riddhi, G.; Dharamsi, A. *J. Drug Delivery Ther.* **2013**, *3*, 93-97.
- [11]. Sagar, K.; Alvarez, J. M. F.; Hua, C.; Smyth, M. R.; Munden, R. *J. Pharmaceut. Biomed.* **1992**, *10*, 17-21.
- [12]. Ramu, B. K.; Raghobabu, K. *Int. J. Appl. Biol. Pharm. Technol.* **2011**, *2*, 86-91.
- [13]. Ramu, B. K.; Raghobabu, K. *Int. J. Pharm. Biomed. Sci.* **2010**, *1*, 49-52.
- [14]. Ramu, B. K.; Raghobabu, K. *Int. J. Pharm. Pharm. Sci.* **2011**, *3*, 175-178.
- [15]. Ramu, B. K.; Raghobabu, K. *Der Pharma Chemica* **2011**, *3*, 223-228.
- [16]. Satyanarayane, K. V. V.; Rao, P. N. *E-J. Chem.* **2011**, *8*, 269-275.
- [17]. Ayad, M. M.; Abdellatef, H. E.; Hosny, M. M.; Kabil, N. A. *Zag. J. Pharm. Sci.* **2011**, *20*, 9-21.
- [18]. Chitlang, S. S.; Ranjane, M.; Wankhede, S. B.; Sakarkar, D. M. *Int. J. Pharm. Tech.* **2009**, *1*, 844-851.
- [19]. Sun, H.; Li, L.; Su, M. *Chromatographia* **2008**, *67*, 399-405.
- [20]. Vilchez, J. L.; Araujo, L.; Prieto, A.; Navalon, A. *J. Pharmaceut. Biomed.* **2001**, *26*, 23-29.
- [21]. Limig, D.; Qingqin, X.; Jianmei, Y. *Pharmaceut. Biomed.* **2003**, *33*, 693-698.
- [22]. Du, L. M.; Yang, Y. Q.; Wang, Q. M. *Anal. Chim. Acta* **2004**, *516*, 237-243.
- [23]. Geffken, D.; Salem, H. *Am. J. Appl. Sci.* **2006**, *3*, 1952-1960.
- [24]. Kaur, K.; Singh, B.; Malik, A. K. *Thai J. Pharm. Sci.* **2010**, *34*, 58-66.
- [25]. Lu, J. Q.; Jin, F.; Sun, T. Q.; Zhou, X. W. *Int. J. Biol. Macromol.* **2007**, *40*, 299-304.
- [26]. Salem, H. *Am. J. Appl. Sci.* **2005**, *2*, 719-729.
- [27]. Gomes, G. C.; Salgado, H. R. N. *Acta Farmaceutica Bon.* **2005**, *24*, 406-408.
- [28]. Askal, H.; Refaat, I.; Darwish, I.; Marzouq, M. *Chem. Pharm. Bull.* **2007**, *55*, 1551-1556.
- [29]. Issa, Y. M.; Abdel-Gawad, F. M.; Abou-Table, M. A.; Hussein, H. M. *Anal. Lett.* **1997**, *30*, 2071-2084.
- [30]. Amin, A. S.; Dessouki, H. A.; Agwa, I. A. *Arabian J. Chem.* **2008**, *1*, 209-215.
- [31]. Suhagia, B. N.; Shah, S. A.; Rathod, I. S.; Patel, H. M.; Rao, Y. M. *Indian J. Pharm. Sci.* **2006**, *68*, 247-249.
- [32]. Darwish, I. A.; Sultan, M. A.; Al-Arfaj, H. A. *Int. J. Res. Pharm. Sci.* **2010**, *1*, 43-50.
- [33]. Elazazy, M. S.; Elmasry, M. S.; Hassan, W. S. *Int. J. Electrochem. Sci.* **2012**, *7*, 9781-9794.
- [34]. Maria, S.; Dorneanu, V.; Ghimicescu, G. *Talanta* **1997**, *24*, 140-142.
- [35]. Issa, Y. M.; Abdel-Ghani, N. T. *Microchim. Acta* **1999**, *132*, 83-88.
- [36]. Issa, Y. M.; Youssef, A. F. A.; Mutair, A. A. *Il Farmaco* **2005**, *60*, 541-546.
- [37]. Lingane, J. J. *Electroanalytical Chemistry*, 2nd Edition, Interscience, New York, 1958.
- [38]. Andropov, L. L. *Theoretical Electrochemistry*, Izdatelstvo Mir: Moscow, 1977.
- [39]. Anis, S. M.; Hosny, M. M.; Abdellatef, H. E.; El-Balkiny, M. N. *E-J. Chem.* **2011**, *8*, 1784-1796.
- [40]. Issa, Y. M.; Shoukry, A. F.; El-Nashar, R. M. *J. Pharmaceut. Biomed.* **2001**, *26*, 379-386.
- [41]. Ayad, M. M.; Abdellatef, H. E.; Hosny, M. M.; Kabil, N. *Int. J. Pharm. Biomed. Res.* **2012**, *3*, 121-126.