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Conductometric Determination of Commercial Chloride Drugs and Pharmaceuticals using Ammonium Molybdate as Precipitating Agent

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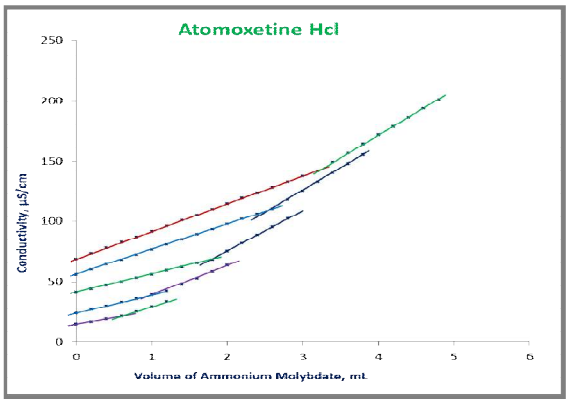
ABSTRACT

Simple, sensitive, accurate, cost effective and precise Conductometric method for quantitative determination of Five Cationic commercial drugs viz. Atomoxetine HCl(ATM), Ciprofloxacin HCl(CIP), Epinastine HCl(EPN), Itopride HCl(ITP) and Mebeverine HCl(MEB) were developed. The method was based on the formation of insoluble salt ($[Drug]_6Mo_4O_7$) between the Drug Cation of Drug Molecules and Molybdate anion of Ammonium Molybdate(AMB) solutions. Aliquots of standard drug solution (2.5-15 mL) which is containing 2.5-15 mg pure drug and 2.5x 10^{-3} M Ammonium Molybdate taken in burette was used for titration. The observed conductance reading was taken and corrected conductance i.e.Ω^{-1}correct = Ω^{-1}obs [V1+V2/V1]. A graph of corrected conductivity Vs volume of added titrant was constructed and the endpoint was determined graphically at the intersection of two lines. The amount of drugs under study was calculated according to the equation for amount of drug = V.M.R /N. The proposed method was successfully applied in the determination of the above five metal anionic Drugs and Pharmaceutical formulations, with results in close agreement at a 95% confidence level with those obtained using spectrophotometric determination method.

Graphical Abstract



Conductometric curves of 2mg, 4mg, 6mg, 8mg and 10mg of ATM with AMB

Keywords: Anionic Drugs, Conductometric, Determination, Ammonium Molybdate, Hydrochloride.

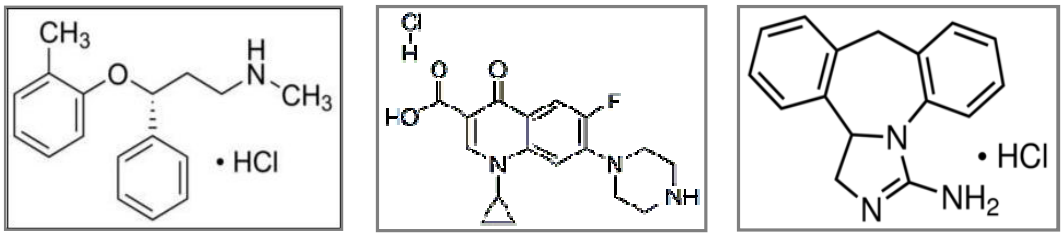
INTRODUCTION

Atomoxetine is chemically, (-)-N-methyl-3-phenyl-3-(o-tolyloxy) propan-1-amine hydrochloride) [Fig.1a]. ATM is widely used in the treatment of attention-deficit hyperactivity syndrome. It is act as a selective norepinephrine reuptake inhibitor. An extensive literature survey shown that some of the analytical methods were developed for the determination of CIP such as Reverse phase-High Performance Liquid Chromatography (RP-HPLC) [**1-3**], High Performance Thin Layer Chromatography (HPTLC) [**4**], Liquid Chromatography(LC) [**5**], UV-Spectrophotometry [**6-8**].

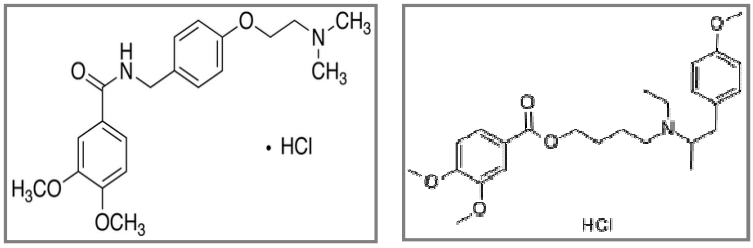
Ciprofloxacin is chemically, 1-Cyclopropyl-6-fluoro-1, 4-di hydro-4-oxo-7-(pi perazinyl-1)-3-quinolone and carboxylic acid (Fig.1b). It is a flouroquinolone, antibiotic drug. CIP recommended for prevention of bacterial toxicities. It functions by inhibiting DNA gyrase, gastrointestinal and abdominal infections. Some of the analytical methods were developed for the determination of CIP such as high performance liquid chromatography- Mass Spectroscopy [**9-11**], UV- Spectrophotometry [**12-16**], Spectrofluorimetry [**17**], NIR Spectroscopy [**18**], Atomic absorption spectroscopy [**19-20**] and Raman Spectroscopy [**21**].

IUPAC name of Epinastine hydrochloride is 3-amino-9, 13b-dihydro-1H-dibenz(c,f) imidazo (1,5-a)] azepine hydrochloride (Fig.1c). It is a selective H1-receptor antagonist and also has an anti-allergic effect by inhibiting the release of allergy-inducing substances such as histamine. A thorough survey literature shown that, several analytical techniques were developed for quantification of Epinastine HCl viz. HPLC [**22**], HPLC-UV-Spectrophotometry [**23**], HPLC-UV-Derivative Spectrophotometry [**24**].

Itopride hydrochloride chemically known as N-[[4-(2-dimethyl amino ethoxy) phenyl] methyl]-3,4-di methoxy benzamide hydrochloride (Fig.1d). ITP is a gastroprokinetic negotiator, it raises the acetylcholine which is inhibiting dopamineD2 receptor and results in increasing of gastrointestinal problems. Some analytical methods for determination of Itopride HCl are reported in the literature such as RP-HPLC [**25-30**], HPTLC [**31**], LC-MS [**32**], Chromatography [**33**], Spectroflurometry-HPLC [**34**], Spectrophotometry-HPLC35, UV-Spectrophotometry [**36-42**], Extractive Spectrophotometry [**43**].



a. Structure of ATM **b.** Structure of CIP **c.** Structure of EPN



d. Structure of ITP **e.** Structure of MEB

Figure 1. Drug Structures

Mebeverine hydrochloride is included in the group of anti-spasmodic drugs of muscular tropic pharmaceuticals (Fig.1e). MEB is mainly used to treat bowels irritable syndrome and diarrhea. MEB was determined by many analytical methods, such as RP-HPLC [**44-48**], HPLC [**49-52**], TLC [**53**], Chromatography [**54-55**], UV-Spectrophotometric methods [56-60], Ultra performance Liquid Spectroscopy [**61**], HPTLC [**62**], NMR [**63**], Extractive Spectrophotometry [**64**], Colorometry [**65**] and Chemiluminiscence [**66**].

Through survey of literature on the above mentioned anionic drugs revealed that Conductometric determination based on the use of Ammonium Molybdate as Precipitating agent [**69-70**] have not been yet reported. The present work is an attempt to develop accurate, simple, sensitive, and cost effective method for the quantitative analysis of the above drugs.

MATERIALS AND METHODS

Instruments: Conductance for the study required has been measured by using Systronics Conductometer 306 portable conductivity /TDS meter. AC-C10 dipped type Conductometer Cell was used with a cell constant K cell of 0.97 in the study. A Dhona 200 electrical balance which is having single pan is used for weighing all the samples.

Reagents: All reagents used were of analytical-reagent grade and distilled water was used throughout the investigation. 0.309gm of Ammonium Molybdate is dissolved in 100ml double distilled water to get 2.5x 10^{-3} M of Ammonium Molybdate. 7.54 gm. of KCl was dissolved in 1000ml double distilled water to get 0.1M KCl. Standard drug solution (200 µg mL^{-1}) was prepared by dissolving 20 mg of drug with distilled water to the mark in 100 ml standard flask. The stock solution was diluted appropriately to get the working concentration.

Method development: Aliquots of standard drug solution (2.5-15 mL) containing 2.5-15 mg pure drug were transferred to 50 ml calibrated flasks volumes were made up to the mark using double distilled water. The contents of the flask were transferred to a beaker. The conductivity cell was immersed in it and 0.0025 M Ammonium Molybdate taken in burette was used for titration. The conductance reading was taken subsequent to each addition of titrant after stirring for 2 min and corrected for dilution effects by means of the following equation, assuming that conductivity is a linear function of dilution.

$$\Omega\text{-}1 \text{ correct} = \Omega\text{-}1\text{obs } [V1+V2/V1]$$

Where Ω-1correct is the corrected electrolytic conductivity, Ω-1obs is the observed electrolytic conductivity, V1 is the initial volume and V2 is the volume of reagent added. A graph of corrected conductivity vs. volume of added titrant was constructed and the endpoint was determined graphically at the intersection of two lines.

The amount of drugs under study was calculated according to the following equation

$$\text{Amount of drug} = V.M.R / N$$

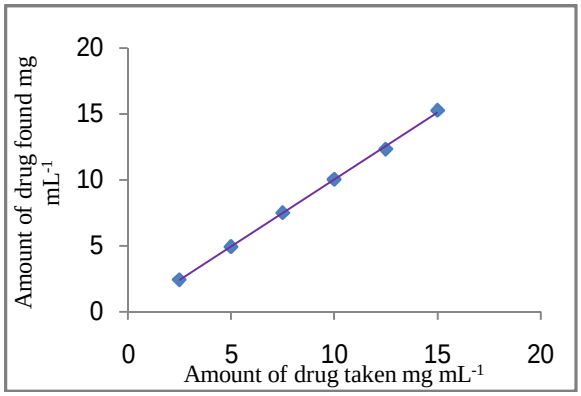
Where, V is volume (mL) of titrant, M is molecular weight of drug, R is molar concentration of titrant and N is number of moles of titrant consumed by one mole of drug.

Optimization of the parameters of quantification

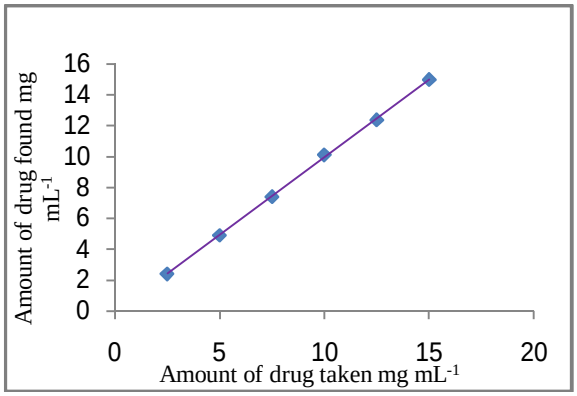
Effect of Solvent: Titrations in different solvents were performed to obtain the best results 1) Drug and reagent in ethanolic solution 2) Drug and reagent in acetone solution 3) Drug and reagent in methanol solution 4) Aqueous solutions of both drug and reagent. Preliminary experiments showed

that procedure in aqueous media was the most suitable solvent for best results which gives higher conductance and most sharp endpoint.

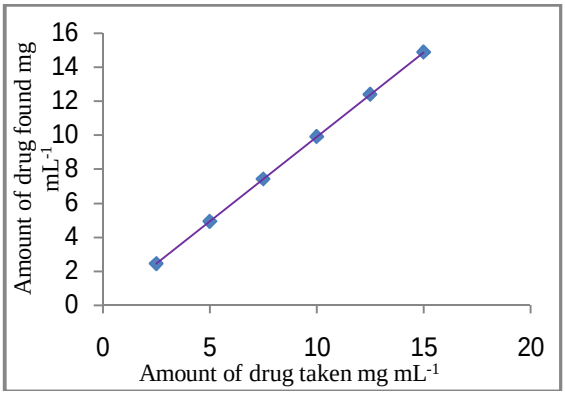
Effect of reagent concentration: A fixed weight of investigated drugs were dissolved in 25 mL bi distilled water and titrated against $1x10^{-3}$, $1.5x10^{-3}$and $2.5x10^{-3}M$ Ammonium Molybdate solution. The results indicated that, titrant solutions lower than $2.5x10^{-3}M$ are not suitable for Conductometric titrations as the conductance readings were unstable, more time was needed to obtain constant conductance values and inflection at the end point was very poor. So, the reagent concentration must be not less than ten times that of the drug solution in order to minimize the dilution effect on the conductivity throughout the titration. The optimum concentration of Ammonium Molybdate is $2.5x10^{-3}M$ to get a highly stable conductance reading after 2 minutes of mixing.



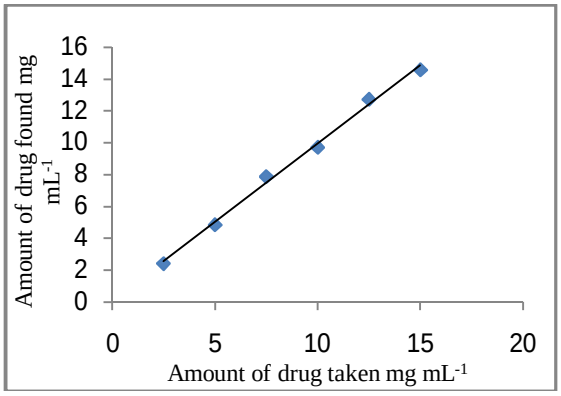
a. Calibration graph of ATM.



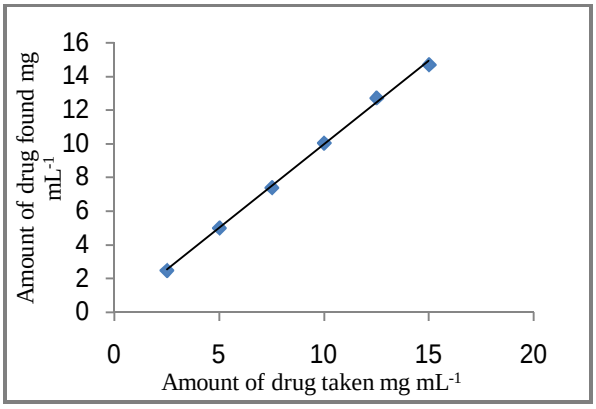
b. Calibration graph of CIP.



c. Calibration graph of EPN.



d. Calibration graph of ITP.



e. Calibration graph of MEB.

Figure 2. Calibration graphs of ATM, CIP, EPN, ITP and MEB.

Effect of Temperature: The experiment was performed at room temperature. The rise in temperature to 40^0C showed that the conductivity of the whole solution increases, as the temperature increases.

Linearity: In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression of observed drug concentration against the volume of Ammonium Molybdate was calculated. Student's t-test (at 95% confidence level) was applied to the slope of the regression line and showed that it did not differ significantly from the ideal value of unity. The standard deviation (SD) can be considered satisfactory, at least for the level of concentrations examined (Figure 2).

Accuracy and precision: To assess the precision, each experiment was repeated at least four times and accuracy is estimated in terms of percent recovery and percent RSD. Excellent per cent recovery and RSD being less than 2 for each drug demonstrates accuracy and precision of the methods. Further t-test and F-test values have also been calculated using a standard reference method. The t-test and F-test values are less than their permissible range indicating high accuracy and precision of the methods. LOD and LOQ can be determined for each drug.

Procedure for analysis of Pharmaceuticals

Atomoxetine Hydrochloride: Twenty tablets of Axepta each containing 10 mg were collected and crushed into powder. 150 mg equivalent of Atomoxetine Hydrochloride was weighed from tablet powder and transferred into 150 mL volumetric standard flask, completely dissolved in bi distilled water by sonication technique for 30 minutes and filtered with Eisco qualitative filter paper. After that the Solution converted to working concentration on dilution with bi distilled water for conductometric titration of Atomoxetine Hydrochloride solution with ammonium molybdate reagent.

Ciprofloxacin Hydrochloride: Two tablets (Lincip 500 mg) were collected and crushed into powder. 200 mg equivalent of Ciprofloxacin Hydrochloride was weighed from tablet powder and transferred into 200 mL volumetric standard flask, completely dissolved in bi distilled water by sonication technique for 30 minutes and filtered with Eisco qualitative filter paper. After that the Solution converted to working concentration on dilution with bi distilled water for conductometric titration of Ciprofloxacin Hydrochloride solution with ammonium molybdate reagent.

Epinastine Hydrochloride: Twenty five tablets of Alesion -10 mg were collected and crushed into powder. 200 mg equivalent of Epinastine hydrochloride was weighed from tablet powder and transferred into 200 mL volumetric standard flask, completely dissolved in bi distilled water by sonication technique for 30 min and filtered with Eisco qualitative filter paper. After that the Solution converted to working concentration on dilution with bi distilled water for conductometric titration ofEpinastine Hydrochloride solution with ammonium molybdate reagent.

Itopride HCl: Ten tablets of Itopride50 mg were collected and crushed into powder. 200 mg equivalent of Itopride HCl was weighed from tablet powder and transferred into 200 mL volumetric standard flask, completely dissolved in bi distilled water by sonication technique for 30 minutes and filtered with Eisco qualitative filter paper. After that the Solution converted to working concentration on dilution with bi distilled water for conductometric titration of Itopride hydro chloride solution with ammonium molybdate reagent.

Mebeverine Hydrochloride: Three tablets of Normaxin each containing 200 mg were collected and crushed into powder. 200 mg equivalent of Mebeverine Hydrochloride was weighed from tablet powder and transferred into 200 mL volumetric standard flask, completely dissolved in bi distilled water by sonication technique for 30 minutes and filtered with Eisco qualitative filter paper. After that, the Solution converted to working concentration on dilution with bi distilled water for conductometric titration of Mebeverine Hydrochloride solution with ammonium molybdate reagent.

RESULTS AND DISCUSSION

Conductometric measurements can be used in quantitative precipitation titrations in which the conductance of the solution varies before and after the equivalence point, so that two intersecting lines can be drawn to indicate the end-point (Figures 3-7). On using Ammonium Molybdate as a titrant for the determination of studied drugs, Drug Cation and Molybdate Anion is precipitated leading to a straight line during the first segment of the titration curve. The second segment of this curve corresponds to the excess of Ammonium Molybdate (Table 1 and 2).

To know the validity of the proposed method, a statistical analysis of the data obtained from its application on drugs in the pure form and in pharmaceutical formulations was performed. Results show that the proposed method is satisfactorily accurate, precise and reproducible over a concentration range of 2.5-15 mg for all the studied drugs (Table 3 and 4).

Table 1. Conductometric determination of the drugs with Ammonium Molybdate as reagent and calculation of regression and Analytical parameters.

Name of the Drugs/Analytical Parameter	ATM	CIP	EPN	ITP	MEB
Concentration of drug (mg mL^{-1})	2.5-15	2.5-15	2.5-15	2.5-15	2.5-15
Sandell's sensitivity (mg/cm^2)	0.001	0.001	0.001	0.001	0.001
Limit of detection ($mgmL^{-1}$)	8.6×10^{-4}	0.00223	8.3×10^{-4}	0.00512	1.96×10^{-4}
Limit of quantification ($mgmL^{-1}$)	2.6×10^{-4}	6.75×10^{-3}	0.0025	1.55×10^{-4}	5.9×10^{-3}
Slope, b	1.013	1.005	0.995	0.985	0.99
Intercept, a	0.115	0.081	0.0429	0.079	0.0722
Correlation co-efficient, R^2	0.999	0.999	1	0.995	0.998
Regression equation Y*	1.0134X - 0.1149	1.0047X – 0.081	.9945X –0.0429	0.985X + 0.079	0.9904X + 0.0722
SD of intercept curve(Sa)	2.65×10^{-4}	7×10^{-4}	2.5×10^{-4}	1.53×10^{-3}	5.9×10^{-4}

Table 2. Precision and accuracy parameters evaluation by recovery studies method for quantitative determination of pure drugs by Conductometric titration with Ammonium Molybdate.

Name of the Drug Sample	Drug Taken (µg mL^{-1})	Drug Found (µg mL^{-1})	Percentage of Error	Percentage of drug Recovery	Regression SD of drug	Mean ± SD of Proposed method
ATM	5	4.99	0.2	99.8		
	10	10.03	0.3	100.3	0.217	99.99±0.217
	12	11.99	0.088	99.91		
	14	13.99	0.07	99.92		
CIP	6	5.96	0.67	99.33		
	12	11.95	0.42	99.59	0.310	99.68±0.309
	13	12.97	0.23	99.77		
	15	15.01	0.07	100.07		
EPN	5	4.96	0.8	99.2		
	10	9.98	0.2	99.8	0.406	99.76±0.404
	12	12.02	0.17	100.13		
	15	14.98	0.13	99.89		
ITP	6	5.98	0.33	99.67		
	8	8.01	0.13	100.13	0.263	99.97±0.263
	12	12.03	0.25	100.25		
	14	13.98	0.14	99.86		
MEB	7	6.98	0.29	99.71		
	10	10.01	0.1	100.1	0.160	99.89±0.160
	13	12.98	0.15	99.85		
	15	13.98	0.13	99.87		

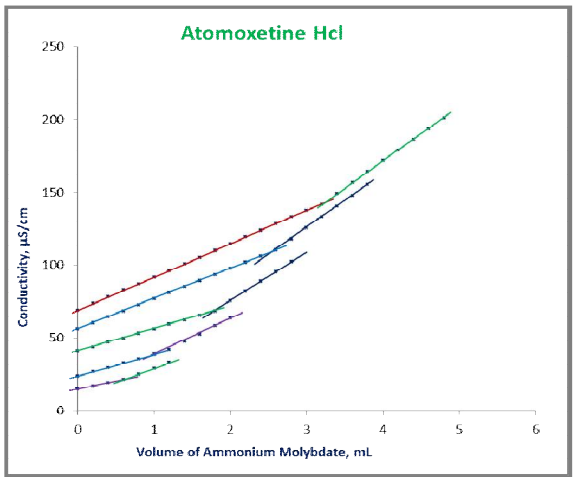


Figure 3. Conductometric curves of 2mg, 4mg, 6mg, 8mg and 10mg of ATM with AMB.

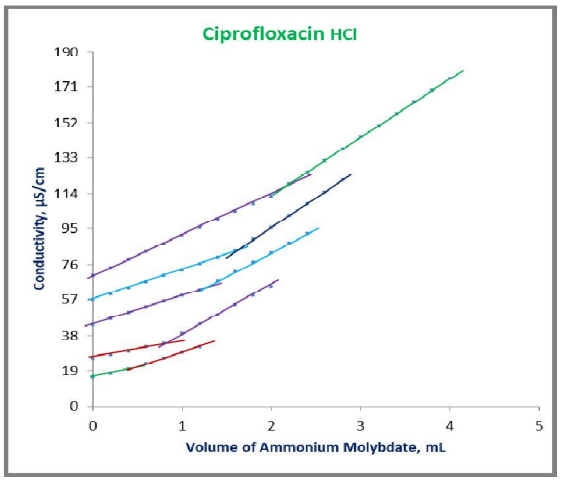


Figure 4. Conductometric curves of 2mg, 4mg, 6mg, 8mg and 10mg of CIP with AMB.

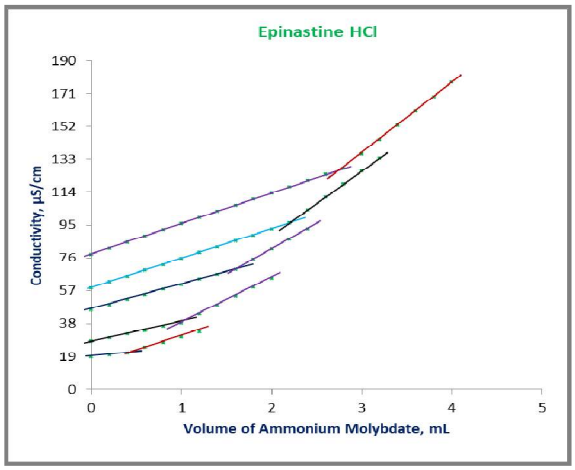


Figure 5. Conductometric curves of 2mg, 4mg, 6mg, 8mg and 10mg of EPN with AMB.

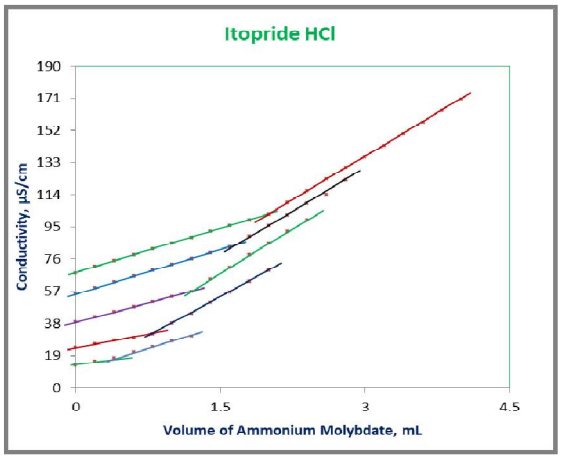


Figure 6. Conductometric curves of 2mg, 4mg, 6mg, 8mg and 10mg of ITP with AMB.

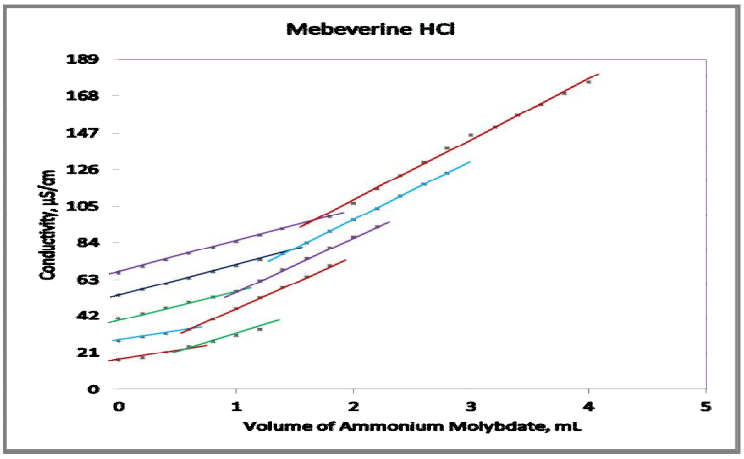


Figure 7. Conductometric titration curves of 2mg, 4mg, 6mg, 8mg and 10mg of MEB with AMB.

Table 3. Precision, accuracy, t-test and F-test evaluation by recovery studies method for quantitative determination of tablets by Conductometric titration with Ammonium Molybdate.

Tablet	Drug Taken (mg mL^{-1})	Drug Found (mg mL^{-1})	% of Error	% of Drug Recovery	Regression SD of drug	Mean± SD (Reference method)	Mean ± SD (Proposed method)
ATM	3	2.96	1.33	98.67			
(Axepta	6	5.98	0.33	99.67	0.645	99.59±0.642	99.4±0.675
10 mg)	9	9.01	0.11	100.11			
	12	11.99	0.08	99.9			
CIP	7	6.98	0.29	99.71			
(Lincip	9	9.01	0.11	100.11	0.219	99.81±0.2193	97.8±0.56
500 mg)	10	9.96	0.4	99.6			
	12	11.98	0.17	99.83			
EPN	3	2.96	1.34	98.66			
(Alesion	5	5.02	0.4	100.4		99.67±0.725	100.2±0.846
10 mg)	9	8.98	0.22	99.78	0.727		
	12	11.98	0.17	99.83			
ITP	6	5.96	0.67	99.33			
(Itopride	7	6.98	0.29	99.71		99.68±0.25	98.6±0.512
50 mg)	11	10.97	0.2	99.8	0.251		
	15	14.99	0.07	99.93			
MEB	4	5.02	0.5	100.5			
(Normaxin	8	7.99	0.12	99.88	0.321	100.02±0.321	99.8±0.73
200 mg)	12	11.98	0.17	99.83			
	15	14.98	0.13	99.87			

Table 4. t-test and F-test evaluation by recovery studies method for quantitative determination of tablets by Conductometric titration with Ammonium Molybdate.

Tablets/ parameter	ATM (Axepta 10 mg)	CIP (Lincip 500 mg)	EPN (Alesion 10 mg)	ITP (Itopride 50 mg)	MEB (Normaxin 200 mg)
t-test	0.0868	1.385	0.207	1.13	1.26
F-test	0.905	0.154	0.734	0.238	0.192

APPLICATION

The Conductometric method used in the quantitative determination of the drugs in pure and Pharmaceutical formulations.

CONCLUSION

The present study described the successful development of new, simple, sensitive, selective, accurate and rapid spectrophotometric method for the accurate determination of drugs each one in its pharmaceutical forms Ammonium Molybdate as precipitating reagent. There is no interference from additives and excipients. The method thus can be used in the determination of these drugs in pure and pharmaceutical formulations. So, it is the good alternative to the reported methods for the determination of these drugs.

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REFERENCES

[1]. Chhabra, Gurmeet, Jain, Chandraprakash, Banerjee, K Saurabh, Development and validation of RP-HPLC method for the determination of Atomoxetine hydrochloride in pharmaceutical dosage forms, *International Journal of Drug Development and Research* **2011**, 3(4), 275-279

[2]. H. Prajapati, R. Raveshiya, J. M Prajapati, RP-HPLC determination of Atomoxetine hydrochloride in bulk and pharmaceutical formulations, *E-Journal of Chemistry*, **2011**, 8(4), 1958-1964.

[3]. Jagadeesh, B. V. V. S, Raju, S. Satyanarayana, Rao, V. Jayathirtha, Rao, J. V. L. N. Seshagiri, Reverse phase HPLC analysis of Atomoxetine in pharmaceutical dosage forms, *Asian Journal of Chemistry*, **2009**, 21(2), 829-833.

[4]. S. S. Kamat, Vele, T. Vinayak, Choudhari, C. Vishal, Prabhune, S. Swarup, HPTLC determination of Atomoxetine hydrochloride from its bulk drug and pharmaceutical preparations, *Asian Journal of Chemistry*, **2008**, 20(7), 5409-5413.

[5]. Kamat, S. Sudhir, Choudhari, B. Vishal,Vele, T. Vinayak, Prabhune, S. Swarup, RP-LC determi nation of Atomoxetine HCl from its pharmaceutical dosage form. Chromatographia 2008, 67(1/2), 143-146.

[6]. Reddy, D. Suresh, E. Yashaswini, Kumar, A. Ashok, A simple assay method development and validation of Atomoxetine hydrochloride in tablets by UV Spectrophotometry, *Indo American Journal of Pharmaceutical Sciences*, **2016**, 3(5), 393-398.

[7]. Pathade, Parag, Pawar, Amol, Gaikwad, Abhijit, Panhalkar, Ashwini, Development and validation of stability indicating UV spectrophotometric method for the estimation of Atomoxetine hydrochloride in bulk and tablet dosage form, *International Journal of Pharma and Bio Sciences*, **2011**, 2(4), 596-602.

[8]. S. K. Koradia, P. T. Shah, R. R. Rana, S. S. Vaghani, S. Pandey, N. P. Jivani, Spectrophotometric determination of Atomoxetine Hydrochloride from its pharmaceutical dosage forms, *Asian Journal of Research in Chemistry*, **2009**, 2(3), 258-259.

[9]. El-Bagarya, Ramzia, El-Zaherb, Asmaa Ahmed, Elkadyb, Ehab, Mandoura, Asmaa Abdelkerim, Simultaneous determination of ciprofloxacin hydrochloride and metronidazole in spiked human plasma by ultra performance liquid chromatography-tandem mass spectroscopy, *Journal of Applied Pharmaceutical Science*, **2016**, 6(3), 41-47.

[10]. Nygren, Olle, Lindahl, Roger, Development of a method for screening spill and leakage of antibiotics on surfaces based on wipe sampling and HPLC-MS/MS analysis, *Journal of ASTM International*, **2011**, 8(6), JAI103544/1-JAI103544/10.

[11]. Kim Hyo-Ji, Seo Kyung-Ah, Kim Hyun-Mi, JeongEun-Sook; Ghim Jong Lyul,Lee Seung Heon, Lee Young Min, Kim Dong Hyun, Shin Jae-Gook, Simple and accurate quantitative analysis of 20 anti-tuberculosis drugs in human plasma using liquid chromatography-electrospray ionization-tandem mass spectrometry, *Journal of pharmaceutical and biomedical analysis*, **2015**,1029-16.

[12]. Raghunath, Malathi, Dhamne, Amol, UV spectrophotometric assay method for determination of ciprofloxacin, tinidazole and dicyclomine in combined tablet formulation using methanol: 0.1N HCl, *European Journal of Biomedical and Pharmaceutical Sciences*, **2015**, 2(4), 1041-1048.

[13]. Naveed, Safila, Naseem, Yusra, Samie, Siddiqua, Khan, Sheerana, Ramzan, Salma, Degradation study of five different brands of ciprofloxacin using UV visible spectrophotometer and their comparative study, *International Research Journal of Pharmacy*, **2014**, 5(3), 189-190, 2.

[14]. Chavan, Gajanan Jalindar, Charya, Swapnali Roshan, Baris, IoanNuw, Patil, Sachin Dhondiram, Development and validation for simultaneous estimation of ciprofloxacin HCL, Doxycycline and Phenazopyridine HCL in combined dosage form by UV method, *American Journal of Pharmacy and Health Research*, **2013**, 1(2), 55-63.

[15]. Nijhu, Rajia Sultana, Development of an assay method for simultaneous determination of ciprofloxacin and naproxen by UV spectrophotometric method, *Stamford Journal of*

Pharmaceutical Sciences, **2011**, 4(1), 84-90.
[16]. Sharma, Rajesh, Pathodiya, Geetam, Mishra, P. Ganesh, Sainy, Jitendra, A novel spectrophotometric methods for quantitative determination of ciprofloxacin hydrochloride and tinidazole in tablets using hydrotropic solubilizing agent, *Journal of Pharmacy Research*, **2011**, 4(3), 859-861.
[17]. Abdel-Hay, H. Mohamed, Hassan, M. Ekram, Gazy, A. Azza, Belal, S. Tarek, Kinetic spectrophotometric analysis and spectrofluorimetric analysis of ciprofloxacin hydrochloride and norfloxacin in pharmaceutical preparations using 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole (NBD-Cl), *Journal of the Chinese Chemical Society (Taipei, Taiwan)*, **2008**, 55(4), 818-827.
[18]. L. Z. Zhao, Y. Guo, Y. Dou, B. Wang, H. Mi, Y. L. Ren, Application of artificial neural networks to the nondestructive determination of ciprofloxacin hydrochloride in powder by short-wavelength NIR spectroscopy, Journal of Analytical Chemistry, **2007**, 62(12), 1156-1162.
[19]. A. L. El-Ansary, W. F. El-Hawary, Y. M. Issa, A. F. Ahmed, Application of ion-pairs in pharmaceutical analysis. Atomic absorption spectrophotometric determination of promazine, chlorpromazine, promethazine, imipramine and ciprofloxacin hydrochlorides with sodium cobaltinitrite, *Analytical Letters*, **1999**, 32(11), 2253-2269.
[20]. A. L. El-Ansary; W. F. El-Hawary, Y. M. Issa, A. F. Ahmed, Ion-pair formation in pharmaceutica analysis. Atomic absorptionspectrophotometric determination of promazine, chlorpromazine, promethazine, imipramine and ciprofloxacin hydrochlorides with potassium ferricyanide, *QuimicaAnalitica (Barcelona)*, **1998,** 17(4), 199-203.
[21]. Navin, V. Chelliah, Tondepu, Chaitanya, Toth, Roxana, Lawson, S. Latev, Rodriguez, D. Jason, Quantitative determinations using portable Raman spectroscopy, *Journal of Pharmaceutical and Biomedical Analysis*, **2017**, 136, 156-161.
[22]. Ubale, B. Milind, Bharad, V. Jagdish, Chaudhary, R. Vilas, A validated stability-indicating HPLC assay method for epinastine HCl in bulk drug, *Journal of Current Chemical and Pharmaceutical Sciences*, **2012**, 2(2), 107-112.
[23]. El-Bagary, I. Ramzia, Boshra, Amal, El-Hakeem, M. Maha, Abdelra'oof, M. Amira, Three analytical methods for determination of epinastine hydrochloride in bulk and in ophthalmic solutions, *Journal of Chemical and Pharmaceutical Research*, 2012, 4(2),1361-1369.
[24]. Dal MolimGhisleni, Daniela, Steppe, Martin, Schapoval, E. S. Elfrides, Development and validation of liquid chromatographic and ultraviolet derivative spectrophotometric methods for determination of epinastine hydrochloride in coated tablets, *Journal of AOAC International*, **2007**, 90(5), 1266-1271.
[25]. Vunnam, Rama Rao, S. N. Sriharsha, V. V. Rajesham, A new validated RP-HPLC method for simultaneous estimation of Itopride and Metformin HCl in bulk formulation, *Pharmacia Lettre*, **2014**; 6(6), 76-81.
[26]. P. Ravisankar, G. Devala Rao, M. Krishna Chaitanya, Ch. Devadas, G. Sudhakar Saibabu, A novel validated RP-HPLC method for the determination of Itopride hydrochloride in bulk and pharmaceutical tablet dosage forms, *International Research Journal of Pharmacy*, **2013**, 4(4), 145-151.
[27]. M. Rama Chandraiah, Y. V. Rami Reddy, RP-HPLC method for estimation of Itopride hydrochloride from tablets dosage form. *Journal of Chemical and Pharmaceutical Research*, 2012, 4(5), 2649-2651.
[28]. R. Gupta, Krishna, B. Chawla, Rajesh, Wadodkar, G. Sudhir, Stability indicating RP-HPLC method for simultaneous determination of pantoprazole sodium and Itopride hydrochloride in bulk and capsule, *Orbital: The Electronic Journal of Chemistry*, **2010**, 2(3), 209-224.
[29]. Shaik Harun Rasheed, Mogili Ramakotaiah, Konda Ravi Kumar, C. H. Nagabhushanam, C. H. M. M. Prasada Rao, Estimation of rabeprazole sodium and Itopride hydrochloride in tablet dosage form using reverse phase high performance liquid chromatography, *E-Journal of Chemistry*, **2011**, 8(1), 37-42.
[30]. D. Umamaheswari, M. Kumar, B. Jayakar, Chatakonda, Rajesh, Method development and validation of Itopride hydrochloride and rabeprazole sodium in pharmaceutical dosage form by

reversed phase HPLC, *Journal of Chemical and Pharmaceutical Research*, **2010**, 2(5), 399-417.

[31]. B. Dhandapani, N. Anjaneyulu, Kumar, K. Vinod, Rasheed, Shaik Harun, M. Ramakotaiah, HPTLC method development and validation for the estimation of rabeprazole sodium and Itopride hydrochloride in tablet dosage form, Research *Journal of Pharmacy and Technology*, **2010**, 3(2), 475-477.

[32]. Bose, Anirbandeep, Bhaumik, Uttam, Ghosh, Animesh, Chatterjee, Bappaditya, Chakrabarty, Uday Sankar, Sarkar, AmlanKanti, Pal, Tapan Kumar, LC-MS Simultaneous determination of Itopride Hydrochloride and Domperidone in Human Plasma. Chromatographia, **2009**, 69(11/12), 1233-1241.

[33]. Kaul, Neeraj, Agrawal, Himani, Maske, Pravin, Rao, Janhavi Ramchandra, Mahadik, KakasahebRamoo, Kadam, S: Shivajirao, Chromatographic determination of Itopride hydrochloride in the presence of its degradation products, *Journal of Separation Science*, **2005**, 28(13),1566-1576.

[34]. Ibrahim, Fawzia, Nasr, Jenny Jeehan, Fourth-derivative synchronous spectrofluorimetry and HPLC with fluorescence detection as two analytical techniques for the simultaneous determination of Itopride and domperidone, Luminescence, **2016**, 31(1), 255-263.

[35]. A. E. El-Gendy, M. A. Mohamed, O. Abd El-Aziz, R, Mahmoud, Novel validated stability-indicating methods for determination of itopride hydrochloride. Analytical Chemistry, *An Indian Journal*, **2011**, 10(4), 254-263.

[36]. Rao, P. V. Lakshmana, C. Rambabu, Use of ion association complex formation for the spectrophotometric determination of Itopride Hcl in bulk and its pharmaceutical preparations, International Journal of Current Pharmaceutical Research, **2017**, 9(1), 81-84.

[37]. Mukherjee, Prosenjit, Bagchi, Anindya, Raha, Anusree, Simultaneous determination and method validation of ranitidine hydrochloride and Itopride hydrochloride by UV-spectrophotometery, African Journal of Pharmacy and Pharmacology, **2015**, 9(33),834-842.

[38]. Gupta, R. Krishna, Chawla, B. Rajesh, Wadodkar, G. Sudhir, Spectrophotometric methods for simultaneous estimation of pantoprazole and Itopride hydrochloride in capsules. Orbital, *The Electronic Journal of Chemistry*, 2010, 2(2), 181-188.

[39]. K. R. R. R.Joshi, R. B Chawla, and S G .Wadodkar, UV spectrophotometric method for the estimation of Itopride hydrochloride in pharmaceutical formulation, *E-Journal of Chemistry*, **2010**, 7(Suppl. 1), S49-S54.

[40]. Felice, C. Shechinah, K. Srinivasulu, Kumar, V. Praveen, Saradhi, S. Vijaya, Visible spectrophotometric determination of Itopride hydrochloride in pharmaceutical formulations. International Journal of Chemical Sciences, **2008**, 6(2), 832-838.

[41]. S. S. Patro, T. K. Panda, Kumar, B. V. V. Ravi, M. E. B. Rao, S. Santra, Spectrophotometric determination of Itopride hydrochloride in bulk and in pharmaceutical dosage forms, *Acta Ciencia Indica, Chemistry*, **2007**, 33(3), 219-221.

[42]. P. Pattanayak, R. Sharma, S. C. Chaturvedi, Simultaneous spectrophotometric determination of rabeprazole Sodium and Itopride HCl, *Analytical Letters*, **2007**, 40(12), 2288-2294.

[43]. G. Smitha, Hussainy, S. Areefulla, P. V. Swamy, Raju, S. Appala, Extractive spectrophotometric determination of Itopride hydrochloride, *Asian Journal of Chemistry*, **2007**, 19(5), 3445-3448.

[44]. M. B. Kekare, M. P. Choukekar, V. V. Vaidya, G. R Singh, Simultaneous RP-HPLC determination of mebeverine HCl and chlorodiazepoxide in pharmaceutical preparations, *Analytical Chemistry An Indian Journal*, **2008**,7(8), 602-605.

[45]. C. S. Jagadeesh, G. P. Senthilkumar, R. Chandan, Method development and validation of mebeverine HCl in bulk drugs by RP-HPLC method, *World Journal of Pharmacy and Pharmaceutical Sciences*, **2017**, 6(4), 1543-1551.

[46]. V. V. Vaidya, G. R. Singh, M. B. Kekare, M. P. Choukekar, Simultaneous RP-HPLC determination of bambuterol HCl and montelukast sodium in pharmaceutical preparations, *Analytical Chemistry An Indian Journal*, **2008**, 7(8), 598-601.

[47]. V. V. Vaidya, A. Y.Desai, P. S. Barde, Roy, M. N. Shikha, K. V. Mangaokar, Simultaneous RP

HPLC determination of bambuterol HCl in pharmaceutical preparations, *Analytical Chemistry An Indian Journa*, **2008**, 7(8), 595-597.

[48]. Arayne, M. Saeed, Sultana, Najma, Siddiqui, Farhan Ahmed, A new RP-HPLC method for analysis of mebeverine hydrochloride in raw materials and tablets, *Pakistan Journal of Pharmaceutical Sciences*, 2005, 18(2), 11-14.

[49]. Elmasry, S. Manal, Blagbrough, S. Ian, Rowan, G.,Michael; Saleh, M. Hanaa, Kheir, AfafAboul, Rogers, J. Philip, Quantitative HPLC analysis of mebeverine ,mesalazine, sulphasalazine and dispersible aspirin stored in a Venalink monitored dosage system with co-prescribed medicines, *Journal of Pharmaceutical and Biomedical Analysis*, **2011**, 54(4), 646-652.

[50]. Radwan, A. Mahasen, Abdine, H. Heba, Aboul-Enein, Y, Hassan, A validated chiral HPLC method for the determination of mebeverine HCl enantiomers in pharmaceutical dosage forms and spiked rat plasma, *Biomedical Chromatography*, **2006**, 20(2), 211-216.

[51]. El-Shaheny, N. Rania, Belal, F. Fathalla, Simultaneous HPLC determination of chlordiazepoxide and mebeverine HCl in the presence of their degradation products and impurities, *Journal of Chemistry*, **2015**, 293719.

[52]. S. Elmasry Manal, S, Blagbrough Ian, G, Rowan Michael, M, Saleh Hanaa, KheirAfafAboul, J. Rogers Philip, Quantitative HPLC analysis of mebeverinemesalazine, sulphasalazine and dispersible aspirin stored in a Venalink monitored dosage system with co-prescribed medicines, *Journal of pharmaceutical and biomedical analysis*, **2011**, 54(4), 646-52.

[53]. El-Ghobashy, R. Mohamed, Abo-Talib, F, Nisreen, Application of derivative ratio and TLC-densitometric methods for determination of a ternary mixture containing metronidazole, diloxanide furoate and mebeverine hydrochloride, Bulletin of the Faculty of Pharmacy (Cairo University), **2008**, 46(1), 75-86.

[54]. Abdelaleem, EglalAdelhamid, Abdelwahab, Nada Sayed, Validated chromatographic and spectrophotometric methods for analysis of some amoebicide drugs in their combined, *Pakistan Journal of Pharmaceutical Sciences*, **2013**, 26(1), 175-183.

[55]. Babu, Mannem Durga, K. Surendrababu, K. Uma, Maheswar, Simultaneous determination of 2-chloro methyl propionate, 1,4-di-bromo butane and para anisic aldehyde in mebeverine hydrochloride API by gas chromatography-mass spectrometric with selected-ion-monitoring mode, *Asian Journal of Pharmaceutical and Clinical Research*, **2016**, 9 (Suppl.2), 168-175.

[56]. Bedair, M. Mona,Korany, A. Mohamed, Ebdel-Hay, A. Mohamed, Gazy, A. Azza, Derivative spectrophotometric determination of glibenclamide mebeverine hydrochloride and clopamide in the presence of their alkaline-induced degradation products, *Analyst (Cambridge, United Kingdom)*, **1990**, 115(4), 449-53.

[57]. M, El-DidamonyAkram, Spectrophotometric determination of benzydamine HCl, levamisole HCl and mebeverine HCl through ion-pair complex formation with methyl orange.Spectrochimica acta, *Part A, Molecular and biomolecular spectroscopy*, **2008**, 69(3), 770-5.

[58]. Abdelwahab, S. Nada, Abdelaleem, A. Eglal, Application of fourier function to double divisor ratio spectra curves for analysis of some amoebicide drugs in their ternary mixtures, *Pharmaceutica Analytica Acta*, **2012**, 3(2), 148.

[59]. El-Didamony, M. Akram, Spectrophotometric determination of benzydamine HCl, levamisole HCl and Mebeverine HCl through ion-pair complex formation with methyl orange, *Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy*, **2008**, 69A(3), 770-775.

[60]. S. I. M. Zayed, Simultaneous determination of Mebeverine hydrochloride and sulpiride using the first derivatives of ratio spectra and chemometric methods, *Analytical Sciences*, **2005**, 21(8), 985-989.

[61]. V. Srinivasan, H. Sivaramakrishnan, B. Karthikeyan, T. S. Balaji, S. Vijayabaskar, Stress degradation studies on mebeverine hydrochloride and development of a validated stability indicating UPLC method, *Journal of Liquid Chromatography & Related Technologies*, **2011**, 34(16), 1631-1644.

[62]. P. S. Barde, Roy, M. N. Shikha, A. Y. Desai, V. Vaidya, K. V. Mangaokar, K.V. Mangaokar, Simultaneous HPTLC determination of bambuterol HCl in pharmaceutical preparations, *Analytical Chemistry an Indian Journal*, **2011,** 10(3), 204-206.
[63]. Blagbrough, S. Ian, Elmasry, S. Manal, Woodman, J. Timothy, Saleh, M. Hanaa, Kheir, AfafAboul, Quantitative determination of mebeverine HCl by NMR chemical shift migration, *Tetrahedron*, **2009**, 65(25), 4930-4936.
[64]. Reddy, M. Narayana, Rao, K.V. Srinivasa, D. G. Sankar, K. Sridhar, Extractive spectrophotometric determination of Mebeverine using Eriochrome black and Alizarin Red S. dian Drugs **1996**, 33(12), 604-606.
[65]. H. Ragab Gamal; S. Elmasry Manal Kheir, Afaf A. Aboul, Utility of 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) for Colorimetric determination of some drugs containing methoxyl groups. Analytical Chemistry, *Analytical Chemistry an Indian Journal*, **2007**, 3(4-6), 140-145.
[66]. A. J. Al Lawati Haider, M. Al DahmaniZeiyana, B, Varma Gouri, O. Suliman FakhrEldin, Photoinduced oxidation of a tris(2,2'-bipyridyl)ruthenium(II)-peroxodisulfate chemiluminescence system for the analysis of mebeverine HCl pharmaceutical formulations and biological fluids using a two-chip device. Luminescence, *the journal of biological and chemical luminescence*, **2014**, 29(3), 275-283.
[67]. P. R. S. Ribeiro, L. Pezza, H. R. Pezza, A simple spectrophotometric method for the determination of captopril in pharmaceutical preparations using ammonium Molybdate, *EcléticaQuímica*, 2010, 35, 3.
[68]. A. Kowalczyk-Marzec, Marzanna Kurzawa, Aleksandra Szydłowska-Czerniak, Edward Szłyk, Conductometric determination of phenothiazine derivatives by precipitation titration, *Chem. Anal., (Warsaw)*, **2004**, 49, 91
[69]. Marzanna Kurzawa, Aneta Jastrzębska, Edward Szłyk, Application of isotachophoretic and conductometric methods for neomycin trisulphate determination, *Chemical Papers*, **2009**, 63(3), 255–260.
[70]. Y. K. Agrawal F. D. Majumdar, Spectrophotometric Determination of Indapamide and Its Formulations Using Ammonium Molybdate Reagent, *Analytical Letters*, **1995**, 28(9, 1619-1627.