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Conductometric Method for Determination of Drugs and Pharmaceuticals by Using Sodium Tetra Phenyl Borate

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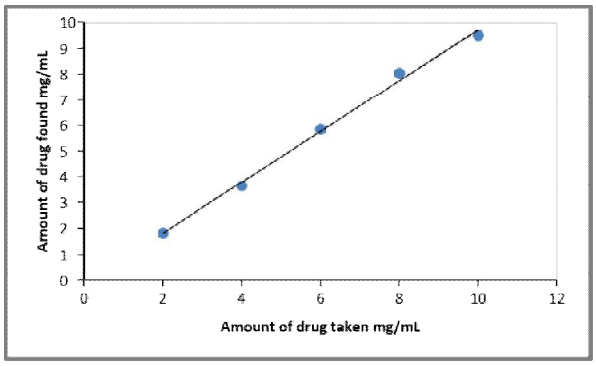
ABSTRACT

Simple, sensitive, accurate, cost effective and precise Conductometric method for quantitative determination of Five cationic salt commercial drugs viz.,Cefepime HCl(CEFE), Ractopamine HCl(RAC), Quetiapine fumarate(QUE), Escitalopram Oxalate (ESC), Sumatriptan Succinate(SUM) were developed. The method was based on the formation of insoluble salt ($[Drug]^{+}[TPB]^{-}$) between the Drug Cation of salt drugs and tetra phenyl borate anion of Sodium tetra phenyl borate(NaTPB) solutions. Aliquots of standard drug solution (1-10 mL) which is containing 1-10 mg pure drug and 0.01 M NaTPB taken in burette was used for titration. The observed conductance reading was taken and corrected conductance i.e. $\Omega^{-1}correct = \Omega^{-1}obs\ [V1+V2/V1]$. 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 cationic Drugs and Pharmaceutical formulations, with results in close agreement at 95% confidence level with those obtained using spectrophotometric determination method.

Graphical Abstract



Calibration graph of CEF.

Keywords: Cationic Drugs, Conductometric, Determination, Sodium tetra phenyl borate.

INTRODUCTION

Conductometric titration is mainly measures the conductance of ions present in the solution. Conductance decreases when more mobile ion replaced by less mobile ion and increases when less mobile ion is replaced by more mobile ion. The end point of titrations is determined from the intersection points of two straight lines obtained during conductometric titrations.

Some HCl, fumarate and Succinate containing drugs form precipitates with NaTPB and so the applicability of conductometric titration of these drugs with the mentioned reagents, were tested [1-9].

Cefepime HCl: Cefepime hydrochloride (CEFE) is a cephalosporin antibiotic for parenteral administration. Various methods revealed that several liquid chromatography methods had been reported for the determination of CEFE alone [10-13] (Figure 1).

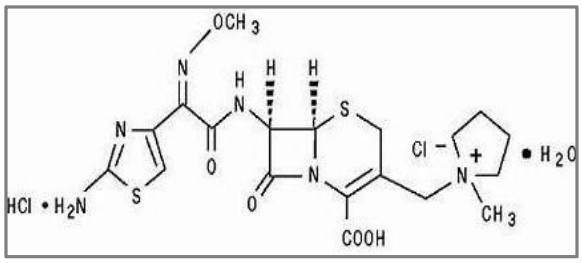


Figure 1. Structure of Cefepime HCl

Ractopamine HCl: Ractopamine acts as a beta-agonist, are used as an alternative to clenbuterol in the swine industry as a tissue repartitioning feed additive, as well as improve feed conversion ratio [14]. Various methods have been studied for RAC [15-21].

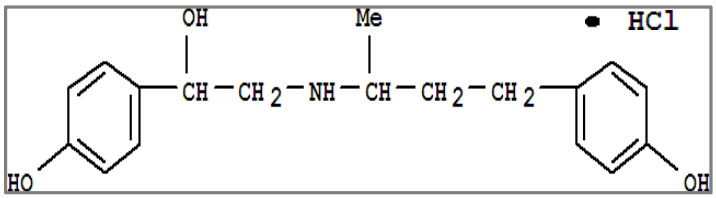


Figure 2. Structure of Ractopamine HCl

Quetiapinefumarate: Quetiapine fumarate is mainly used to treatment of schizophrenia disease [22, 23]. Various methods have reported that the developed validated methods for Quetiapine Fumarate with RP-HPLC [24-27].

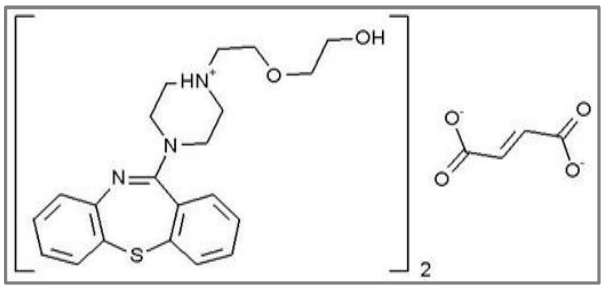


Figure 3. Structure of Quetiapine fumarate HCl.

Escitalopram Oxalate (ESC): Escitalopram oxalate (ESC) is a highly used to treatment of depression and anxiety disorders. Preclinical studies have shown that the therapeutic activity of citalopram resides in escitalopram and that the R enantiomer is approximately one-thirtieth as potent as escitalopram [28]. Several analytical methods have been reported for the determination of ESC [29-32].

Sumatriptan Succinate: Sumatriptan Succinate (SUM) is used in the treatment of migraine attacks. SUM is most effective when taken early after start of the pain. Literature survey reveals many methods for estimation of SUM [33, 34] and very few methods are available for simultaneous determination by UV, HPTLC [35] and HPLC [36-38].

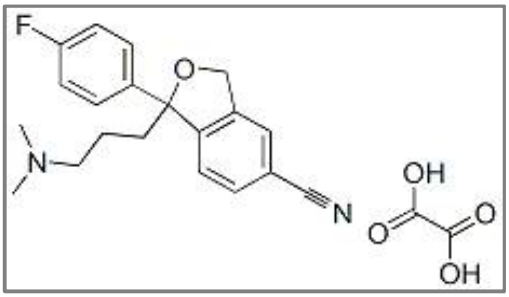


Figure 4. Structure of Escitalopram oxalate

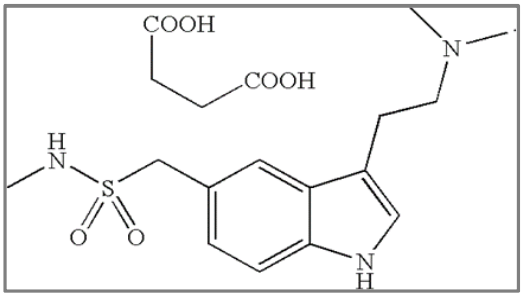


Figure 5. Structure of Sumatriptan Succinate.

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.

Materials and Reagents: All reagents used were of analytical-reagent grade and distilled water was used throughout the investigation. 0.309 gm of Sodium Tetra Phenyl Borate is dissolved in 100 mL double distilled water to get 1x 10^{-2} M of Sodium Tetra Phenyl Borate. 7.54 gm. of KCl was dissolved in 1000 mL 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: Drug solution (1-9 mL) containing 1-9 mg drug taken in 50 mL vol flask filled with double distilled water. The reaction mixture was taken in to a beaker. The conductivity cell was dipped 1×10^{-2}M NaTPB was used for titration. The corrected conductivity can be calculated by using following equation.

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

The amount of drugs can be calculated by using following equation Amount of drug

$$= V.M.R / N$$

Where V is volume 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.

The different concentrations of drugs have been mentioned in the [Table 1] and Slope, intercept, LOD, LOQ, are calculated and tabulated in [Table 1].

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 [Table 2]. 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 [Table 3].

Table1. Analytical and regression parameters for the determination of the drugs by Conductometric titration with NaTPB.

Parameter	CEFE	RAC	QUE	ESC	SUM
Concentration of drug	1-10	1-10	1-10	1-10	1-10
Sandell's sensitivity	0.000913	0.000986	0.000978	0.000943	0.000944
LOD	0.001604	0.144444	0.001066	0.001445	0.000742
LOQ	0.004861	0.43771	0.00323	0.004379	0.002248
Slope, b	1.095	1.014	1.023	1.061	1.059
Intercept, a	0.005	0.001	0.002	0.006	0.006
Correlation co-efficient	0.991	0.996	0.996	0.995	0.995
Regression Equation Y*	Y=1.095X – 0.005	Y=1.014X – 0.001	Y=1.023X – 0.002	Y =1.061X -0.006	Y =1.059 X -0.006
Stdev. of slope	0.013435	0.001414	0.00495	0.000707	0.000707
Stdev.of intercept	0.000532	0.044384	0.00033	0.000465	0.000238

Table 2. Recovery studies to evaluate accuracy and precision for the determination of drugs by conductometric titration with NaTPB

Drugs	Amount taken mg mL^{-1}	Amount found mg mL^{-1}	Error (%)	Recovery (%)	RSD (%)	Proposed method mean±SD
CEF	2	1.97	1.5	98.5		
	5	5.01	0.2	100.2	1.14376	99.9±1.51
	8	7.94	0.75	99.25		
RAC	5	4.96	0.8	99.2		
	7	6.97	0.42	99.571	0.39228	99.4±0.24604
	9	8.98	0.22	99.77		
QUE				100.66		
	3	3.02	0.666	67	1.39838	100.1±1.49355
	5	4.93	1.4	98.6		
	8	7.95	0.625	99.375		
ESC	2	1.98	1	99		
	4	4.01	0.25	100.25	0.87758	99.9±1.05612
	7	6.95	0.7142	99.285		
SUM	2	2.03	1.5	101.5		
	6	5.96	0.6666	99.333	1.66697	100.7±1.79182
	9	8.94	0.6666	99.333		

Optimization of the parameters of quantification

Effect of Solvent: Conductometric titration depends on the solvent nature. In water medium sharpest end point was detected. So water was the best and cheapest choice medium for conductometric titration.

Effect of reagent concentration: Different concentrations of the reagents solution were tried ranging from $1x10^{-3}$, $5x10^{-3}$and $1x10^{-2}$M NaTPB solution. The results indicated that, titrant solutions lower than 10^{-2}M is not suitable for conductometric titrations as the conductance readings were unstable.

Effect of Temperature: It was observed that increase of temperature increases the conductivity of the solution.

Accuracy and precision: Accuracy and precision, inter and intraday accuracy and precision were determined by preparing three different concentration of each drug and each concentration is analysed

in 3 replicates. The relative standard deviation as a precision (RSD %) and percentage relative error (Er %) as accuracy of the suggested methods were calculated.

Method for analysis of Pharmaceuticals:

Cefepime HCl: Thirty tablets (Biopime, 500 mg) were grinded into a fine powder. Hundred mg of Cefepime was weighed and taken to 100 mL volumetric flask, diluted in sufficient quantity of double distilled water and the volume was diluted with same solvent. The compound was filtered through filter paper. The final solution was diluted to obtain standard solution.

Table 3. Recovery studies to evaluate accuracy and precision for the determination of Tablets by conductometric titration with NaTPB

Drugs	Amount taken mg mL^{-1}	Amount found mg mL^{-1}	Error (%)	Recovery (%)	RSD (%)	Proposed method mean±SD	Reference method mean±SD	t-test	F-test
CEFE	3	2.99	0.3333	99.666		100.1±1.0793	99.89±0.71	0.1054	0.885274
(Biopime, 500mg)	5	5.09	1.8	101.8					
	7	6.98	0.2851	99.712	1.61				
RAC	6	6.03	0.5	100.5	1.21	99.8±1.0569	99.4±0.754	0.007639	0.991218
Topmax, 25 mg]	8	8.01	0.125	100.15					
	9	8.89	1.2222	98.778					
QUE	4	3.89	2.75	97.25	2.62	99.5±1.603592	99.2±0.857	0.069968	0.922361
[Seroquel,25 mg]	6	6.02	0.3333	100.33					
	7	7.06	0.8574	100.87					
ESC	2	1.99	0.5	99.5	2.598	98.5±1.569351	101.2±1.47	-0.0272	1.031998
[Lexapro, 20mg]	3	2.89	3.6667	96.333					
	5	4.99	0.2	99.8					
SUM	3	2.98	0.6666	99.333	1.129	99.6±0.69126	98.24±2.84	0.0248	1.0290
[Imigran, 50m g]	5	5.03	0.6	100.6	55				
	7	6.93	1	99					

Ractopamine HCl: Four tablets (Topamax, 25 mg) were crushed in to powder. Hundred mg was taken quantitatively into100 mL volumetric flask filled with distilled water. The final solution was diluted to obtain standard solution.

Quetiapine fumarate: Six tablets (Seroquel, 25 mg) were weighed and grinded into powder. Hundred mg was taken into a 100 mL vo*lumetric* flask, and few mL of bi distilled water is added and the solution was filtered using filter paper. The final solution was diluted to obtain standard solution.

Escitolapram oxalate: Twenty tablets (Lexapro, 20 mg) were crushed into powder. Hundred mg was taken into 100 mL vo*lumetric* flask and dissolved well in about 10 mL of *double* distilled water. The final solution was diluted to obtain working standard solution.

Sumatriptan Succinate: Ten tablets (Imigran, 50mg) were crushed in to powder. 100 mg was taken quantitatively into100 mL vo*lumetric* flask and made up to the mark with *double* distilled water. The final solution was diluted to obtain working standard solution.

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. On using Sodium tetra phenyl borate as a titrant for the determination of studied drugs, sodium chloride or sodium bromide or sodium citrate or sodium succinate 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 NaTPB (Figures 6-15).

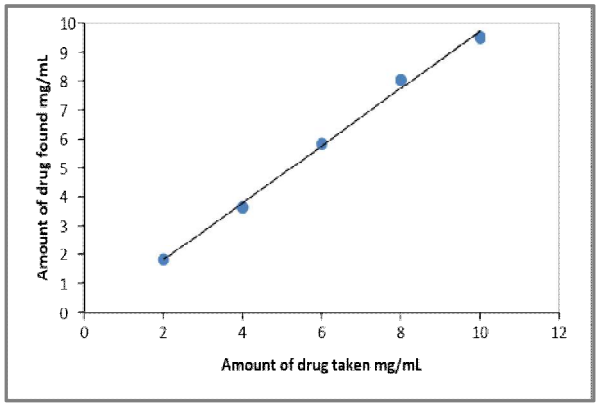


Figure 6. Calibration graph of CEF.

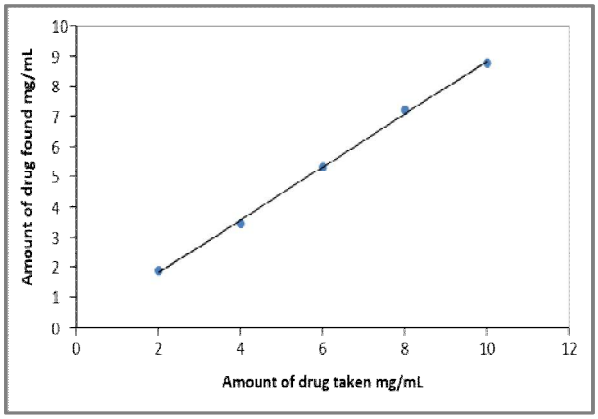


Figure 7. Calibration curve of RAC.

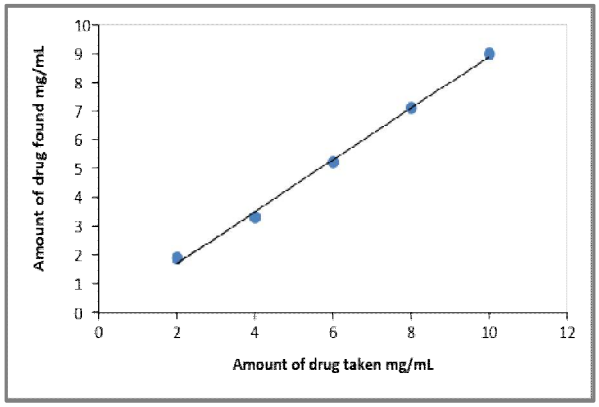


Figure 8. Calibration graph of QUE.

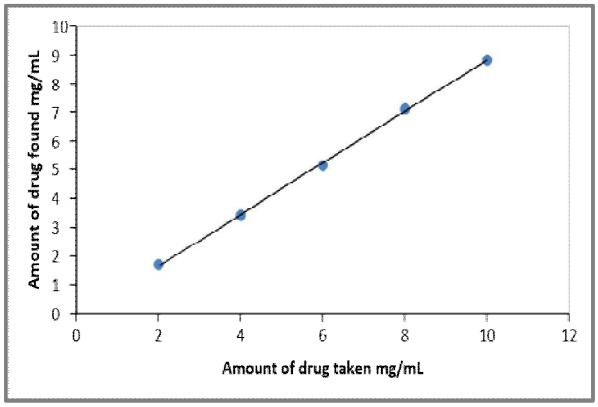


Figure 9. Calibration graph of ESC

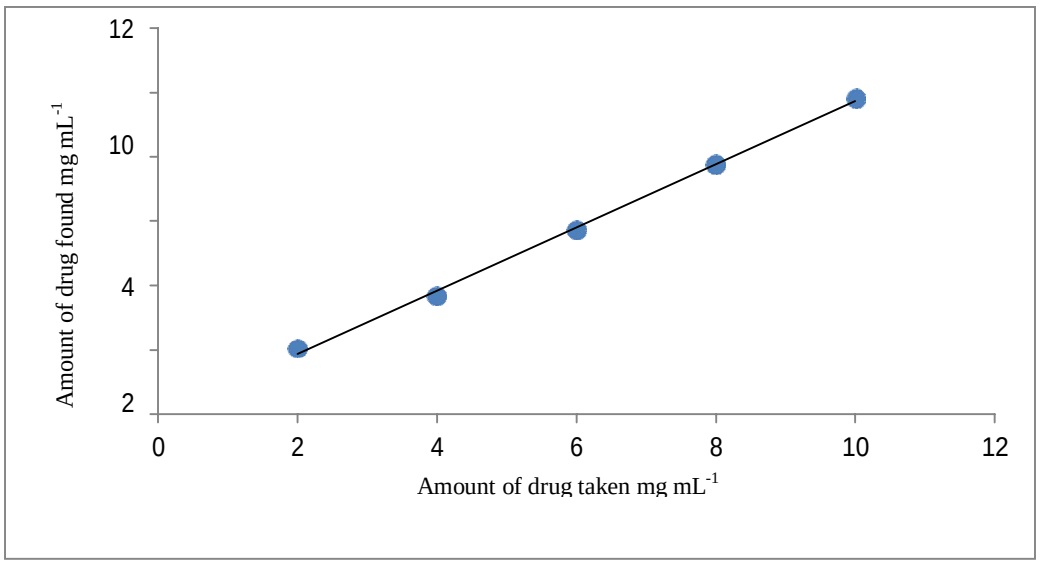


Figure 10. Calibration graph of SUM.

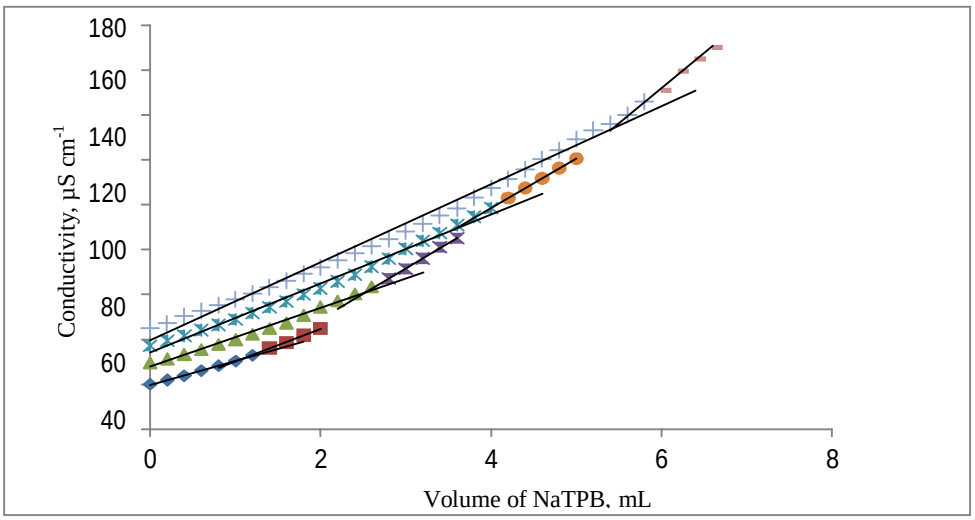


Figure 11. Conductometric titration curves of 2mg, 4mg, 6mg and 8mg of CEF.

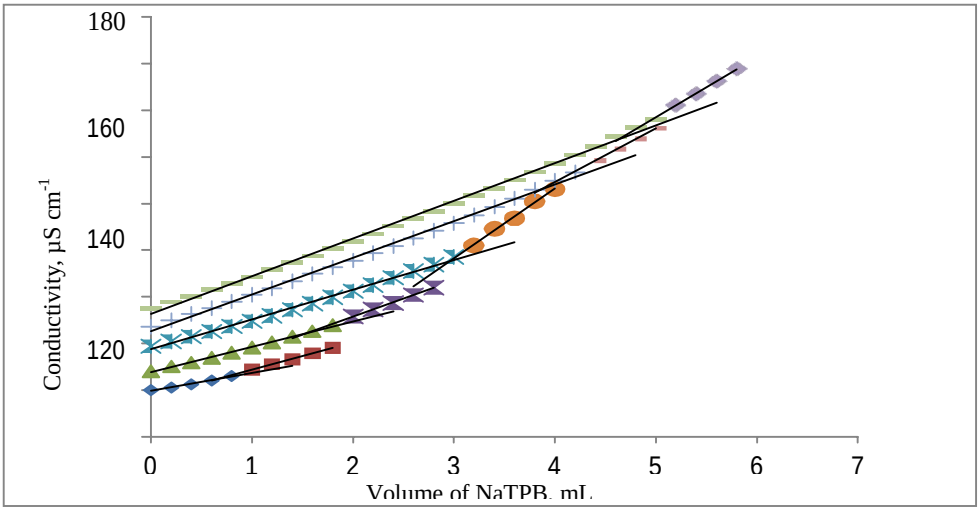


Figure 12. Conductometric titration curves of 2mg, 4mg, 6mg, 8mg and 10mg of RAC.

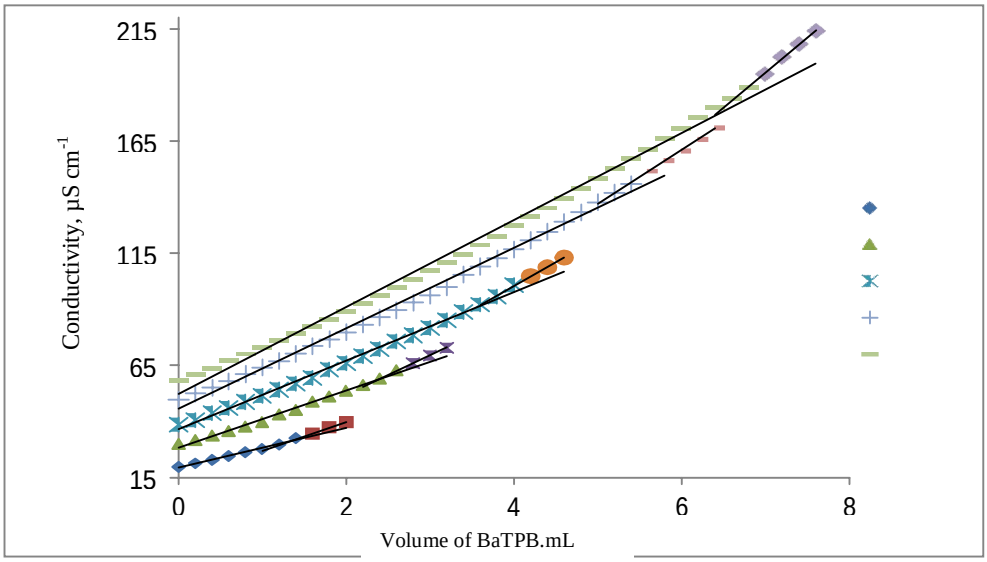


Figure 13. Conductometric titration curves of 2mg, 4mg, 6mg, 8mg and 10mg of QUE.

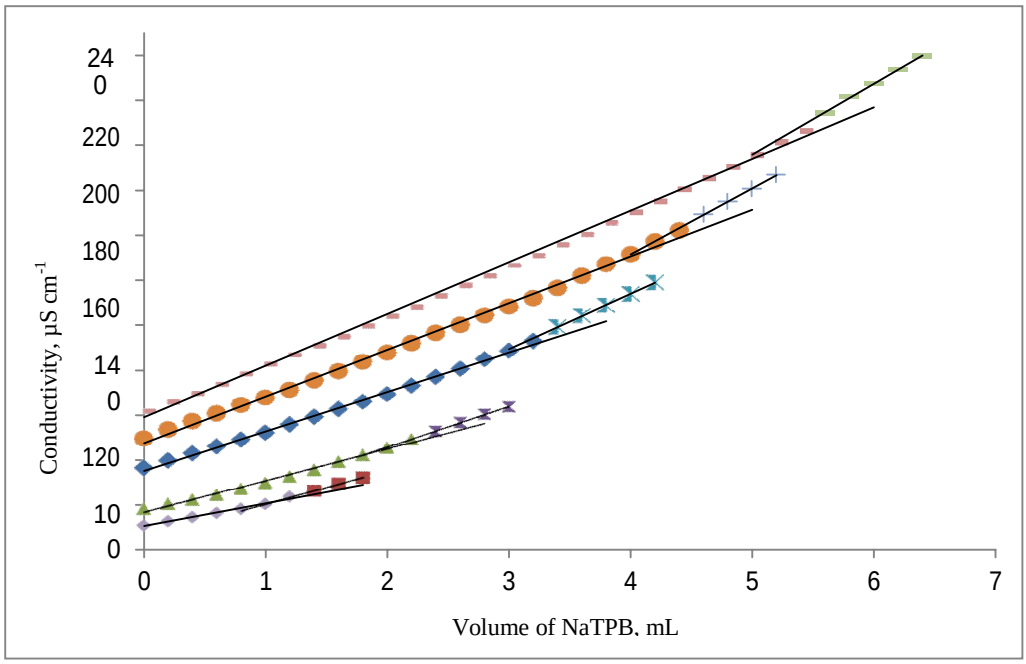


Figure 14. Conductometric titration curves of 2mg, 4mg, 6mg, 8mg and 10mg of ESC.

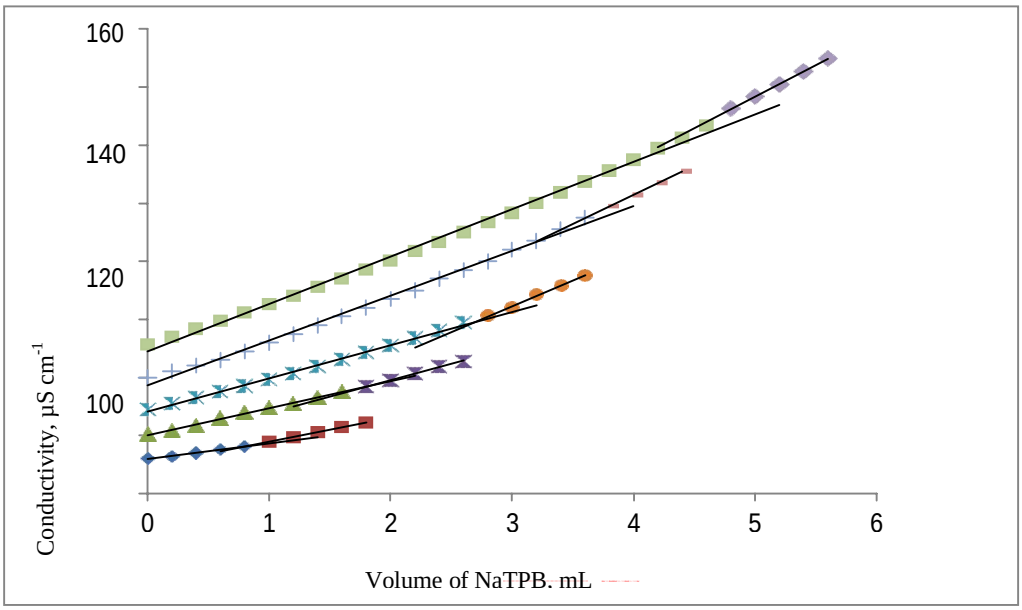


Figure 15. Conductometric titration curves of 2mg, 4mg, 6mg, 8mg and 10mg of SUM.

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 1-9 mg for all the studied drugs.

APPLICATION

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 like, Spectrophotometric methods

HPLC, UPLC etc., for the determination of these drugs.

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 and Sodium tetra Phenyl Borate 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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