Research Article

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Quantitative Determination of Commercial Metal Anion Drugs and Pharmaceuticals using Silver Nitrate as Precipitating Agent: Conduct metric Titration Method

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Abstract: Simple, sensitive, accurate, cost effective and precise Conductometric method for quantitative determination of Five anionic commercial drugs viz.,Montelukast Sodium(MOT), Penicillin Sodium(PEN), Potassium Dobesilate(POD) , Rosuvastatin Calcium(ROS), Warfarin Sodium (WAR)were developed. The method was based on the formation of insoluble salt ($Ag^{+}[Drug]^{-}$) between the Drug anion of metal salt drugs and Silver Cation of Silver Nitrate solutions. Aliquots of standard drug solution (2-12 mL) which is containing 2-12 mg pure drug and 0.005 M Silver Nitrate 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 95% confidence level with those obtained using spectrophotometric determination method.

Keywords: Anionic Drugs, Conductometric, Determination, Silver Nitrate, Sodium.

INTRODUCTION:

Montelukast sodium (Fig.1a), sodium salt of 2-[3-(7-chloro-quinoline-2- yl) phenyl vinyl]] -3-[2- (methyl ethyl 1-hydroxy-1-) phenyl] propyl – sulfanyl methyl] cyclo propyl] acetic acid. MOT is very useful drug for curing of chronic breathing problems [1]. Several methods like Spectrophotometry for individual [2,3], combined dosage form [4], High performance liquid chromatography [5,6], Capillary electrophoresis [7], have been developed.

Penicillin sodium (Fig.1b) is a sodium salt of thiozolidine carboxylic acid derivative it is a first known antibiotic drug and which is used in the treatment of bacterial growth in living organisms. A few analytical techniques are available for quantitative estimation of PEN [8, 9].

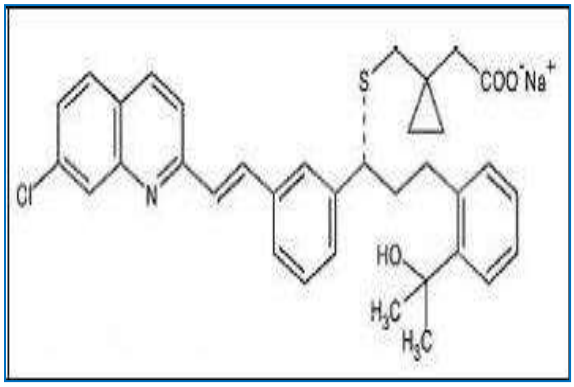


Fig.1a: Structure of MOT

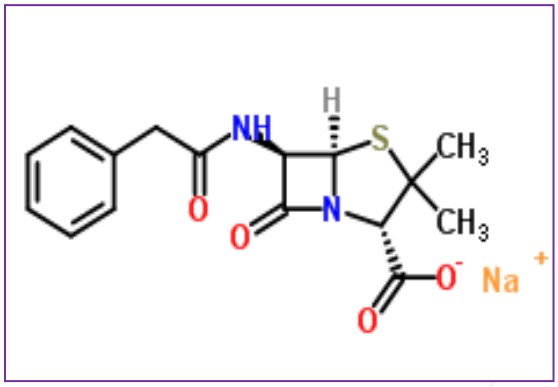


Fig.1b: Structure of PEN

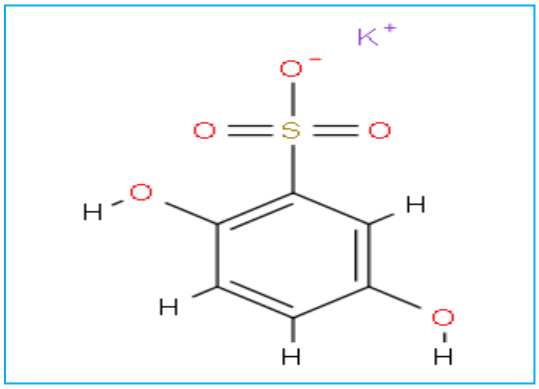
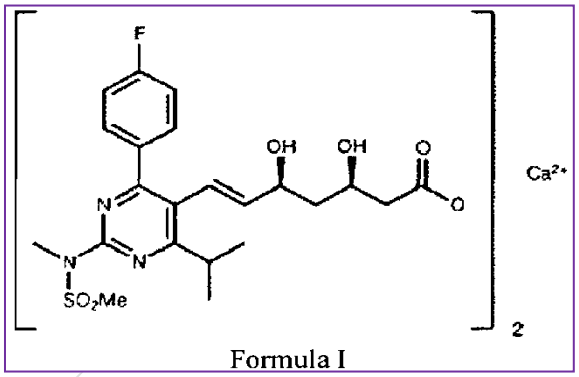


Fig.1c: Structure of POD



Formula I

Fig.1d: Structure of ROS

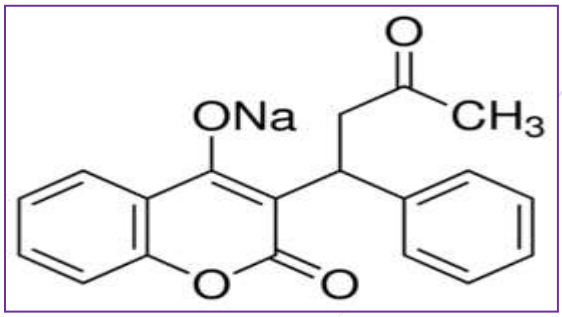


Fig.1e: Structure of WAR

Potassium Dobesilate (Fig.1c) is chemically Potassium 2, 5-dihydroxybenzenesulfonate. POD is used in the treatment of cancer due to its antitumorigenic activity. A few techniques appears for the estimation of Potassium Dobesilate in literature High performance liquid chromatography (HPLC) method [10], UV- spectrophotometry method [11-12] in bulk drug formulation.

Rosuvastatin calcium (Fig.1d.) is belongs to pyrimidine type of drugs and used for lowering of bad cholesterol levels in human body due to its inhibition of cholesterol synthesis enzyme. Several quantification techniques has been reported for ROS viz,. liquid chromatography-mass spectroscopy [18-20], high performance liquid chromatography [14-17], UV-SPM [13] .Warfarin Sodium (Fig.1e) is chemically coumarine acetonyl benzyle derivative. This drug has an asymmetric carbon atom and exists in R- and S- enantiomeric forms. It is used for blood clotting and it's known as anti-

coagulation drug It has an empirical formula $C_{19}H_{16}O_4$ with molecular weight 308.33 g/mol. Analysis of the literature demonstrated the existence of few methods for the quantitative determination of Warfarin sodium was mentioned [21-26].

Through survey of literature of the above mentioned anionic drugs revealed that Conductometric determination of anionic drugs based on the use of Silver Nitrate as Precipitating agent [27-31] 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 compare to other techniques like HPLC.

MATERIAL 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.0.850gm of Silver Nitrate is dissolved in 100ml double triple distilled water to get 0.005M of Silver Nitrate.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.

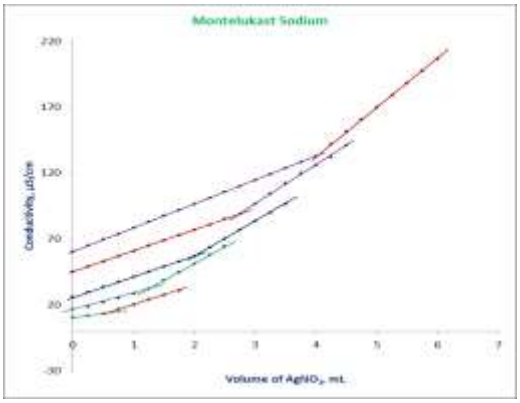


Fig. 2: Conductometric curves of 2mg, 4mg, 6mg, 8mg and 10mg of MOT.

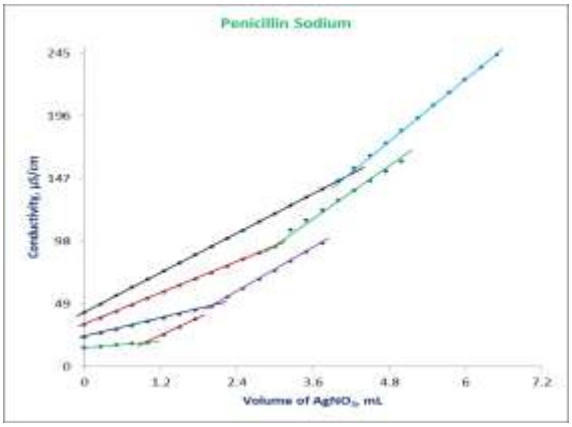


Fig. 3: Conductometric curves of 2mg, 4mg, 6mg and 8mg of PEN.

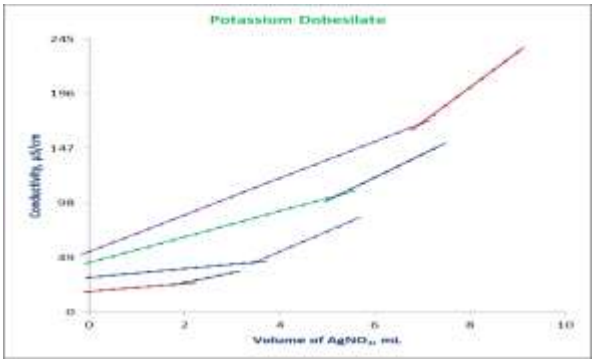


Fig. 4: Conductometric curves of 2mg, 4mg, 6mg and 8mg of POD.

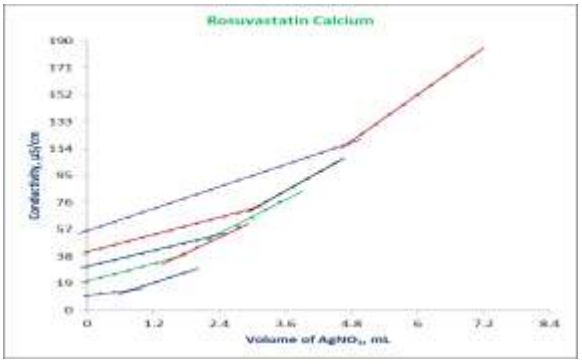


Fig. 5: Conductometric curves of 2mg, 4mg, 6mg, 8mg and 10mg of ROS.

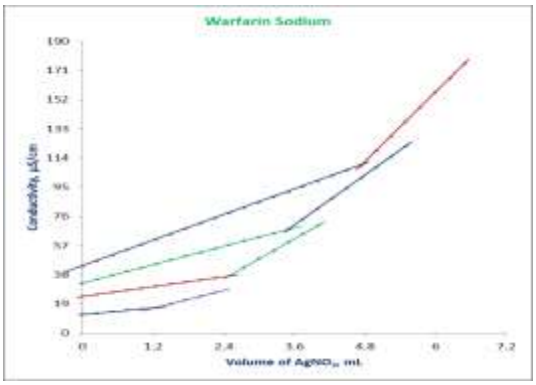


Fig. 6: Conductometric titration curves of 2mg, 4mg, 6mg and 8mg of WAR.

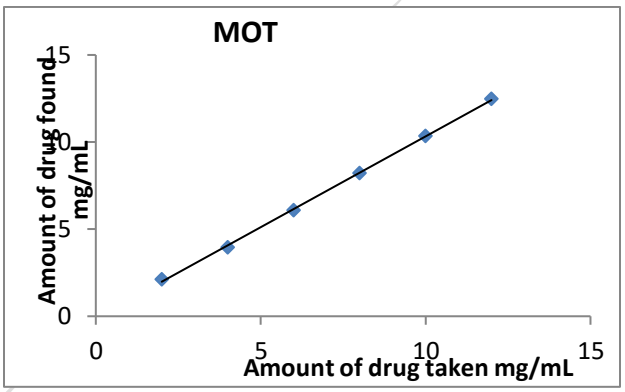


Fig. 7a: Calibration graph of Montelukast Sodium.

Method development: Aliquots of standard drug solution (2-12 mL) containing 2-12 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 0.005 M Silver Nitrate 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.

Ω^{-1}correct = Ω^{-1}obs [V1+V2/V1]

Where Ω^{-1}correct is the corrected electrolytic conductivity, Ω^{-1}obs 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 (Fig.2, 3, 4, 5, &6). The amount of drugs under study was calculated according to the following equation

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.

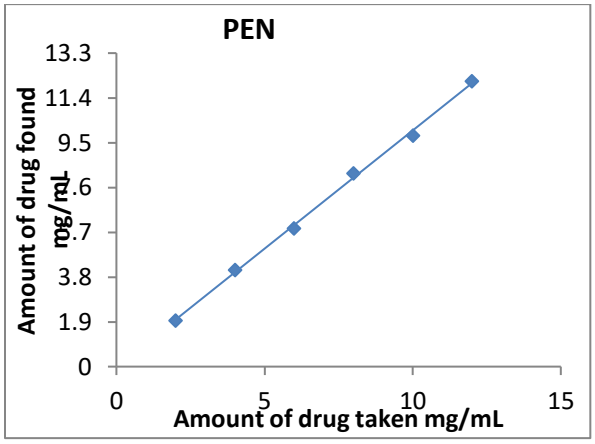


Fig. 7b: Calibration graph of PEN

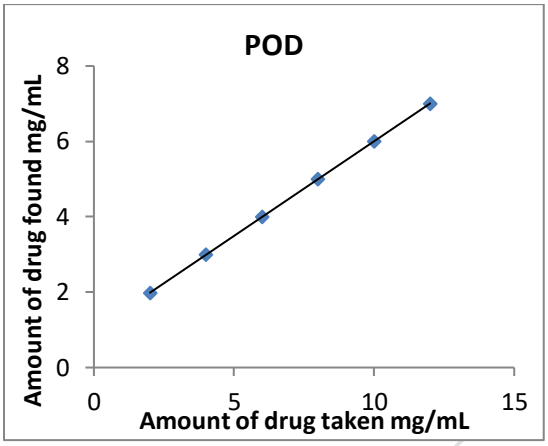


Fig. 7c: Calibration graph of POD

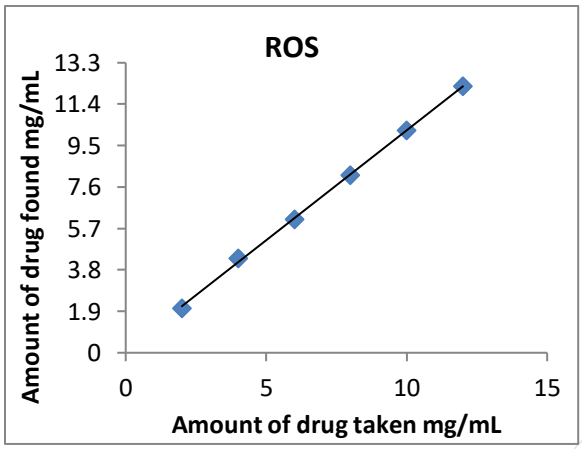


Fig. 7d: Calibration graph of ROS.

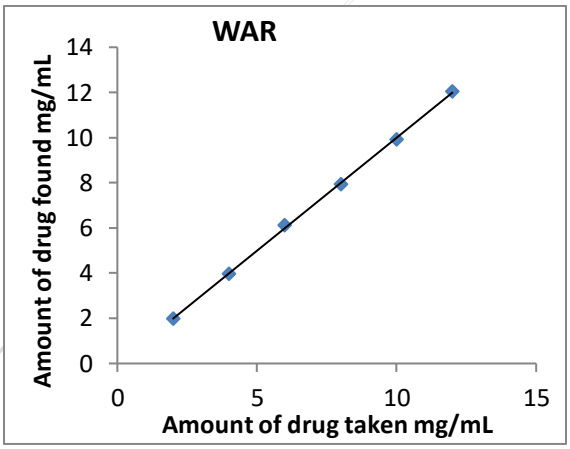


Fig. 7e: Calibration graph of WAR**.**

Procedure for analysis of Pharmaceuticals:

Montelukast sodium: Twenty five tablets of 10mg APOTAX CORP were collected and crushed into powder, 150 mg equivalent ofMontelukast sodium 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 stock Solution converted to working concentration solution on dilution with bi distilled water for Conductometric titration of Montelukast sodium solution with Silver Nitrate reagent.

Table 1: Analytical and regression parameters for the determination of the drugs by Conductometric titration with $AgNO_3$ Reagent.

Parameter/ Name of the Drug	MOT	PEN	POD	ROS	WAR
Concentration of drug mg/mL	2-12	2-12	2-12	2-12	2-12
Sandell's sensitivity mg/cm^2	0.001	0.001	0.0011	0.002	0.001
LOD mgmL^{-1}	0.41	0.007	0.0085	0.0084	0.145
Limit of quantification mg/mL	1.24	0.022	0.0257	0.256	0.44
Slope, b	1.042	1.002	0.502	1.008	1.0
Intercept, a	-0.101	-0.011	0.981	0.118	-0.011
Correlation co-efficient, R	0.999	0.998	1.0	0.999	0.999
Regression equation Y*	1.042x – 10^{-1}	1.002x – 10^{-1}	0.502x + 0.98	1.008x + 0.118	1.000x – 10^{-1}
SD of intercept	$1.29x10^{-1}$	$2.2x10^{-3}$	0.0013	$2.6x10^{-3}$	0.044

Table 2: Precision and accuracy parameters evaluation by recovery studies method for quantitative determination of pure drugs by Conductometric Study with $AgNO_3$ reagent.

Drug Sample	Drug Taken (mgmL^{-1})	Drug Found (mgmL^{-1})	% of Error	% of drug Recovery	Regression SD of drug	Mean ± SD of Proposed method
MOT	2	2.02	1.0	101	0.611	100.17±0.612
	4	4.01	0.25	100.25		
	7	6.98	0.29	99.71		
	10	9.97	0.3	99.7		
PEN	3	3.01	0.33	100.33	0.368	100.1±0.368
	4	4.02	0.50	100.5		
	7	6.98	0.30	99.71		
	9	8.99	0.11	99.88		
POD	3	2.98	0.67	99.33	0.478	99.66±0.478
	4	3.97	0.75	99.25		
	7	7.02	0.29	100.28		
	9	8.98	0.22	99.78		
ROS	3	2.98	0.67	99.3	0.5005	100.05±0.5
	4	4.02	0.50	100.5		
	6	6.01	0.17	100.17		
	10	10.02	0.2	100.2		
WAR	4	4.02	0.5	100.5	0.258	100.16±0.259
	6	6.01	0.17	100.17		
	8	7.99	0.12	99.87		
	11	11.01	0.09	100.1		

Penicillin sodium: 400mg of two PENTADIS tablets were collected and crushed into powder. 200 mg equivalent of Penicillin sodium 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 stock Solution converted to working concentration solution on dilution with bi distilled water for Conductometric titration of Penicillin sodium solution with Silver Nitrate reagent.

Table 3: Precision, Accuracy, t-test and F-test evaluation by recovery studies method for quantitative determination of tablets by Conductometric Study with $AgNO_3$reagent.

Tablet Sample	Drug Taken (µg/mL)	Drug Found (µg/mL)	%of Error	% of drug Recovery	Regression SD of drug	Mean± SD (Reference method)	Mean ± SD (Proposed method)
MOT (10mg Apotax)	3	2.96	1.33	98.67	0.719	99.7±0.717	97.65±1.72
	5	4.99	0.2	99.8			
	6	6.01	0.16	100.17			
	10	10.02	0.2	100.2			
PEN (Pentadis 400mg)	4	4.02	0.5	100.5	0.370	99.96±0.369	99.61±0.456
	6	5.98	0.33	99.67			
	8	7.99	0.12	99.87			
	10	9.98	0.2	99.8			
POD (Pot.Dob -esilate- 10mg)	6	5.98	0.33	99.67	0.599	99.79±0.598	99.92±0.862
	7	7.02	0.29	100.29			
	8	7.92	1	99			
	9	9.02	0.22	100.22			
ROS (Lipigo 10mg)	4	3.98	0.5	99.5	0.478	99.78±0.477	97.68±0.78
	6	6.01	0.17	100.17			
	8	7.94	0.75	99.25			
	10	10.02	0.2	100.2			
WAR (Antovan, 10 Mg)	4	4.03	0.75	100.7	0.646	100.031±0.646	99.64±0.846
	6	5.98	0.33	99.67			
	8	8.03	0.37	100.37			
	9	8.94	0.67	99.33			

Tablets/ parameter	MOT (10mgApotax)	PEN (Pentadis 400mg)	POD (Pot.Dobesilate-10mg)	ROS (Lipigo10mg)	WAR (Antova 10 Mg)
t-test	1.32	0.363	0.616	0.808	0.457
F-test	0.654	0.174	0.481	0.375	0.585

Potassium Dobesilate: Twenty five tablets of each containing 10mg Pot. Dobesilate were collected and crushed into powder. 150 mg equivalent of potassium Dobesilate was weighed from tablet powder and transferred into 100 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 stock Solution converted to working concentration solution on dilution with bi distilled water for conductometric

titration of potassium Dobesilate solution with Silver Nitrate reagent.

Rosuvastatin Calcium: Twenty five ATROLIP tablets of each contains 10mg were collected and crushed into powder. 200 mg equivalent of Ampicillin sodium 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 stock Solution converted to working concentration solution on dilution with bi distilled water for Conductometric titration of ampicillin sodium solution with Silver Nitrate reagent.

Warfarin sodium: Twenty tablets of 10mg ANTOVAN were collected and crushed into powder. 150 mg equivalent of Ampicillin sodium 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 stock Solution converted to working concentration solution on dilution with bi distilled water for Conductometric titration of ampicillin sodium solution with Silver Nitrate 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 .On using Silver Nitrate as a titrant for the determination of studied Anionic drugs is precipitated and leading to a straight line during the first segment of the titration curve. The second segment of this curve corresponds to the excess of Silver Nitrate.

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 2-12 mg for all the studied drugs (Table1, 2&3).

Optimization of the parameters of quantification:

Effect of Solvent: Titrations in different solvents were performed to obtain the best results1) 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 $5x10^{-3}$, $3x10^{-3}$and $1x10^{-3}M$ Silver Nitrate reagent solution. The results indicated that, titrant solutions lower than $5x10^{-3}M$ 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 Silver Nitrate is $5x10^{-3}M$ to get a highly stable conductance reading after 2 minutes of mixing.

Effect of Temperature: The experiment was performed at room temperature. The rise in temperature to40^0 C 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 Silver Nitrate 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.

Accuracy and precision: To assess the precision, each experiment was repeated at least 3 times and accuracy is estimated in terms of percent recovery and percent RSD. Excellent percent 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 (Table.1, 2 &3).

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 Silver Nitrate 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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