Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(7):3740-3748

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Determination of Alfuzosin hydrochloride and Tamsulosin hydrochloride in pure state and pharmaceutical preparations by conductimetric methods

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ABSTRACT

Three reagents phosphotungestic acid (PTA), silicotungestic acid (STA) and sodium tetraphenylborate (NaTPB) were used as titrants for the conductimetric determination of alfuzosin hydrochloride (AlfCl) and tamsulosin hydrochloride (TamCl) through ion- associate formation. The effect of the reagent concentration, the temperature, the molar combining ratio, and the solubility products of the formed ion-associates were studied and calculated. The suggested method has applied to the determination of alfuzosin hydrochloride and tamsulosin hydrochloride in its pure state and pharmaceutical preparations with mean recovery values of 99.50 - 99.80 % for alfuzosin hydrochloride in pure state and 99.05 – 100.03% in Xatral tablet, and 99.59 – 99.92% for tamsulosin hydrochloride in pure state and 99.73 – 99.93% in Ominic capsule. The relative standard deviations are less than 1.0%. The accuracy of the method was indicated by excellent recovery and low standard deviation. The results were compared with the pharmacopoeial methods.

Keywords: Tamsulosin hydrochloride, Alfuzosin hydrochloride, Conductimetric titration, Phosphotungestic acid, Silicotungestic acid, Sodium tetraphenylborate.

INTRODUCTION

Alfuzosin hydrochloride (AlfCl) is N-[3-[4-Amino-6, 7-dimethoxyquinazolin-2-yl (methyl) amino] propyltetrahydro-2-furamide and Tamsulosin hydrochloride (TamCl) is 5-[(2R)-2-[[2-(2-Ethoxyphenoxy) ethyl] amino] propyl]-2-methoxybenz-ene sulfonamide (Figure.1). These drugs are (5α-reductase) inhibitor with anti androgenic activity used in treatment of benign prostatic hyperplasia and androgenic alopecia. These drugs decrease the level of available (5α-reductase) prior to testosterone binding with the enzyme thus reducing the levels of dihydrotestestrone that derives from such bonds. These drugs adverse reaction are generally dose dependent; common ADRs include impotence, decreased libido, decreased ejaculate volume, erectile dysfunction, ejaculate disorder, breast tenderness and enlargement (gynecomastia) and testicular pain, vertigo, dizzness, and syncope or malaise, hypotension or headache are common in patient over 75 years and during first week of treatment [1].

These drugs are absorbed from gastrointestinal tract and are almost completely bioavailable; the extent and rate of absorption are reduced by food. After oral doses peak plasma concentration occur after about 1 hour, about (90 - 99%) bound to plasma protein it is metabolized slowly in liver primary by cytochrome P450, Isoenzyme CYP2D6, CYP3A4 [2].

They are excreted mainly in the urine as metabolites and some unchanged drug, the plasma elimination half-life has been reported to be between 4 and 5.5 hours [3].

Several techniques have been used to determine AlfCl including mass spectrometry [4], spectrophotometry [5-8], electrochemical [9-10], and HPLC [4,11-17].

Several techniques have been used to determine TamCl including voltammetry [18], mass spectrometry [19-23], LC [24-27], and HPLC [28-33].

The present work, aims to study the application of conductimetric method in the quality control of alfuzosin hydrochloride, and tamsulosin hydrochloride. The conductimetric method is very simple and of low expensive in comparison to the above mentioned techniques but at the same time offering a high degree of accuracy and precision when compared to other techniques.

EXPERIMENTAL SECTION

2.1. Apparatus

The conductimetric measurements were carried out with a conductivity meter model (702) Conda. A dip type conductivity cell (K=1.00) was used.

2.2. Materials

2.2.1. Pure sample and pharmaceurical preparations

Alfuzosin hydrochloride (AlfCl, M.W. = 425.9) and its pharmaceutical preparation (Xatral tablets labeled to contain 5 mg alfuzosin / tablet) were provided from AMRIYA for pharmaceutical industries, Alexandria, Egypt, under license of Robinson, France, and tamsulosin hydrochloride (TamCl, M.W. = 445) and its pharmaceutical preparation (Omnic capsules labeled to contain 0.4 mg tamsulosin / capsule) were provided from Astellas Pharma Europe B.V. Leiderdrop, The Netherlands.

2.2.2. Reagents

Phosphotungestic acid (PTA) $H_3[PW_{12}O_{40}.xH_2O]$, silicotungestic acid (STA) $H_4[SiW_{12}O_{40}]$, or sodium tetraphenylborate (NaTPB) $Na[C_{24}H_{20}B]$; were obtained from Aldrich chemical company.

Aqueous solutions of PTA, STA and NaTPB were prepared by dissolving the accurately weighed amounts of the pure solid in bi-distilled water using analytical grade purity chemicals, and the exact concentrations of these solutions were determined by the appropriate recommended methods [34,-35], and the solutions were kept in the refrigerator for no more than 1 week. Working solutions of were freshly prepared by appropriate dilution.

2.3. General procedure

Aliquots of working solution containing 4.25-42.59 mg AlfCl and 4.45-44.50 mg TamCl were transferred to 50 ml volumetric flask and made up to the mark with bi-distilled water. The contents of the volumetric flask were transferred to the titration cell, then 1.0 $x10^{-2}$ M PTA, STA and NaTPB were added from a micro burette, and the conductance was measured after 1-2 minutes after each addition of reagent through stirring. The conductance reading was corrected for dilution [36] by means of the following equation, assuming that conductivity is a linear function of dilution:

$$\Omega_{corr} = \Omega_{obs} [(V_1 + V_2)/V_1]$$

Where Ω_{corr} and Ω_{obs} are the corrected and the observed electrolytic conductivities, respectively, V_1 is the initial volume and V_2 is the volume of the added reagent.

A graph of corrected conductivity values versus the volume of the added titrant was constructed and the end point was determined. The drug-titrant ratio is then determined from the intercept of the two linear segments of the graph.

2.4. Procedure for determining the drug-titrant ratio

Volumes of 1.0-10.0 ml 10^{-2} M AlfCl and TamCl solutions then transferred separately to a 50 ml volumetric flask and diluted up to the mark with bi-distilled water. The contents were transferred quantitatively to a conductimetric

titration cell, and the solution was then titrated conductimetrically against 10^{-2} M PTA, STA, or NaTPB delivered from a micro-burette, and the conductance was measured subsequent to each addition of the reagent solution, and after thorough stirring for 2 min. A graph of the corrected conductance recordings versus the volume of the added titrant was constructed, and the drug-titrant stoichiometric ratio is then determined from the intercept of the two linear segments of the graph.

2.5. Procedure for dosage forms or pharmaceutical forms

For analysis of Xatral tablets (5 mg AlfCl /tablet), tablets were powdered and an accurately weighed portion equivalent to 0.425 g AlfCl was taken and dissolved in 50 ml water. For Ominic capsules (0.4 mg TamCl/capsule), capsules were accurately weighed portion equivalent to 0.445 g were mixed with 50 ml water, for both tablets and capsules, shake in a mechanical shaker for about 30 min, and filtered into a 100 ml volumetric flask. The solution was completed to the mark with bi-distilled water and shaken. Different volumes of the solution (1.0-10.0 ml) were taken, and subjected to the conductimetric determination as mentioned above.

2.6. Conductimetric determination of the solubility product constants of the ion-associates

A series of solutions of molar concentrations (C) 10^{-2}M was prepared for each of AlfCl and TamCl, PTA, STA, and NaTPB. The conductances of these solutions were measured at 25˚C, and the specific conductivities (λ_o), corrected for the effect of dilution, were calculated and used to obtain the equivalent conductivities (λ) of these solutions. Straight line plots of λ versus $\sqrt{c}$ were constructed and $(\lambda_o)_{AlfCl}$, $(\lambda_o)_{TamCl}$, $(\lambda_o)_{PTA,}$ $(\lambda_o)_{STA,}$ and $\lambda_{o\ NaTPB}$ were determined from the intercept of the respective line 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 $\lambda_{o(Alf\text{-}PT)}$, $\lambda_{o(Alf\text{-}ST)}$, $\lambda_{o(Alf\text{-}TPB)}$, $\lambda_{o(Tam\text{-}PT)}$, $\lambda_{o(Tam\text{-}ST)}$, and $\lambda_{o(Tam\text{-}TPB)}$, were calculated using Kohlrausch's law of independent migration of ions.[37]

The solubility (S) and solubility product (K_{sp}) values of the ion associates were calculated using the following equations:

$S = K_S \times 1000/ \lambda_{o\ (ion\text{-}associate),}$

$K_{sp} = S^2$ for 1:1 ion-pairs
$K_{sp} = 4\ S^3$ for 1:2 ion-associates
$K_{sp} = 27\ S^4$ for 1:3 ion-associates, and
$K_{sp} = 256\ S^5$ for 1:4 ion-associates

Where, K_s are the specific conductivity of the saturated solution of the ion associate, determined at 25˚C and corrected for the effect of dilution. Such saturated solution was made by stirring a suspension of the solid precipitate in distilled water for 2 h, and then leaving it for 24 h at 25˚C before measuring the conductivities.

RESULTS AND DISCUSSION

Conductimetric measurements are used, successfully, for the equivalent point determination in titration of systems in which the conductance of the solution varies before, and after the end point. One of the valuable features of the conductance method of titration is that it permits the analysis of the components of a precipitation reaction. In this case, the formation of a precipitate alters the number of ions present in the solution and consequently the conductance varies. After the equivalent point, the addition of excess titrant increases the number of ions and so the conductance increases. The titration curve, representing the relation between the conductance and the volume of the titrant added can be constructed as two lines intersecting at the end point.

Alfuzosin hydrochloride and tamsulosin hydrochloride are able to form precipitates with heteropoly acids, phosphotungestic, silicotungestic, and sodium tetraphenylborate so the applicability of conductimetric titration of these drugs with the above mentioned reagents, was tested. The different parameters affecting the end point, such as temperature, and concentration of both titrant and titrand, were studied.

3.1. Factors affecting the end point of titration

3.1.1. Effect of temperature

The effect of temperature on the end point of the conductimetric titration was studied by carrying out titrations at 25, 35 and 50^{o}C. The results showed that as the temperature increases, the conductivity of the whole solution increases,

and no effect was observed on the shape of the titration curve and the position of the end point up to 50^{o}C, then room temperature was used for carrying out the other variables Figure. 2.

3.1.2. Effect of dilution of titrant and titrand

A weight of the investigated drugs 21.29 mg of AlfCl and 22.25 mg of TamCl were dissolved in 50 ml water was titrated against $1x10^{-3}$, $5x10^{-3}$, and $1x10^{-2}$ M PTA, STA, and NaTPB solutions. The results indicated that, titrant solutions lower than 10^{-2} M are not suitable for conductimetric titrations as the conductance readings were unstable and the inflection at the end point was very poor.

On the other hand, when the same above mentioned amounts of the investigated drug were dissolved and diluted up to 50, 75 and 100 ml with distilled water and titrated against 10^{-2} M PTA, STA, or NaTPB solution (optimum titrant concentration). The results showed that, dilution of the titrand up to 100 ml has no effect on the position of the end point and the shape of the titration curve Figure. 3.

3.2. Determination of the drug–titrant ratio

From the above discussion it was found that the systems under investigation showed a regular rise in conductance up to the equivalence point where a sudden change in the slope occurs. After the end-point, more titrant is added and the conductance increases more rapidly. Curve break is observed at drug-reagent molar ratio 3:1, 4:1, and 1:1 for PTA, STA, and NaTPB, respectively, in case of the two mentioned drugs. The conductimetric titration curves of the drug versus PTA, STA, or NaTPB deduce the molar ratios of the drug-reagent are given in Figures. 4 and 5.

3.3. Conductimetric determination of alfuzosin hydrochloride and tamsulsin hydrochloride in pure solution

Aliquots solutions containing 4.25-42.59 mg AlfCl and 4.45-44.50 mg TamCl were titrated conductimetrically against 10^{-2} M PTA, STA and NaTPB standard solutions following the procedure described in the experimental section. Graphs of corrected conductivity versus the volume of titrant added were constructed and the end points were determined 1 ml 10^{-2} M PTA is theoretically equivalent to 12.77mg AlfCl and 13.35 mg TamCl, while 1 ml 10^{-2} M STA, are equivalent to 17.03 mg AlfCl and 17.8 mg TamCl and 1 ml 10^{-2} M NaTPB is equivalent to 4.25 mg of AlfCl and 4.45 mg TamCl.

The results given in Table 1 & 2 show that, the recovery values for AlfCl are 99.80%, 99.50% and 99.60% and for TamCl 99.59%, 99.92% and 99.75% using PTA, STA and NaTPB, respectively. This indicates the high accuracy and precision of the proposed method.

3.4. Conductimetric determination of the investigated drug in its pharmaceutical preparation

The validity of the proposed method was assessed by its application to the determination of the investigated drugs in its pharmaceutical preparation (Xatral tablets) in case of AlfCl and (Ominic capsules) in case of TamCl using the same procedure and conditions applied for pure solutions. From the results shown in Tables 1 & 2, it is clear that the mean recovery values for Xatral tablets were 99.47%, 99.05% and 100.03% and for Ominic capsules were 99.79%, 99.92% and 99.73% with PTA, STA and NaTPB, respectively.

The results obtained from the conductimetric determination of the drug were subjected to statistical treatment to compare the precision of the employed technique to that methods used as references by applying F and t-tests [38] .The results shown in Tables 3 and 4 are lower than the theoretical tabulated values, i.e. the method applied does not exhibit significant difference which reflects the accuracy and precision of this method.

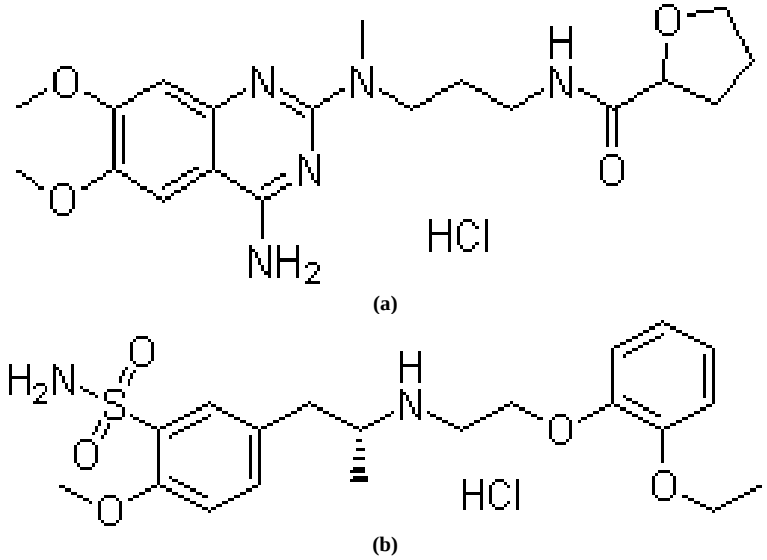
3.5. Determination of the solubility product constants of the ion-associates

Ion-associate formation is the mean 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 solubility products (K_{sp}) of the formed ion-associates were determined conductimetrically [39] as described under the experimental part. The equilibrium constant of the precipitation reaction (K) is inversely proportional to the solubility product (K_{sp}), whereas the smaller the solubility product of the formed ion-associate, the sharper the end point. The solubility product of ion associate of Alf-ST is lower than that of Alf-PT and Alf-TPB, so it is most stable and the solubility product of ion associate of Tam-ST is lower than that of Tam-PT and Tam-TPB, so it is most stable.

The equilibrium constants of the ion-associate formation reactions are calculated and represented as follows:

$3D^{+}+PT^{3-} = D_3PT$,
$4\ D^{+}+ST^{4-} = D_4ST$,
$D^{+}+TPB^{-} = DTPB$.

These equilibrium constant values are 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 [40] , (Table 5).



(a)

(b)

Figure.1: The chemical structure of (a)Alfuzosin hydrochloride(AlfCl) (b)Tamsulosin hydrochloride (TamCl)

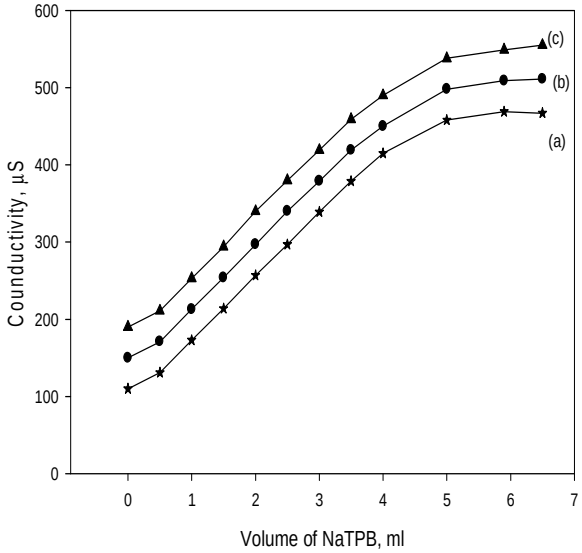


Figure 2: Effect of temperature on the end point of the conductimetric titration of 21.25 mg of AlfCl with 10^{-2} M NaTPB at 25 (a), 35 (b), 50°C (c)

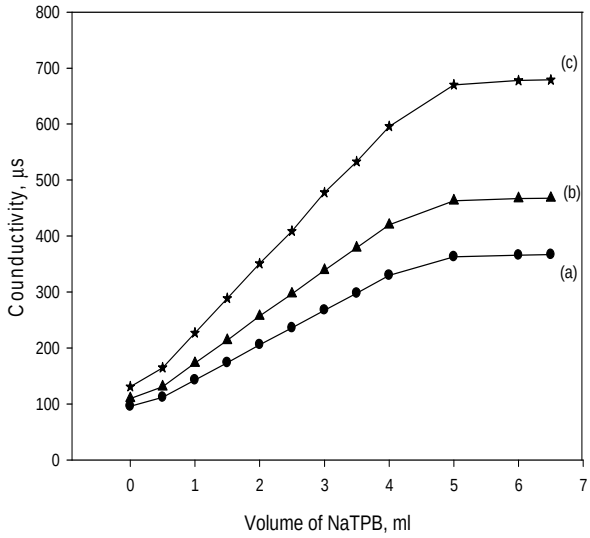


Figure.3: Effect of dilution on the end point of the counductimetric titration of 21.25 mg AlfCl with 10^{-2} M NaTPB in total volume 50 ml (a),75 ml (b),100 ml (c)

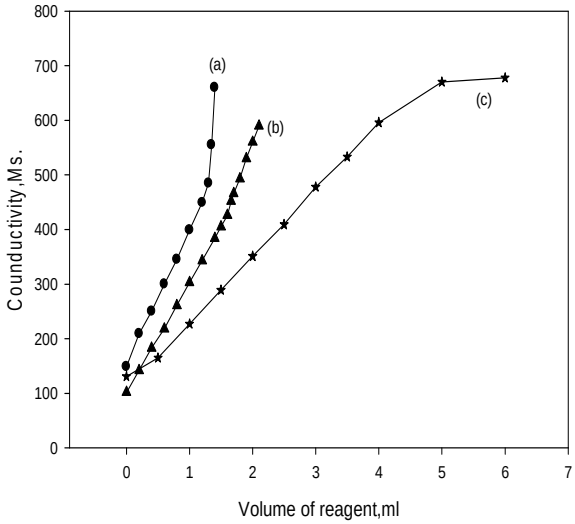


Figure.4: Conductimetric determination of 21.25 mg AlfCl using 10^{-2} M STA (a), PTA (b), NaTPB (c)

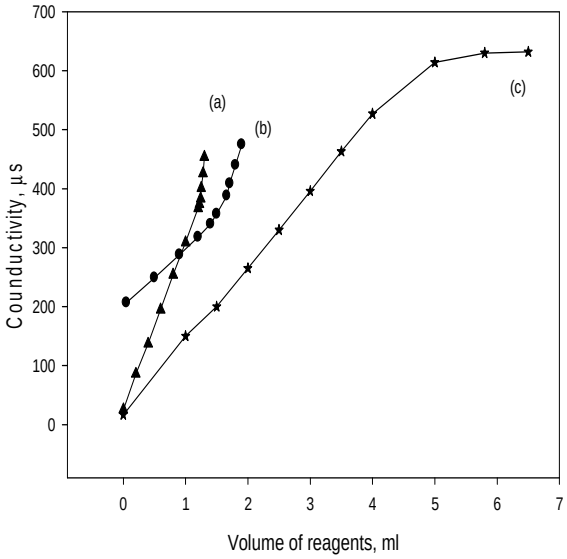


Figure 5: Conductimetric determination of 22.25 mg TamCl using 10^{-2} M STA (a), PTA (b), NaTPB (c)

Table 1: Conductimetric determination of Alfuzosin hydrochloride in pure form and in its pharmaceutical preparation

	PTA		STA		NaTPB	
mg taken	mg found ml^{-1}	Recovery %	mg. found ml^{-1}	Recovery %	mg found ml^{-1}	Recovery %
Pure solutions						
4.25	4.23	99.60	4.24	99.8	4.25	100.00
12.77	12.77	100.00	12.55	98.3	12.80	100.30
21.25	21.37	100.6	21.33	100.4	21.03	99.00
29.81	29.48	98.80	30.10	101.00	29.81	100.00
42.59	42.59	100.00	41.73	98.00	42.20	99.10
Mean ±RSD		99.80±0.66	99.50±1.31		99.60±0.59	
Xatral tablets (5 mg/tablet)						
4.91	4.90	99.80	4.81	98.00	4.91	100.03
14.73	14.56	98.90	14.57	98.93	14.74	100.08
24.55	24.37	99.30	24.51	99.84	24.56	100.05
34.37	34.19	99.50	34.12	99.30	34.39	100.08
49.11	49.03	99.85	48.71	99.20	49.06	99.90
Mean ±RSD		99.47±0.39	99.05±0.68		100.03±0.07	

Table 2: Conductimetric determination of Tamsulosin hydrochloride in pure form and in its pharmaceutical preparation

	PTA		STA		NaTPB	
mg taken	mg found ml^{-1}	Recovery%	mg. found ml^{-1}	Recovery%	mg found ml^{-1}	Recovery%
Pure solutions						
4.45	4.46	100.30	4.45	100.00	4.46	100.40
13.35	13.35	100.00	13.33	99.86	13.32	99.80.
22.25	22.22	99.87	22.18	99.70	21.89	98.40
31.15.	30.58	98.20	31.13	99.94	31.14	99.97
44.50	44.32	99.60	44.53	100.08	44.48	99.96
Mean ±RSD		99.59±0.82	99.92±0.15		99.75±0.69	
Ominic capsules (0.4 mg/capsules)						
4.45	4.44	99.99	4.44	99.90	4.44	99.90.
13.35.	13.34	99.99	13.34	99.93	13.34	100.05
22.25	22.25	100.00.	22.21	99.84	22.11	99.38
31.15	33.84	98.99	31.12	99.93	31.00	99.53
44.50	44.49	99.98	44.51	100.03.	44.41	99.80
Mean ±RSD		99.79±0.45	99.92±0.07		99.73±0.27	

Table 3: Analysis of the results obtained by the proposed method for Alfuzosin hydrochloride in the pure form and in pharmaceutical preparation

Items	Official Method (U.V.) [41]	PTA	STA	NaTPB
Pure solutions				
X±S.D[(a)]	99.99±0.50	99.96±0.41	99.60±0.21	100.13±0.31
F value[(b)]		1.49	5.67	2.60
t value[(b)]		0.10	1.61	0.53
Xatral tablets (5mg/tablet)				
X±S.D	99.97±0.90	98.99±0.01	99.73±0.43	100.48±0.28
F value		3.75	1.95	4.59
t value		1.56	0.73	1.72

[(a)] Mean ±S.D of five determinations
[(b)] F-tabulated is 6.39 and t-tabulated is 2.31 at 95% confidence limit

Table 4: Analysis of the results obtained by the proposed method for Tamsulosin hydrochloride in the pure form and in pharmaceutical preparation

Items	Official Method (HPLC)	PTA	STA	NaTPB
Pure solutions				
X±S.D[(a)]	99.99±0.4	100.6±0.80	100.7±0.35	00.2±0.60
F value[(b)]		4.00	1.31	2.25
t value[(b)]		1.52	2.98	0.65
Ominic capsules (0.4 mg/capsules)				
X±S.D	100.00±0.50	100.40±0.38	100.60±0.44	100.46±0.30
F value		1.37	1.29	2.78
t value		1.42	2.01	1.76

[(a)] Mean ±S.D of five determinations
[(b)] F-tabulated is 6.39 and t-tabulated is 2.31 at 95% confidence limit

Table 5: Calculation of solubility product of the Ion associates of Alfuzosin hydrochloride and Tamsulosin hydrochloride.

Ion associates	S	K_{sp}	$K=1/K_{sp}$
Alf-PT	$1.3x10^{-5}$	$7.7x10^{-19}$	$1.30x10^{18}$
Alf-ST	$1.4x10^{-5}$	$1.37x10^{-22}$	$7.30x10^{21}$
Alf-TPB	$6.5x10^{-5}$	$4.22x10^{-9}$	$2.37x10^{8}$
Tam-PT	$1.45x10^{-5}$	$1.6x10^{-17}$	$6.25x10^{18}$
Tam-ST	$1.34x10^{-5}$	$8.7x10^{-19}$	$1.15x10^{20}$
Tam-TPB	$7.0x10^{-5}$	$4.9x10^{-11}$	$2.04x10^{12}$

Where S is solubility, K_{sp} is solubility product, K is equilibrium constant.

CONCLUSION

The conductimetric method has the advantage of being simple, rapid, accurate, precise and reproducible method as a small amount of the investigated drug can be determined with a good accuracy and without interference from excipients such as micro-crystalline cellulose, talc and magnesium stearate, and hence it can be applied for the determination of AlfCl and TamCl in pure and pharmaceutical form in the quality control laboratories for routine analysis.

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