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Research Article

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Conductometric Titration Method for Determination of Alfuzosin Hydrochloride and Fexofenadine Hydrochloride Using Sodium Tetraphenylborate

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Abstract: A simple, precise and low cost conductometric method for the determination of alfuzosin hydrochloride and fexofenadine hydrochloride in pure form and pharmaceutical formulations using sodium tetraphenylborate has been described. The method is based on the formation of ion association complex of cations coming from the cited drugs with tetraphenylborate anions and the conductance of the solution is measured as a function of the volume of titrant. Various experimental conditions were evaluated. The described procedures allowed the determination of the studied drugs in double distilled water in the range of 2.13 – 10.65 and 2.50 – 13.45 mg of alfuzosin hydrochloride and fexofenadine hydrochloride, respectively. Statistical treatment of the experimental results indicates that the method is precise and accurate. The accuracy of the method is indicated by the excellent recovery 99.85-102.49 and 99.80-100.48% for alfuzosin hydrochloride and fexofenadine hydrochloride, respectively, and the precision is supported by the low relative standard deviation < 3.04%. The method was further applied successively to pharmaceutical formulations, the proposed method offering a high degree of accuracy and precision when compared to potentiometric pharmacopoeial methods.

Keywords: Alfuzosin Hydrochloride, Fexofenadine Hydrochloride, Sodium Tetraphenylborate, Conductometry

1. INTRODUCTION

Alfuzosin hydrochloride is an alpha1-adrenoreceptor blocker. It is used in the symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia and has been tried in the treatment of hypertension. Alfuzosin hydrochloride is chemically designated as N-{3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl(methyl)amino]propyl}tetrahydro-2-furamide hydrochloride [1]. Several methods have been reported for determination of alfuzosin hydrochloride in pharmaceutical formulations

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include RP-HPLC [2-6], HPLC and HPTLC [7,8], conductometry [9], spectrophotometry [10-16], colorimetry [17] and voltammetry [18]. Alfuzosin hydrochloride was also determined in biological fluids by HPLC [19-23] and voltammetric methods [18,24].

Fexofenadine, (±)-4-[1-Hydroxy-4-[4-(hydroxyl diphenylmethyl)-1-piperidinyl]butyl]-alpha, alpha-dimethyl benzene acetic acid, an active metabolite of terfenadine, is a selective histamine H_1-receptor antagonist, and is clinically effective in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria as a first-line therapeutic agent, such as loratadine and cetirizine [1]. Literature survey reveals several methods that have been used for the quantitative determination of fexofenadine hydrochloride in pharmaceutical dosage such as HPLC with ultra violet detection [25-33], HPTLC [34], potentiometry [35] and capillary electrophoresis [36,37]. Spectrophotometric methods have been reported for the determination of fexofenadine hydrochloride [28,38-46] from its individual and combined formulations with other active ingredients. Fexofenadine has been determined in human plasma by HPLC with UV detection [31,32,47], fluorescence detection [48] and tandem mass spectrometry detection [49-51].

The aim of this work was to report new condutometric methods that are simple, time-saving and accurate for the determination of alfuzosin hydrochloride and fexofenadine hydrochloride as a raw material and in some pharmaceutical preparations with no interference of other constituents in their formulations.

2. EXPERIMENTAL

2.1. Apparatus

A conductometer – pH meter Consort C830 (Belgium) equipped with conductivity cell (cell constant of 1.00) and combined glass pH electrode was used. The measurement ranges were 1.0-2000 µs/cm and 1.0-200 ms/cm with a precision ± 0.01 µs/cm. The temperature was maintained at 20 ± 0.1 ^{o}C with circulating water-bath thermostat connected to a jacket around the analysis vessel.

2.2. Chemicals

All chemicals and reagents used throughout this work were of analytical-reagent grade and solutions were made with double distilled water. Alfuzosin hydrochloride (AFZ) was obtained from Farmak, Czech, its purity was found to be 99.84% according to BP [52] and fexofenadine hydrochloride (FEX) was obtained from Ind-SWIFT Laboratories Limited, India, its purity was found to be 100.15% according to BP [52]. Sodium tetraphenylborate (NaTPB) was obtained from Aldrich. Methanol and ethanol (Merck) were also used. Pharmaceutical preparations containing AFZ and FEX were purchased from commercial sources in the local market.

2.3. Solutions

Solution of 0.01 M NaTPB was prepared by dissolving appropriate weight in 100 mL of double distilled water. The solution was standardized and kept in light-resistant, well-closed container. Stock standard solutions, 1.0 mg/mL of AFZ and FEX were prepared in double distilled water, stored in dark bottles and kept in the refrigerator for not more than 10 days. Other concentrations of working solutions were then prepared by suitable dilution of the stock solution with double distilled water.

2.4. General procedure

Aliquots of standard solution containing 2.13 – 10.65 mg of AFZ and 2.50 – 13.45 mg of FEX were transferred to a 25 mL calibrated flasks and made up to the mark with double distilled water. The

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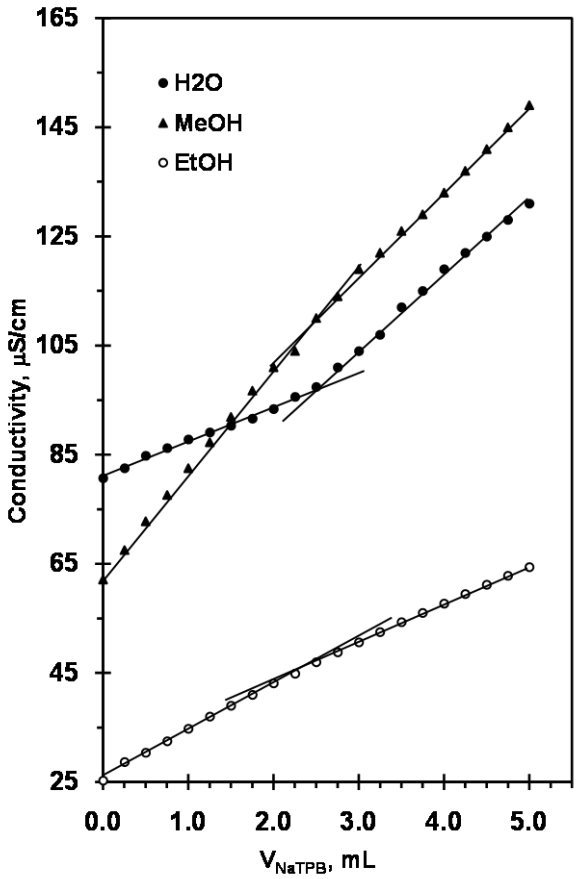

Figure 1. Effect of solvent on the end point of the conductometric titration of 25 mL of AFZ 1.0×10^{-3} M with 10^{-2} M NaTPB at 20 °C.

contents of the calibrated flask were transferred quantitatively to a conductometric titration cell, the conductivity cell was immersed in the sample solution, the solution was then titrated conductometrically against 10^{-2} M NaTPB and the conductance was measured subsequent to each addition of the reagent solution and after thorough stirring for one min. The conductance was corrected for dilution [53] by means of the equation (1), assuming that conductivity is a linear function of dilution.

$$\Omega^{-1}_{correct} = \Omega^{-1}_{obs} [V_1+V_2/V_1] \quad (1)$$

where $\Omega^{-1}_{correct}$ is the corrected electrolytic conductivity, Ω^{-1}_{obs} is the observed electrolytic conductivity, V_1 is the initial volume and V_2 is the volume of reagent added.

A graph of corrected conductivity versus the volume of added titrant was constructed and the endpoint was determined conductomerically.

The amount of drugs under study was calculated according to the equation (2),

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

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.

2.5. Procedure for the pharmaceutical formulations

Twenty tablets or the contents of 20 capsules were weighed and finely powdered. An accurately

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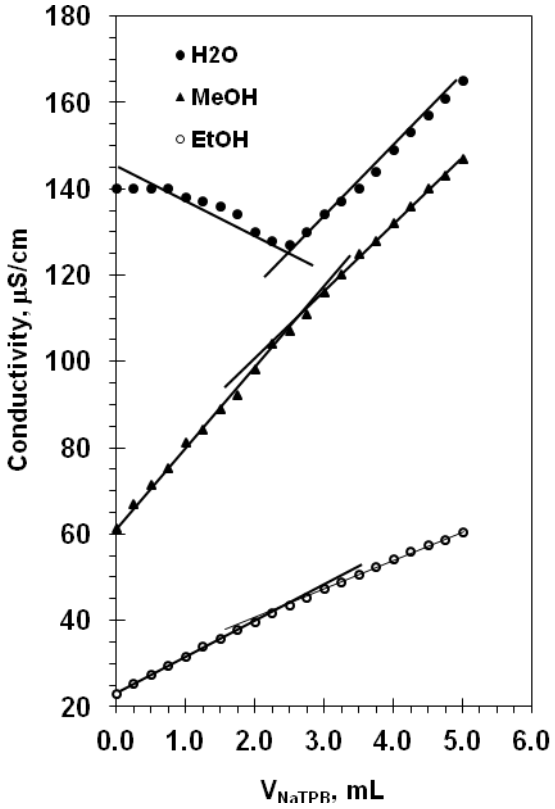

Figure 2. Effect of solvent on the end point of the conductometric titration of 25 mL of FEX 1.0×10^{-3} M with 10^{-2} M NaTPB at 20 ^{o}C.

weighed quantity of the powder equivalent to 100 mg of drug was dissolved in a 100 mL of methanol and sonicated for 5 minutes and then filtered. The combined filtrate was evaporated to the dryness. The remaining portion of the solution was dissolving in a 100 mL volumetric flask to the volume with double distilled water, and the resulting solution was used for analysis by the recommended procedures in the concentration ranges mentioned above.

3. RESULTS AND DISCUSSION

Conductometric measurements can be used in quantitative titrations of ionic solutions 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. The shape of the titration curve depends on all the species present during the titration process and other factors such as viscosity, dielectric constant of the solvent used, solvation, ion-pair association and proton transfer.

Alfuzosin hydrochloride and fexofenadine hydrochloride are able to form precipitates with sodium tetraphenylborate so the applicability of conductometric titration of these drugs with the mentioned reagent, was tested. The different parameters affecting the end point, such as solvent, temperature and concentration of both titrant and titrand, were studied.

3.1. Effect of solvent

Three different titrations were described for each drug: (i) aqueous solutions of both drug and

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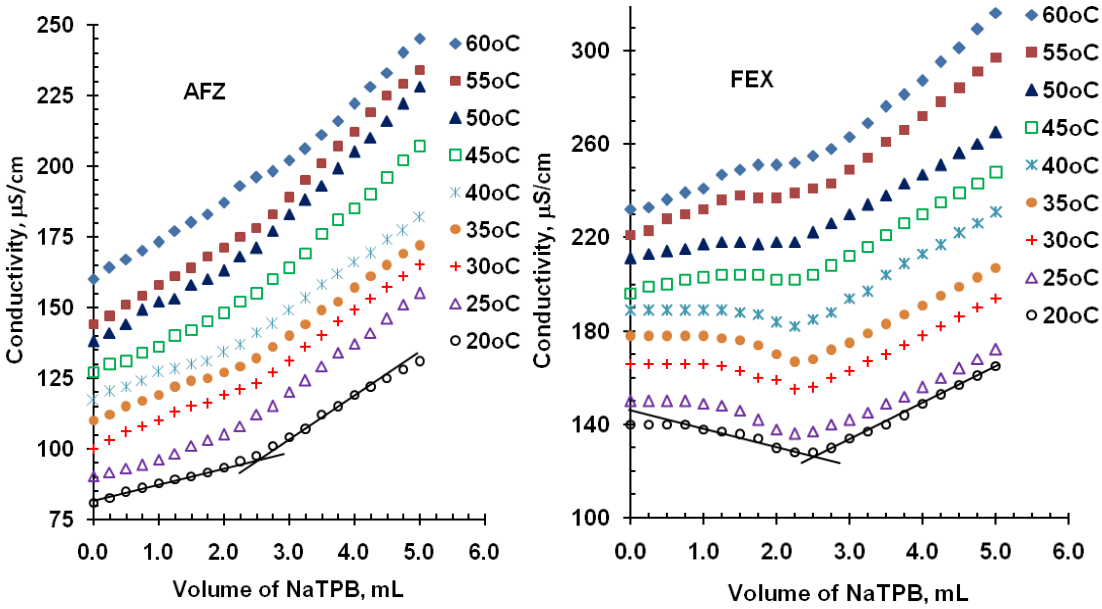

Figure 3. Effect of temperature on the end point of the conductometric titration of 25 mL of AFZ and FEX 1.0×10^{-3} M with 10^{-2} M NaTPB in aqueous medium at 20 -60 ^{o}C.

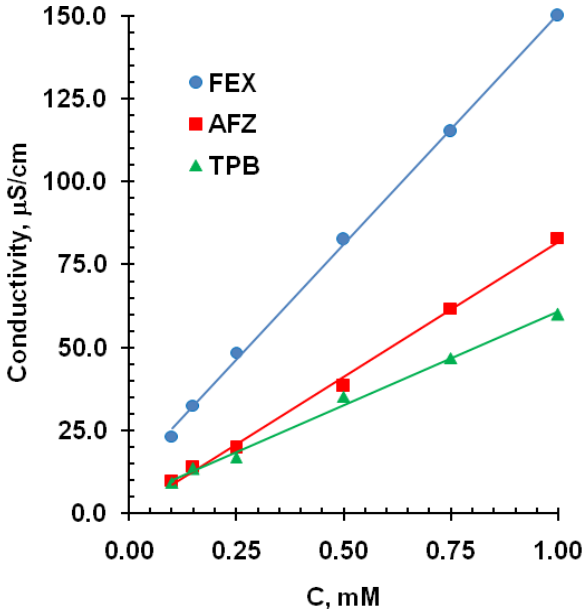

Figure 4. Effect of electrolyte concentration on the conductivity in double distilled water.

reagent, (ii) methanolic solutions of both drug and reagent and (iii) ethanolic solutions of both drug and reagent at 20 ^{o}C. It was found that procedure (i) in aqueous media was the most suitable for successful results as shown in Figures 1 and 2, because in procedures (ii) and (iii) the end-point detection is very difficult and so the precision is very low, whereas in water medium sharpest end point was detected. So water was the best and cheapest choice medium for conductometric titration.

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3.2. Effect of temperature

The relation between the conductance values and temperature of the solutions of AFZ, FEX and NaTPB was linear increasing in aqueous media in the range of 20-60 ºC. The effect of temperature on the end point of the conductometric titration was tested by carrying out titrations at 20 - 60 ^{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 40 ^{o}C, then 20 ^{o}C was used for carrying out the other variables (Figure. 3).

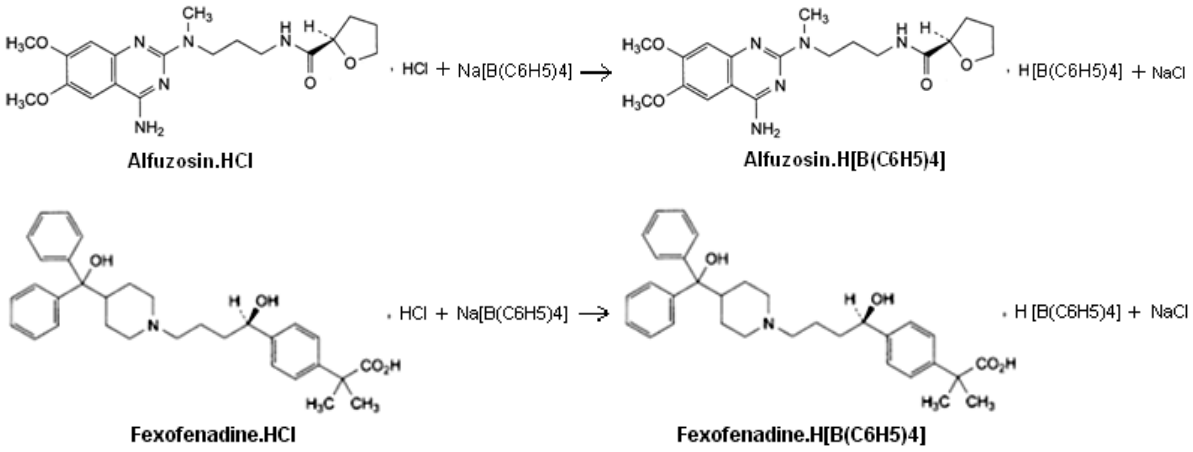
3.3. Effect of reagent concentration

The relationship between the conductance values and the concentration of AFZ, FEX and NaTPB solutions was linear increasing in the range of 0.1-10 mM for AFZ and FEX, and 0.1-20 mM For NaTPB. Figure 4 shows this relationship in the range of 0.1-1.0 mM. The conductance value of AFZ and FEX solution was greater than that for NaTPB solution at the same concentration with about two and three times, respectively. The effect of electrolyte concentration on the specific electrical conductivity was studied and indicated that the values were decreased as follows FEX > AFZ > NaTPB in aqueous medium and the order becomes NaTPB > AFZ > FEX in alcoholic media.

A weight of the investigated drugs 6.38 mg of AFZ and 8.07 mg of FEX were dissolved in 25 mL double distilled water was titrated against 1×10^{-3}, 5×10^{-3} and 1×10^{-2} M NaTPB solution. The results indicated that, titrant solutions lower than 10^{-2} M are not suitable for conductometric titrations as the conductance readings were unstable and the inflection at the end point was very poor. So, The reagent concentration in each titration must be not less than ten times that of the drug solution in order to minimize the dilution effect on the conductivity throughout the titration. The optimum concentration of NaTPB was 1×10^{-2} M to achieve a constant and highly stable conductance reading after 1 minute mixing. On the other hand, when the same above mentioned amounts of the investigated drug were dissolved and diluted up to 25, 50 and 75 mL with distilled water and titrated against 10^{-2} M NaTPB solution (optimum titrant concentration). The results showed that, dilution of the titrand up to 75 mL has no effect on the position of the end point and the shape of the titration curve.

3.4. Determination of the drug–titrant ratio

The conductometric technique was used for the determination of AFZ and FEX using NaTPB as a titrant; the ion- associates are formed between the studied drugs and NaTPB as shown in the following equation:



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The investigated systems showed two straight lines are obtained, intersecting at the end-point. In the case of AFZ, the titration curve showed a steady increase in conductance values up to the equivalence point where a sudden change in the slope occurs. This divergence from linearity can be attributed to the formation of an ion-associate, presumably, by replacing the drug cation ($AFZH^+$) with the highly mobile Na^+ ions and formation of alkali halide in the solution as a result of the reaction, so the conductivity increases. After the endpoint, more Na^+ reagent is added and the conductivity changes more rapidly as shown in Figure 5. In the case of FEX, the first branch gradually decreasing and the second sharply ascending .The decrease of conductance may be attributed to the formation of more stable FEX.H $[B(C_6H_5)_4]$ complex in the solution as a result of the reaction. After the end-point, more Na^+ reagent is added, the titration curve indicate a sharply increase of conductance (Figure 5). The results show an obvious inflection point in the conductance titration curve at drug-reagent molar ratio of 1:1 (AFZ:TPB, FEX:TPB) as shown in Figure 5.

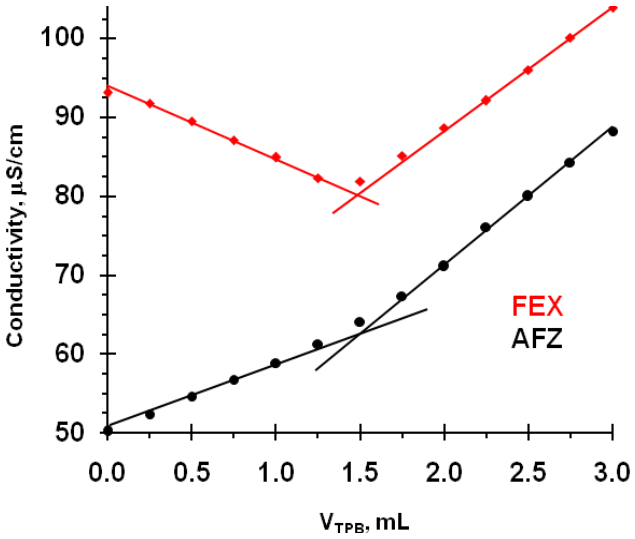

Figure 5. Conductometric titration curves of 6.38 mg AFZ and 8.07 mg FEX in total volume 25 mL (0.6 mM of both) with 10^{-2} M NaTPB at 20 ^{o}C.

3.5. Linearity

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression [54] of observed drug concentration against the theoretical values (6 points) was calculated. Student's t-test (at 95% confidence level) was applied to the slope of the regression line (Table 1) and showed that it did not differ significantly from the ideal value of unity. Hence, it can be concluded that there are no systematic differences between the determined and true concentrations over the cited range. The standard deviation (SD) can be considered satisfactory, at least for the level of concentrations examined.

3.6. Validation of the methods

The validity of the methods for the analysis of AFZ and FEX in pure state and formulations was

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examined by analyzing the samples using the proposed procedures. The results obtained for pure drug are given in Table 2 and show that good recoveries and standard deviations were obtained. The optimum concentration ranges for determining AFZ and FEX using NaTPB were 85 – 426 and 100 – 538 μg/mL, respectively, at which well-definite inflections and stable conductance values were obtained. The precision and accuracy of the methods were tested by analyzing six replicates of the drugs. The low values of relative standard deviation (RSD) indicate good precision and reproducibility of the methods and the average percent recoveries obtained were quantitative, indicating good accuracy of the methods.

Table 1. Linear regression analysis for alfuzosin hydrochloride and fexofenadine hydrochloride using sodium tetraphenylborate

Parameters	AFZ	FEX
Optimum concentration range (mg/mL)	0.085 – 0.426	0.100 – 0.538
Intercept of the regression line[a]	- 1.436	1.227
Slope of regression line	1.003	0.993
Student's t[b] (2.310)[c]	1.907	1.837
Range of error (%)	± 0.82	± 0.74

[a] Observed versus theoretical. [b] Comparison with pharmacopoeial method [52]. [c] Value in parenthesis is the theoretical t-value for five degrees of freedom.

Table 2. Accuracy and precision of the proposed conductometric titration methods.

Method	μg/mL		Relative error (%)	RSD (%)	Recovery %
	Taken	Found*			
AFZ	85	87.12	2.49	2.93	102.49
	170	169.75	-0.15	1.75	99.85
	255	255.25	0.10	1.33	100.10
	340	341.09	0.32	1.37	100.32
	426	426.00	0.00	0.50	100.00
FEX	100	99.80	-0.20	3.04	99.80
	200	200.20	0.10	1.18	100.10
	250	250.10	0.04	0.85	100.04
	300	300.07	0.02	0.81	100.02
	400	401.30	0.33	0.76	100.33
	500	502.40	0.48	0.61	100.48

**Average of six determinations*

3.7. Application to the pharmaceutical dosage forms

The proposed technique was applied to the tablets and capsules. The ingredients in the tablets and capsules did not interfere in the experiments. The applicability of the proposed methods for the assay of

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Table 3. Determination of AFZ and FEX in different pharmaceutical formulations by the proposed and official methods

Drug	Label claim	%Found[a] ± SD	
		Proposed method	Official method [52]
Alfosin 2.5	2.5 mg AFZ/tab	100.32 ± 0.47 *t* =1.50 *F* =2.09	100.58±0.68 *t* =1.90
Alfosin 5	5 mg AFZ/tab	100.60 ± 0.94 *t* =1.42 *F* =3.14	99.68±0.53 *t* =1.35
Allergy stop	60 mg FEX/cap	101.04 ± 0.17 *t* =1.91 *F* =1.71	100.79±0.13 *t* =1.32
	120 mg FEX/tab	100.01 ± 0.19 *t* =2.01 *F* =1.60	101.05±0.15 *t* =1.28
	180 mg FEX/tab	99.91 ± 0.16 *t* =1.73 *F* =1.31	99.78±0.14 *t* =1.79
Fexodine	60 mg FEX/cap	100.95 ± 0.21 *t* =1.82 *F* =1.72	99.71±0.16 *t* =1.24
Fenadin	120 mg FEX/tab	100.22 ± 0.14 *t* =1.07 *F* =1.47	99.69±0.17 *t* =1.23
	180 mg FEX/tab	100.30 ± 0.32 *t* =2.09 *F* =3.16	100.52±0.18 *t* =1.81

[a]*Five independent analyses. At 95% confidence level t-value is 2.776 and F-value is 6.26.*

alfuzosin hydrochloride and fexofenadine hydrochloride in formulations was examined by analyzing various formulations and the results are tabulated in Table 3 were compared to the official non-aqueous titration method for alfuzosin hydrochloride and fexofenadine hydrochloride [52] by means of *t*- and *F*-values at 95% confidence level. In all cases, the average results obtained by proposed methods and official method were statistically identical, as the difference between the average values had no significance at 95% confidence level. The low values of RSD show the results are reproducible. The proposed methods are simple, sensitive and reproducible and can be used for routine analysis of fexofenadine hydrochloride in pure form and in formulations. The commonly used additives such as starch, lactose, glucose, titanium dioxide, and magnesium stearate do not interfere

4. CONCLUSION

The simple, rapid and accurate conductimetric method described in this paper can be an alternative to the more complex and expensive methods for assay of alfuzosin hydrochloride and fexofenadine hydrochloride without interference from common excipients. The proposed method is easy, cheap, accurate and very useful for the determination of the studied drugs in their pharmaceutical

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formulations and can be applied in laboratories for routine analysis. The developed method for AFZ is higher sensitivity as compared to similar reported method [9].

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