Full Paper

Spectroscopic and Conductometric Characterization of the Ion-Pairs Constituted by Oxyphenonium Bromide in Aqueous Solutions

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Abstract- In this study, spectroscopic and conductometric investigations of the interactions between oxyphenonium bromide (OXBr) and two dyes; chromotrope 2R (C2R) and ammonium reineckate (AMRT) are reported. The solubility product constant as well as other parameters related to the process of precipitating OXBr is premeditated operating the conductometric procedure. Moreover, contemporary approaches towards equivalence point localization have been pursued and compared. In this itinerary, the numerical differential conductivity methods were objective and systematic. However, Boltzmann sigmoid fitting model was more adequate for data analysis with less errors compared to the conventional and the differential methods. A molar ratio of (1:1) (OXBr:reagent) complexes in aqueous solutions have been determined conductometrically.The described procedures allowed the investigation of OXBr within the range of 3-15 mg using both reagents. Moreover, the obtained precipitate has been spectroscopically characterized using IR and ^{1}H-NMR. The proposed conductometric method was applied successively to pharmaceutical formulations containing OXBr and the results obtained were favorably compared with those obtained using the reference method.

Keywords- Conductometry, Spectroscopy, Oxyphenonium bromide, Pharmaceuticals, Solubility product constant, Differential conductivity, Boltzmann sigmoid

1. INTRODUCTION

Chemically assigned as alpha-phenylcyclohexaneglycolic acid ester diethyl(2-hydroxyethyl)methylammonium bromide "Scheme 1", oxyphenonium bromide (OXBr) is a widely used antispasmodic with parasympatholytic effects. With pharmacological actions similar to those of atropine - a model anticholinergic agent – oxyphenonium is commonly used in treatment of gastric and duodenal ulcersand in eye drops for its mydriatic effect [1]. Being non official in any pharmacopoeia, lots of efforts have been exerted for the determination of OXBr either pure or in biological fluids. In this concern, many techniques have been proposed for its determination. Two main techniques have been extensively reported: spectrophotometric methods [2-7] and chromatographic methods [8-10].
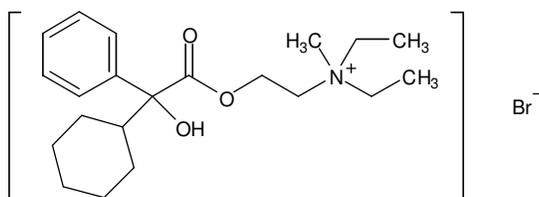
Scheme 1. Oxyphenonium Br$^-$

Two reagents have been utilized in the current study, ammonium reineckate which is Chromate (1-),diaminetetrakis-(thiocyanato-N)-, ammonium, (OC-6-11)- and chromotrope 2R, which is chemically known as disodium 4,5-dihydroxy-3-(2-phenyldiazen-1-yl) naphthalene-2,7-disulfonate. Both reagents have been used for quantitative determination of many pharmaceutical compounds applying various analytical techniques [11-15].

This treatise comes as an extension of our efforts [16,17] in the application of ion pairing reagents in conductometric and spectroscopic characterization of drugs of interest. In the current effort, ion pairs constituted from OXBr and C2R/AMRT are thoroughly investigated and presented. In addition, the solubility product and consequently the equilibrium constants of the formed precipitate were calculated using the available equivalent conductance values.

Moreover, the current study entails the use of Boltzmann sigmoid fitting model and the differential conductivity methods [18-23] for the analysis of conductivity versus volume data with a perspective of locating a precise equivalence point. Treatment of the data with these methods gives more accurate endpoints compared to the conventional method, a concern which is reflected on the main features of the validation procedure: accuracy and precision. Moreover, spectroscopic characterization of OXBr-AMRT ion asscoiate has been done using IR and ^{1}H-NMR.

2. EXPERIMENTAL

2.1. Apparatus

HANNA Conductivity / TDS Meter (HI 8033), with a HANNA Conductivity Probe (HI 76301W) was used. FT-IR measurements were recorded as KBr disks using Mattson 1000 spectrophotometer, Micro analytical Center, Cairo University, Giza.^{1}H-NMR spectra were measured in DMSO-d_6, using Avance II 600 MHz NMR spectrometers National Research Center, Cairo, Egypt. Chemical shifts (ppm) were reported relative to TMS.

2.2. Materials and reagents

All reagents used were chemically pure grade. Doubly distilled water was used throughout all the experiments.
1. Oxyphenonium bromide (OXBr) was provided by (Hi-Pharm Co. Egypt); (MW = 428.46 g/mol and its purity was found to be 99.97 ± 0.33% [6]).
2. Spasmodine® tablets; Hi-Pharm Co., Egypt, (5 mg of oxyphenonium Br/ tablet) was obtained from local pharmacy stores.
3. Ammonium reineckate (AMRT), and chromotrope 2R (C2R) were obtained from Aldrich. Aqueous solutions of drug and reagents (0.1% (w/v) and 5×10^{-3}M) were used throughout the study.

2.3. Procedure

2.3.1. Pure Pharmaceuticals

Various volumes containing 3–15 mg of the pure OXBr solution were transferred into the titration cell and the volume was made with water up to 50 mL. The conductivity cell was immersed in and the solution was titrated with 5×10^{-3}M of the titrant using a microburette. The conductance was measured 2 minutes subsequent to each addition of the reagent after thorough stirring. A conductivity (corrected for dilution) *vs.* volume plot for a particular titrant was constructed and the endpoint was determined. The nominal content of the compound under study was calculated using the following equation:

Amount of the drug (mg) = VMR / N

Where V=volume (mL) of the titrant consumed in the titration, M=relative molecular mass of the analyte, R=molarity of the titrant, and N=number of moles of the titrant consumed per one mole of the analyte. Determination of mole ratio was done using a fixed concentration of the drug and varying concentrations of the titrants. The experimental data was fitted to a non-linear predefined fitting model (PSI Plot software).

2.3.2. Pharmaceutical Formulations

An amount of pulverized tablets equivalent to 250 mg of the active ingredient was weighted accurately and transferred into a 100 mL conical flask. The drug was extracted

three times with 70 mL of distilled water. After extraction, the flask was washed with a few mL of water, then, combined washings, and extracts were filtered into a 250 mL volumetric flask. The volume was made to the mark with distilled water. The nominal content of the active component in tablets was determined as described in the Procedure section.

2.3.3. Preparation of ion-associates for Spectroscopic Characterization

The ion pair with AMRT was prepared by mixing solutions containing 10^{-2} M of the reagent, and the requisite amount of OXBr. The formed precipitate was filtered, thoroughly washed with water, and dried at room temperature. IR and ^{1}H-NMR spectroscopy were used to characterize this precipitate [24].

2.4. Conductometric Determination of the Solubility Product Constant of OXBr-AMRT Ion Pair

The conductivities of solutions of different concentrations (C) [for both OXBr and AMRT] were measured at 25˚C. The specific conductivities (K_s), corrected for the effect of dilution; were calculated and used to obtain the equivalent conductivities (Λ) of these solutions.

Straight-line plots of Λ *vs.* $\sqrt{C}$ were constructed and Λ_{oOXBr} and Λ_{oAMRT} were determined from the intercept of the respective line with the Λ axis. The activity coefficients of the involved ions were taken as unity because all the solutions were sufficiently dilute. Kohlrausch's law of independent migration of ions [25] was used to calculate the value of $\Lambda_{oOXBr-AMRT}$. The solubility (S) and solubility product constant (K_{sp}) values of a particular ion associate were calculated using the following equations;

$$S = K_s \times 1000/\Lambda_{o \text{ "ion-associate"}} \qquad\qquad (1)$$
$$K_{sp} = S^2 \qquad\qquad \text{(for 1:1 Ion Associates)} \qquad (2)$$
$$K = 1/K_{sp} \qquad\qquad (3)$$

Where, "K_s" are the specific conductivity of the saturated solution of the ion associate, Λ_o is the intercept of the Λ *vs.* $\sqrt{C}$ curve and K is the equilibrium constant.

3. RESULTS AND DISCUSSION

3.1. Conductometric Procedure

In the current article, formation of ion pair complexes has been utilized for quantitative determination of a quaternary ammonium compound, oxyphenonium bromide. Having a molecular formula of $[N^+(R_2R'R'')X^-]$, where R, R' and R'' are hydrocarbon chains of different lengths and nature and X^- is a bromide anion, "Scheme 1", OXBr is freely soluble in

water. This property has been exploited for the determination of OXBr via a conductometric procedure [26].

Considering the wide usage of this OTC drug in Egypt and the lack of an economical and straightforward procedure in literature and pharmacopoeias for its determination, we have undertaken this task. Two titrants were used for this purpose, C2R and AMRT. Both titrants were found to react with OXBr forming stable ion pairs with different aqueous solubilities. While the (OX^+-AMRT^-) ion pair was insoluble, the other ion pair (OX^+-C2R^-) was soluble in water, under the described experimental conditions.

Assuming that conductivity is a linear function of dilution, specific conductivity values corrected for dilution, were plotted as a function of volume of titrant [27]. The obtained plots using both titrants exhibit two straight lines of different slopes and they intersect at the change of slope. The point of intersection was presumed to be the equivalence point of titration at which the concentration of the drug can be calculated, Fig. 1. Such a procedure is known as the "conventional procedure" for locating the endpoint.
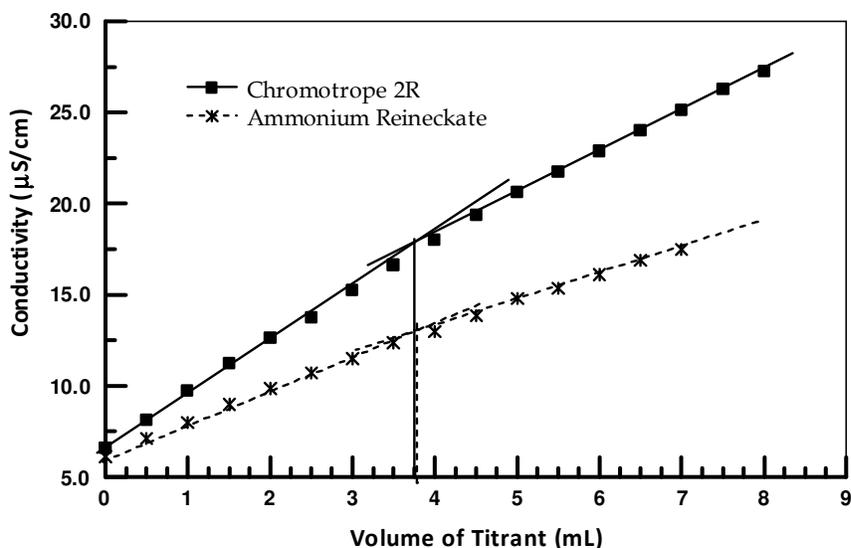
Fig. 1. Conductometric titration curve of 8 mg OXBr titrated using 0.005 M C2R and AMRT, the equivalence point was located following the conventional procedure

3.2. Reaction Mechanism and Molar Ratio

Using AMRT as titrant, the molar conductance (Λ_m) of the drug solution was monitored as a function of mole ratio ([D]/[R]), Fig. 2. The tentative data was fitted using a non-linear least squares fitting model predefined by PSI Plot software. As can be noticed, addition of AMRT to the OXBr solution causes an incessant increase in molar conductance of the solutions. This might be a sign of formation of complexes that are more mobile compared to the solvated

drug molecules. This continuous increase in molar conductance starts to level off at the point where the [D]/[R] ratio is equal to unity, such a behavior further confirms the formation of stable (1:1) ion pairs. Further addition of AMRT causes a slight increase inmolar conductance, however this increase is not linear and less than anticipated, an evidence that might support the formation of insoluble and less conducting ion pair [16,17]. The reactions may be represented by the equation:

$$N^+(R_2R'R'')Br^- + NH_4[Cr(NH_3)_2(CSN)_4] \longrightarrow \{N^+(R_2R'R'')[Cr(NH_3)_2(CSN)_4]\}_s + NH_4Br$$
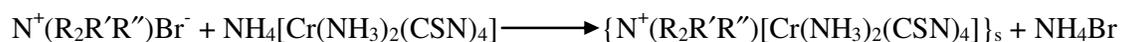
In case of C2R, a similar behavior was observed (Fig. 2), however a soluble 1:1 ion pair was formed. The reaction can be described by the following equation:

$$N^+(R_2R'R'')\,Br^- + C2R \longrightarrow N^+(R_2R'R'')[C2R]^- + NaBr$$
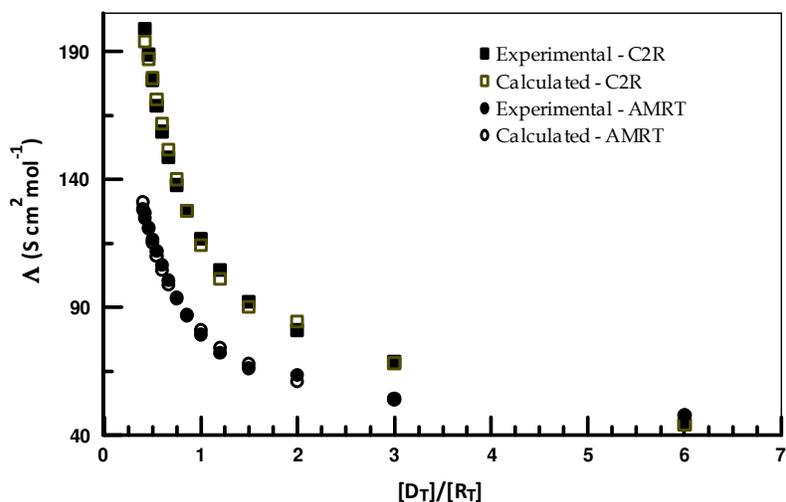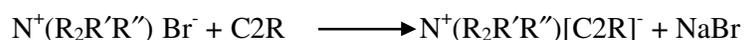
Fig. 2. Molar conductance–Mole ratio plots for the complexes of C2R and AMRT with OXBr in pure water. Experimental values are represented by close squares and circles while the calculated values are represented by open ones. Calculated values are obtained by fitting the experimental values using non-linear least squares fitting algorithm

3.3. Conductivity versus Volume Data Analysis

The conventional procedure which has been illustrated in the preceding sections, is the one used by most of researchers for detecting the endpoint. Nevertheless, application of this method poses some drawbacks under certain conditions. Chief difficulties come from the weak curvature around the endpoint and its dependence on the number of data points selected

to perform the linear fitting before and after the transition. Hereby and based on the previously described behavior, many approaches; basically first and second numerical derivative methods and Boltzmann sigmoid fitting, have been suggested to locate the endpoint. This trend has been pursued to compare the accuracy of the attained endpoint by each of the proposed techniques.

Differentiation of the original conductivity data against the volume of titrant was one of the suggested approaches, (Fig. 3). Locating the equivalence point was easier following the second derivative procedure compared to the first derivative one, since locating the intersection with the X- axis is easier than locating a maximum. This procedure was more objective and consistent compared to the conventional procedure. Yet, and as previously described with the conventional procedure, the probable deficiency in the number of available data points together with the fact that numerical processing of raw data points would intensify the intrinsic experimental errors, might afflict the application of numerical differentiation procedure.
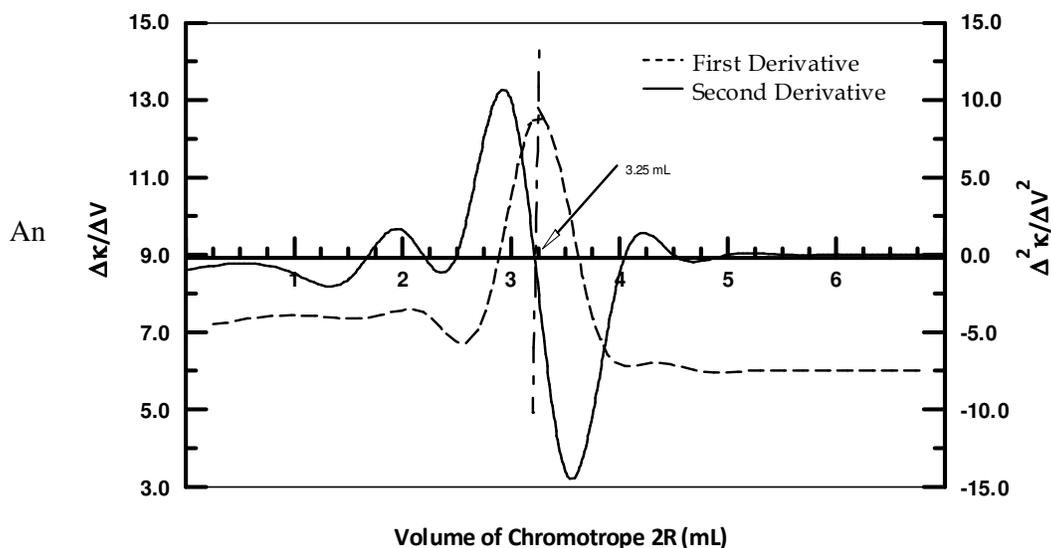
Fig. 3. Conductometric titration of 6.43 mg OXBr with 5×10^{-3} M C2R applying the numerical first derivative plot ($\Delta C/\Delta V$) and numerical second derivative plot ($\Delta^2 C/\Delta V^2$). Arrows show the equivalence point determined using the described procedures

An assessment of the recovery percentage and percentage of error obtained using the three previously depicted techniques is shown in Table 1. From this table, it seems more suitable to obtain such figures from the original data without further handling, which eventually brings in erroneous results.

Table 1. A comparison between the four suggested procedures for conductivity–volume data analysis. C2R was used as a titrant for the determination of 6.43 mg of OXBr

Procedure	Found (mg)	Recovery %	% Error
Conventional	6.43	100.00	0
First Derivative	6.79	105.59	5.59
Second Derivative	6.79	105.59	5.59
Boltzmann Sigmoid	6.43	100.00	0

In order to evade any errors encountered by numerical derivatization of conductivity data, we suggest a fitting model "Boltzmann sigmoid" which explicates the behavior of conductivity versus volume graphs and allows simple fitting of the experimental data. The proposed model has been described using the following equation [18, 23]:

$$f(X) = \frac{A_1 - A_2}{1 + e^{(X - X_0)/\Delta X}} + A_2 \qquad (4)$$

Where A_1 and A_2 represent the asymptotic value for small and large values of x respectively, x_0 represents the endpoint and Δx deals with the width of transition. Fig. 4 shows the determination of OXBr applying Boltzmann model. The % error resulting from applying this model is nothing compared to derivatization of the original data, Table 1.
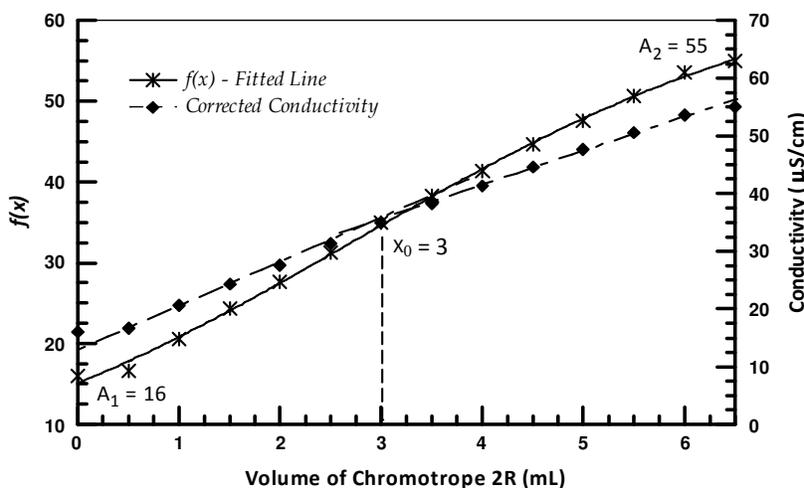

Fig. 4. Conductometric titration of 6.43 mg OXBr with 5×10^{-3}M C2R applying the Boltzmann sigmoid method *f(x)* compared to the conventional method. Value of X_0 denotes the equivalence point determined using Boltzmann model, $f(x_0) = (A_1 + A_2)/2$

3.4. Determination of Solubility Product Constant

The degree of hydrophobicity of OXBr recognition species determines the degree of completeness of the studied reactions. In this itinerary, conductivity data was utilized to find out the solubility product constant of the formed precipitate and therefore other functions related to ion pair formation such as the solubility and the formation constants [23, 28-30]. The solubility product values of the investigated ion-associates were found to be 2.01×10^{-17} using AMRT. As shown in Table 2 and Fig. 5, the equilibrium constant values (K) are high enough to indicate the high degree of completeness of the ion-pairing reaction (> 99.9%).
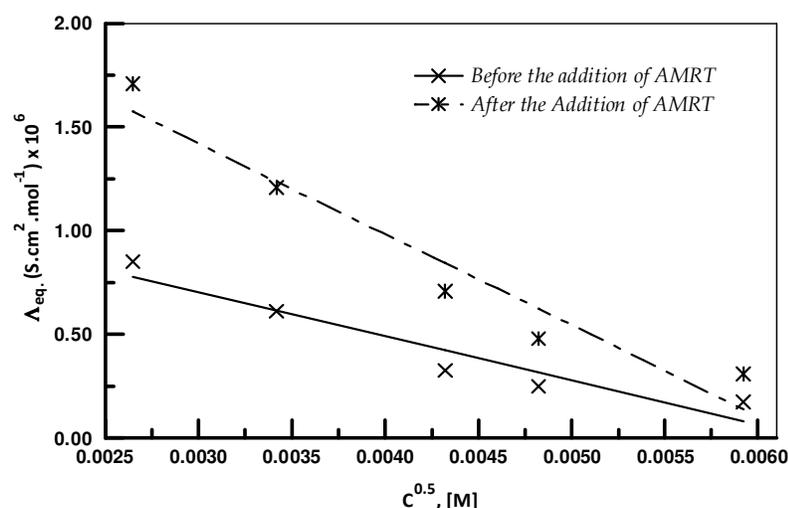
Fig. 5. Equivalent conductance (Λeq.) *vs*. the square root of concentration $C^{0.5}$ for OXBr (Before and after addition of AMRT)

Table 2. Solubility product constant and other functions related to the formation of OXBr-AMRT ion pair:

Solubility (S) M	K_{SP}	$K = 1 / K_{sp}$
4.48×10^{-9}	2.01×10^{-17}	4.98×10^{16}

3.5. IR and ^{1}H-NMR Spectra

Ion pairing of OXBr with AMRT was investigated by comparing IR, and ^{1}H-NMR spectra of the formed ion pair complex with those of the free ligands.

3.5.1. IR Spectra

The formation of an ion pair through the interaction of OXBr and AMRT is strongly supported by detecting the chief infrared bands (function groups) of both in the resultant

complex spectrum. An assessment of the pertinent IR bands and the shifts in their intensities before and after ion pairing noticeably explicates the electronic structure and symmetry changes upon formation of the ion associate.

Generally, the IR spectrum of OXBr reveals characteristic bands at 3351 cm^{-1} assigned to v_{OH} vibration; at 3059 cm^{-1} due to v_{CH} (aromatic). Sharp absorption bands at approximately 2928 and 2852 cm^{-1} and less expressed one at 1454 cm^{-1} was observed. The first two might be assigned to symmetric and asymmetric vibrations of methyl and methylene groups while the third one corresponds to their bending vibrations. A characteristic peak appears at 1731 cm^{-1} corresponding to C=O stretching vibration.

On the other hand, the IR spectrum of AMRT has a characteristic band at 2119 cm^{-1} due to $v_{(CN)}$ "in the Cr-NCS link" stretching vibration, a band at 766 cm^{-1} due to $v_{sym(C-S)}$ and at 499 cm^{-1} due to $\delta_{(NCS)}$ deformation vibration [31].

The IR spectrum of the formed ion associate shows a band corresponding to v_{CH}(aliphatic) at nearly the same frequency (2854-2928cm^{-1}) as that of OXBr. The band corresponding to the stretching vibrations of C=O appears at 1730 cm^{-1}. In addition, the peak due to v_{NCS} is shifted to a lower frequency by 40 cm^{-1}. Peaks due to $v_{sym(C-S)}$ and $\delta_{(NCS)}$ appear at 699 and 489 cm^{-1} respectively. The above arguments indicate that an ion associate has been formed between OXBr and AMRT.

3.5.2. ^{1}H-NMR Spectra

Upon studying the NMR spectra of OX-AMRT complexes, it was noted that some aliphatic protons signals assigned to free OXBr [32] that are peaks of equivalent protons have been observed as singlet peak due to the rapid exchange of OXBr between the ion pair sites and the bulk solution [33]. Some of these peaks are presented in Table 3.

The suggested structure of the formed ion pair according to NMR findings is shown in Scheme 2.

$$Cr(SCN)_4(NH_3)_2$$

Scheme 2. Suggested structure of oxyphenoniumreineckate (OXBr-AMRT) ion associate with NMR numbering

Table 3. Significant chemical shifts (ppm) of the formed OX-AMRT ion-associate compared to free OXBr

OXBr	OX – AMRT
δ 1.55 (3H, m, H6e, H2a, H3a)	δ 1.56 (3H, s, H6e, H2a, H3a)
δ 2.14 (1H, m, H1a)	δ 2.14 (1H, s, H1a)
δ 2.50 (4H, m, He)	δ 2.47 (4H, s, He)
δ 7.24 (1H, m, H4')	δ 7.24 (1H, s, H4')
δ 7.31 (2H, m, H3',5')	δ 7.32 (2H, m, H3',5')
δ 7.52 (2H, m, H2',6')	δ 7.52 (2H, m, H2',6')

3.6. Analytical Applications

In order to evaluate the applicability of the suggested procedure, the proposed methods have been applied for the determination of OXBr in pure forms and in dosage forms (Fig. 6). The mean recovery values of OXBr from its formulation were close to those of the pure drug, demonstrating a high selectivity of the proposed methods and showing that presence of excipients in the studied formulation does not affect the results (Tables 4 and 5). The results obtained were in good agreement with the labeled values for OXBr formulation.

The accuracy and reproducibility with respect to the reference method [6] were assessed by performing student's t and F tests, respectively. Mean values in Tables 4 and 5 do not show any systematic error and indicates no significant difference between the methods compared.
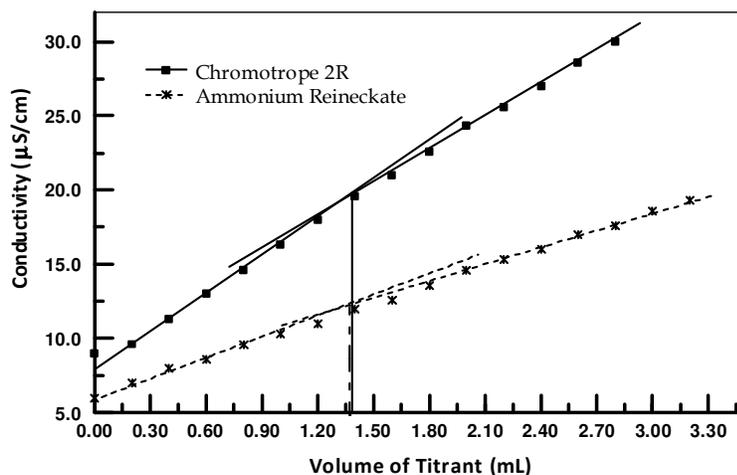

Fig. 6. Conductometric titration of 3 mg OXBr with 5×10^{-3} M C2R and AMRT in Spasmodine®tablets

Table 4. Quantitative determination of OXBr using the proposed C2R and AMRT methods compared to the reference method [6]

Proposed Method						Reference Method [6]
C2R			AMRT			
Taken, mg	Found, mg	Recovery %*	Taken, mg	Found, mg	Recovery %*	
3	3.009	100.31	3	2.99	99.66	
5	5.01	100.24	5	4.999	99.81	
8	7.98	99.87	8	8.03	100.40	
10	10.024	100.24	10	9.96	99.60	
15	15.10	100.67	15	15.16	101.10	
Mean ± SD = 100.26 ± 0.28 n = 5 RSD = 0.27 V = 0.07 SE = 0.125 t = 1.61 (1.81) F = 1.57 (4.53)[b]			Mean ± SD = 100.11 ± 0.63 n = 5 RSD = 0.62 V = 0.39 SE = 0.28 t = 0.508 (1.81)[a] F = 3.5 (4.53)[b]			Mean ± SD = 99.83 ± 0.51 n = 6 RSD = 0.51 V = 0.26 SE = 0.21

[a] and [b] are the Theoretical t-values and F-ratios at $p = 0.05$

Table 5. Statistical analysis of results obtained by the proposed methods for the analysis of Spasmodine®tablets (Hi Pharm Co., Egypt) (5 mg of OXBr/tablet)

C2R			AMRT		
Taken, mg	Found, mg	Recovery %*	Taken, mg	Found, mg	Recovery %*
3	2.99	99.81	3	2.98	99.60
5	5.03	100.67	5	5.01	100.24
8	7.94	99.33	8	7.92	99.06
10	9.939	99.39	10	10.00	100.00
15	14.95	99.67	15	14.88	99.24
Mean ± SD = 99.77 ± 0.538 n = 5 RSD = 0.54 V = 0.28 SE = 0.24			Mean ± SD = 99.62 ± 0.49 n = 5 RSD = 0.49 V = 0.24 SE = 0.219		

[a] and [b] are the Theoretical t-values and F-ratios at $p = 0.05$

4. CONCLUSION

We have studied the ion pairing of oxyphenonium bromide with chromotrope 2R and ammonium reineckate, by means of conductometry and spectroscopy. In general, the proposed conductometric procedures are simple, accurate, rapid and reproducible where RSD values were in the range of 0.27–0.62% for the parent drug and 0.49-0.54% in case of tablets. It is noteworthy to mention that application of the proposed procedure for the determination of OXBr in its dosage forms was successful without interference from excipients. The investigated techniques confirmed 1:1 ion pairing between OXBr and the considered reagents.

Reaction of AMRT with OXBr resulted in formation of insoluble ion associate with the formula $[C_{21}H_{34}NO_3]^+[Cr(NH_3)_2(CSN)_4]^-$. The solubility product constant of this precipitate and hence the equilibrium constant of the reaction were calculated utilizing the conductance data. The attained values were very high demonstrating the high degree of completion of the ion pairing reaction.

In addition, we have shown by means of conductivity data that the suggested fitting model is more satisfactory for data analysis compared to both the conventional and the differential conductivity methods, especially when the conductivity-volume data show a weak transition around the equivalence point. The differential conductivity method is objective and logical; nevertheless, it augments the imprecision of the original data, as well, manipulation of the experimental data is an added source of errors. An assessment of the effect of the equivalence point calculated using the four techniques on the recovery % showed that the proposed fitting model overweighs the other three techniques in terms of reduced % error.

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