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Full Paper

Spectroscopic and Conductometric Assay of Oxyphenonium Bromide in Pure Form and in Pharmaceuticals

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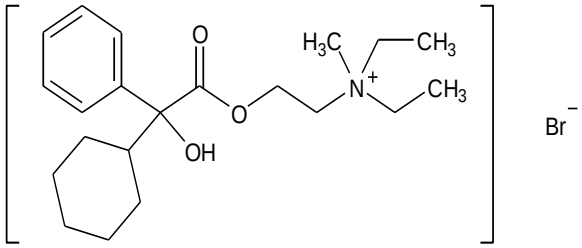
Abstract- The interactions between oxyphenonium bromide (OXBr) and two precipitating reagents, silver nitrate ($AgNO_3$) and phosphomolybdic acid (PMA) have been studied by conductometric and spectroscopic techniques. The equilibrium constant, the solubility product constant and other functions related to the process of precipitating OXBr were calculated exploiting the conductometric procedure. Furthermore, new approaches towards equivalence point detection have been pursued. In this itinerary, differential conductivity methods and Boltzmann sigmoid fitting model were found to be more appropriate compared to the conventional routine. The described procedures allowed the determination of OXBr within the range of 1-20 mg using both reagents. The molar combining ratio reveals that (1:1) (drug: reagent) ion associates are formed for both reagents with OXBr. 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 conductometric method.

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

1. INTRODUCTION

Oxyphenonium bromide (OXBr) is an anticholinergic agent that has antispasmodic and parasympatholytic effects. It is commonly used in treatment of gastric and duodenal ulcers and in eye drops for its mydriatic effect [1].

Chemically, OXBr is diethyl(2-hydroxyethyl)methylammonium alpha-phenyl cyclohexaneglycolate bromide, "Scheme 1". To the best of our knowledge, the drug and its pharmaceutical formulations haven't been reported in any pharmacopoeia. Various methods have been investigated for the determination of OXBr either in pure form or in biological fluids. In this concern, two main techniques have been reported in litrature: spectrophotometry [2-7] and chromatography [8-10].



Scheme1. Oxyphenonium Br^-

The absence of a pharmacopeial method for the determination of OXBr in addition to the wide usage of its formulations in the middle east, were motivating to conduct the current study. Two precipitating agents have been utilized in the current work, PMA and $AgNO_3$. Both reagents have been used for quantitative determination of many pharmaceutical compounds applying conductometric procedures [11-16].

Presence of a methodical procedure for finding the equivalence point and hence the corresponding drug concentration is imperative. Classically, the conventional process for locating the endpoint is a graphical procedure where the equivalence point is located as the intersectional point between two straight lines. This technique, though being well established and generally used by researchers; encloses some difficulties especially when the plot exhibits an obtuse curvature. Usually, it is not easy to corroborate the exact break point and to a great extent this issue varies with the estimate of the investigator. This negative feature with no doubt would be reflected on the quality and the outcomes of the validation procedures in terms of reproducibility, accuracy and precision.

In this article, and in extension of our former efforts [17-19] we compare a number of approaches that have been proposed to locate the endpoint following a conductometric titration. Two techniques, Boltzmann sigmoid fitting and the differential conductivity [20-25] were tested with the objective of overcoming the uncertainty arising from locating the endpoint as a break in the conductance-volume curves. Moreover, the solubility product and

hence the equilibrium constants of the formed precipitates were calculated using the available conductance data. Additionally, spectroscopic characterization of OXBr-PMA ion asscoiates 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 of analytically pure grade. Doubly distilled and deionized water was used throughout all the experiments. Oxyphenonium bromide (OXBr) was provided by (Hi-Pharm Co. Egypt); (M.wt=428.46 g/mol and its purity was found to be 100.11±0.63% according to the reference method [19] and it was used as received). Pharmaceutical formulation (Spasmodine® Tablets; Hi-Pharm Co., Egypt) labeled to contain 5 mg of oxyphenonium Br, was purchased from local pharmacy stores. Silver nitrate ($AgNO_3$) and phosphomolybdic acid (PMA) were obtained from Aldrich.

2.3. Procedure for pure pharmaceuticals

Aliquots of standard drug solutions containing 1 – 20 mg of the pure OXBr solution were transferred into the titration cell, followed by the addition of 1 ml of 0.01 M HCl (in case of PMA) 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 concentration of the titrants. The experimental data were fitted to a non-linear predefined fitting model (PSI Plot software).

2.4. Preparation of ion-associates for Spectroscopic Characterization

The ion associate with PMA was prepared by mixing equimolar (10^{-2} M) solutions containing of both drug and reagent. The obtained precipitate was filtered, thoroughly washed with water, and dried at room temperature. The obtained precipitate was subjected to IR and ^{1}H-NMR spectroscopy [26].

2.5. Procedure for Tablets

An amount of pulverized tablets equivalent to 50 mg of the active ingredient was weighted accurately and transferred into a 50 mL conical flask. The active ingredient was extracted three times with 30 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 50 mL volumetric flask. The volume was completed with distilled water. The nominal content of the active component in tablets was determined as described in the Procedure section.

2.6. Conductometric Determination of the Solubility Product Constant of Ion Associates

A series of solutions of different concentrations (C) were prepared for OXBr and both titrants. The conductivities of these solutions were measured at 25˚C and 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_{oPMA} 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 value of $\Lambda_{oOXBr\text{-}PMA}$ and $\Lambda_{oOXBr\text{-}AgNO3}$ was calculated using Kohlrausch's law of independent migration of ions [27]. The solubility (S) and solubility product constant (K_{sp}) values of a particular ion associate were calculated using the following equations;

$$S = K_s \times 1000 / \Lambda_{o\ \text{“ion-associate”}} \quad (1)$$

$$K_{sp} = S^2 \quad \text{(for 1:1 Ion Associates)} \quad (2)$$

$$K = 1 / K_{sp} \quad (3)$$

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

3. RESULT AND DISCUSSION

3.1. Conductometric Procedure

OXBr is a quaternary ammonium compound with a molecular formula of $[N^+(R_2R'R'')X^-]$, where R, R′ and R″ are hydrocarbon chains of different lengths and X^- is a bromide anion, "Scheme 1". Having this structure, OXBr is freely soluble in water. This property that has been utilized in this article for determination of OXBr via a simple conductometric procedure [28]. Two titrants were used for this purpose, $AgNO_3$ and PMA.

Using both titrants, a precipitate which is sparingly soluble in aqueous solution was formed. The formed precipitates, which can be perceived as a transition phase between two different systems, create the characteristic shape of the titration curve. As a result, volume – conductivity plots show a linear behavior - with a smooth transition - before and after the inflection point. The equivalence point can be determined by intersecting the two straight lines, a classical procedure for the determination of endpoint. Representative titration curves are revealed in Figure 1.

Presuming that conductivity is a linear function of dilution, the dilution factor was calculated using the equation: $\mathbf{X_{corr.} = X_{obs.}\,[(v_1 + v_2) / v_1]}$; where $X_{corr.}$ and $X_{obs.}$ are the corrected and observed conductances, respectively; v_1 is the initial volume, and v_2 is the volume of the added titrant [29].

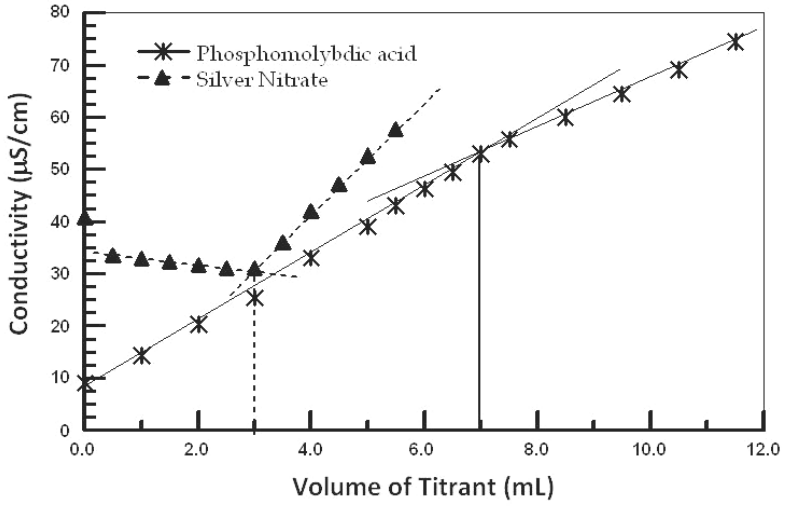


Fig. 1. Conductometric titration curve of 15 mg and 6.43 mg OXBr using 0.005 mol L^{-1} PMA and $AgNO_3$ respectively

3.2. Reaction Mechanism and Molar Ratio

Using $AgNO_3$ as a titrant, a precipitate (AgBr) was formed and the first segment of the titration curve was linear. The second part of the curve corresponded to the excess of $AgNO_3$

[11-12]. All plots constructed using the conventional scheme showed an intersection point corresponding to the addition of a molar amount of $AgNO_3$ equal to that of the original OXBr sample. Furthermore, plots of molar ratio – molar conductance where the experimental data were fitted to a non-linear least squares regression model, (Figure 2). The curve show that addition of $AgNO_3$ to OXBr resulted in a slight decrease in molar conductance, most probably due to formation of complexes with lower mobility. This continuous decrease starts to level off at the point where the value of [R]/[D] is around unity. This supports the postulation of 1:1 molar ratio as expected and according to the following equation. This hypothesis was further confirmed by IR results.

$$N^+ (R_2R'R'')\, Br^- + AgNO_3 \longrightarrow AgBr_{(s)} + N^+(R_2R'R'')NO_3$$

In case of PMA, the ion-associates are formed by replacing the drug cations by the highly mobile H^+ ions, so the conductivity increases. After the endpoint, more acid reagent is added and the conductivity increases more rapidly [30]. A curve break is observed at a drug-reagent molar ratio of 1:1, Figure 1. Mole ratio – molar conductance plots, Figure 2, show a slight change in slope around 1:1 [R]: [D]. This reaction can be represented by:

$$R_2R'R''N^+ Br \; + \; H_3(PMA) \longrightarrow \{[\, R_2R'R''N^+] \, [H_2(PMA)]\}_{(s)} + H^+$$

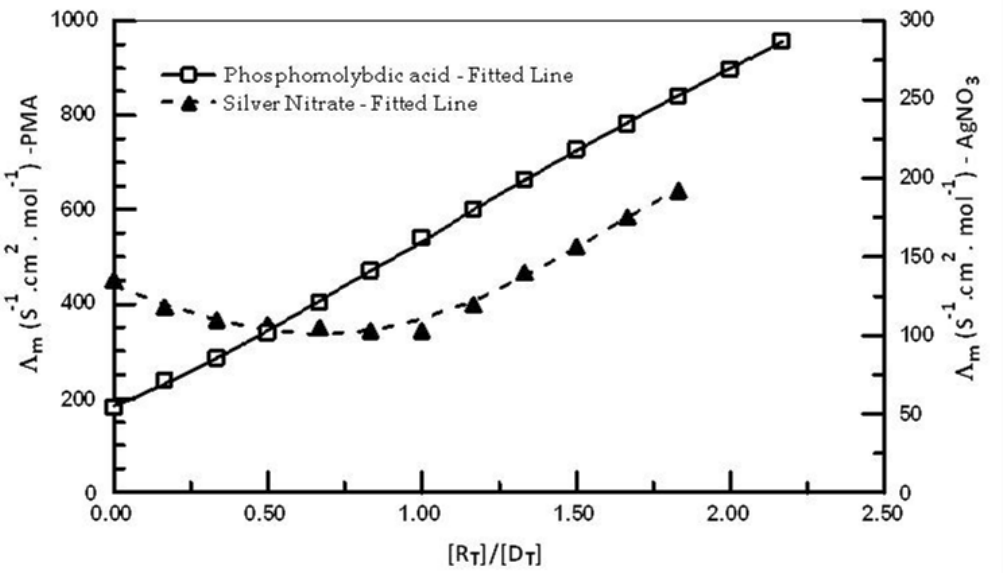


Fig. 2. Molar Conductance – mole ratio plots for the complexes of PMA and $AgNO_3$ with OXBr in pure water. Experimental values are represented by squares and triangles. Calculated values are represented by the continuous and the dashed lines obtained by fitting the experimental values using non-linear least squares fitting algorithm predefined by PSI Plot software

3.3. Conductivity – Volume Data Analysis

As shown in Figure 1, the obtuse curvature around the endpoint (especially on using PMA as a titrant) makes the determination of the equivalence point using the conventional procedure an intricate task. This difficulty is exacerbated when number of data points is few. Such a behavior necessitates the presence of a methodical approach that surmounts these intricacies. For this purpose, numerical derivatization of data and the implementation of data into a Boltzmann model have been scrutinized.

Mathematical differentiation of the experimental conductivity data against the volume of titrant was one of the investigated maneuvers, (Figure 3). The conductivity-volume curves plotted following the conventional procedure (using both titrants) pursue a linear regime before and after the equivalence point. As a result, the corresponding first derivative plot was expected to behave as sigmoid. In case of first derivative, endpoint was located at the halfway between two shoulders, while for a second derivative; endpoint was located as a curve maximum after fitting to Gaussian.

In general, numerical derivatization of data was more reliable and systematic compared to the conventional tactic. Conversely, numerical handling of the experimental figures would join the inherent experimental errors of the original conductivity-volume data. These errors are amplified using the numerical differentiation scheme.

In an attempt to elude the errors came upon numerical derivatization of conductivity data, we have tested many nonlinear fitting models. Providing a direct correlation between the function parameters and the conductivity-volume curve aspects, the Boltzmann fitting model was selected. This model has been described using the following equation [20, 25]:

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

In this equation: A_1 and A_2 represent the asymptotic value for small and large values of x respectively, x_o represents the endpoint, and Δx is related to the width of the function. Figure 4 shows the determination of OXBr applying Boltzmann model.

An evaluation of percentage of error encountered on calculation of recovery percentage obtained using the equivalence point located by each of the described techniques is shown in Table 1. From this table, it was obvious that techniques which involved data processing showed more divergence compared to the ideal value located by the classical procedure. According to these results, it seems more appropriate to get such figures from the original data without further treatment. However, having many data manipulation proposals which appreciably avoid researchers' bias overcomes these inadequacies.

Table 1. A comparison between the proposed procedures for conductivity *vs* volume data analysis. PMA was used as a titrant for the determination of 15 mg of OXBr

Procedure	Found (mg)	Recovery %	% Error
Conventional	15	100.00	0
First Derivative	15.5	103.33	3.3
Second Derivative	15.5	103.33	3.3
Boltzmann Sigmoid	14.85	99.00	1

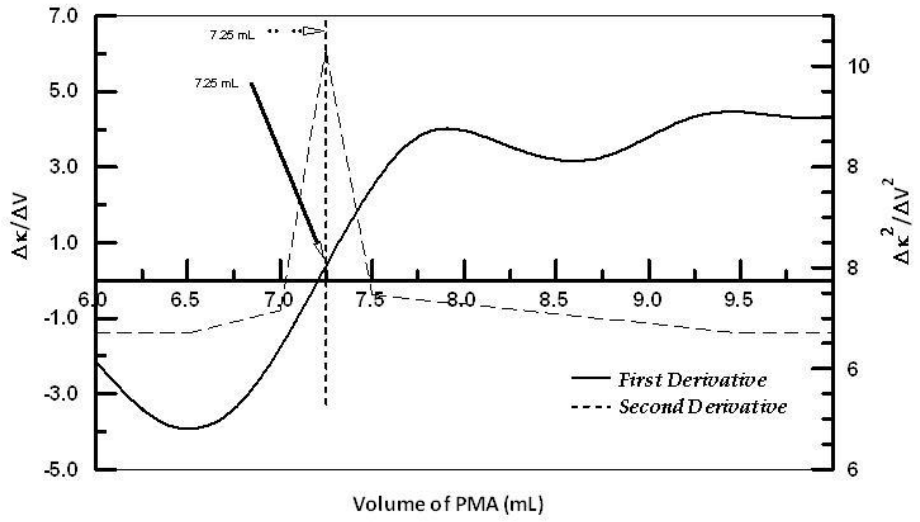


Fig. 3. Conductometric titration of 15 mg OXBr with 5×10^{-3} M PMA applying the numerical first derivative plot ($\Delta C/\Delta V$) with polynomial fitting and numerical second derivative plot ($\Delta^2C/\Delta V^2$). Arrows denote the equivalence points determined by each contrive

3.4. Determination of Solubility Product

Employing conductivity data to determine the solubility product of the formed precipitates is imperative. The solubility of the formed OXBr-PMA ion pairs determines the extent of completeness of the considered reactions [16, 31–33]. Values of the solubility product constant of the inspected ion pair complexes were 1.18×10^{-17} and 1.98×10^{-17} using PMA and $AgNO_3$ respectively. As shown in Table 2 and illustrated in Figure 5, the equilibrium constant values (K) are high enough to indicate the high degree of completeness of the ion-pairing reactions (>99.9%). At equilibrium, the solubility of the undissociated adducts in water (the intrinsic solubility) was omitted due to insignificant contribution to the total solubility.

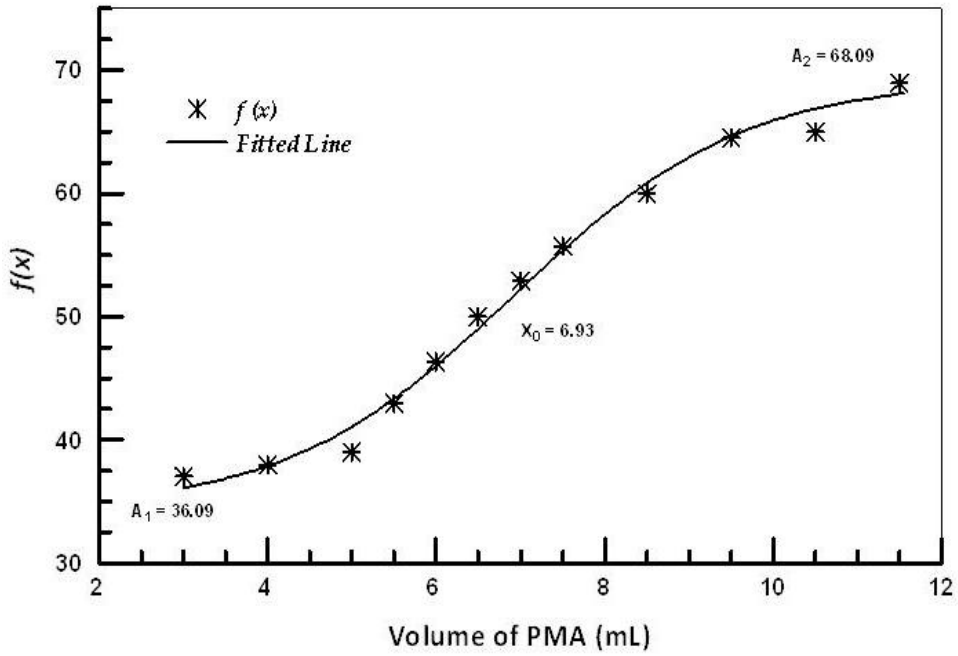


Fig. 4. Conductometric titration of 15 mg OXBr with 0.005 M PMA applying the Boltzmann sigmoid method *f(x)*. Value of X_0 denotes the equivalence point determined using Boltzmann model, $f(x_0)=(A_1+A_2)/2$. The same set of data was drawn following the conventional procedure and the endpoint was determined as 7.10 ml

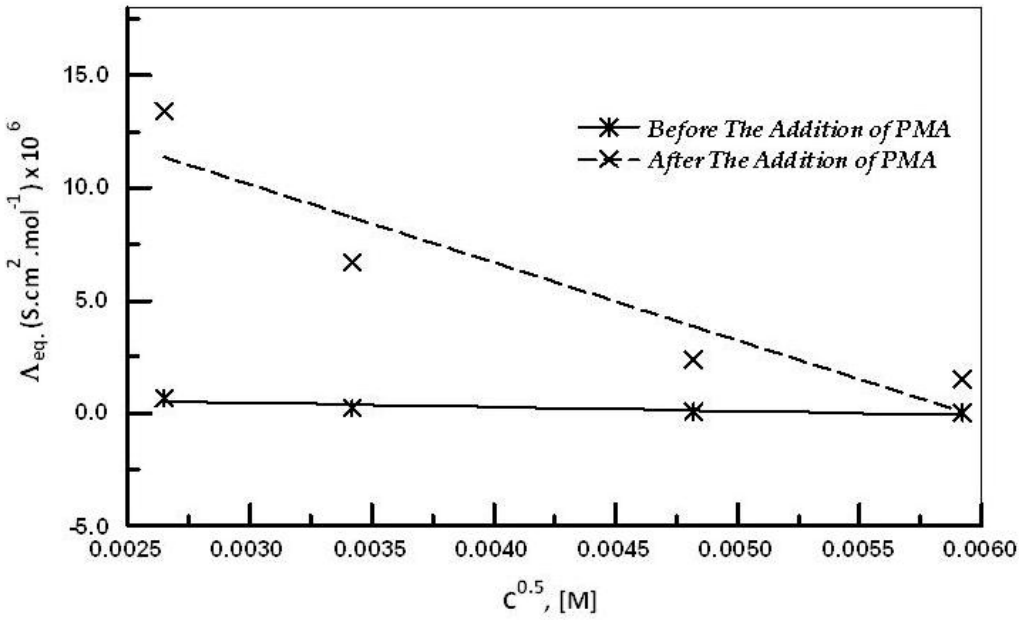


Fig. 5. Equivalent conductance (**Λeq.**) *vs*. the square root of concentration $\mathbf{C^{0.5}}$ for OXBr (Before and after addition of PMA)

Table 2. Solubility product constants of ion-associates

Ion Associate	Solubility (S) mol/L	K_{SP}	K = 1 / Ksp
OXBr-PMA	3.43×10^{-9}	1.18×10^{-17}	8.49×10^{16}
OXBr-$AgNO_3$	4.45×10^{-9}	1.98×10^{-17}	5.06×10^{16}

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

Ion pairing of OXBr with PMA was investigated by comparing IR, and ^{1}H-NMR spectra of the formed ion associate with those of the free ligand.

3.6. IR Spectra

The formation of an ion pair through the interaction of OXBr and PMA is strongly supported by detecting the chief IR bands (function groups) of both in the resultant complex spectrum. An assessment of the relevant IR bands and the shifts in their intensities before and after ion association clearly elucidates the electronic structure and symmetry changes upon formation of the ion pair complex.

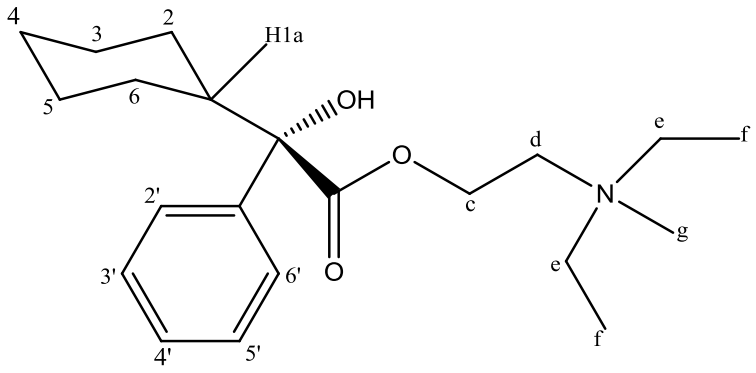
Generally, the IR spectrum of OXBr reveals characteristic bands at 3351 cm^{-1} assigned to ν_{OH} vibration, at 3059 cm^{-1} due to ν_{CH} (aromatic). Sharp absorption bands at approximately 2928 and 2852 cm^{-1} and less expressed one at 1454 cm^{-1} were observed. The first two bands might be assigned to symmetric and asymmetric vibrations of methyl and methylene groups while the third one corresponds to their bending vibrations. On the other hand, the IR spectrum of PMA has two characteristic bands at 1624 and 1065 cm^{-1} due to $\nu_{sym(P=O)}$ and $\nu_{as(P=O)}$ and a strong, broad peak at 3406 cm^{-1} due to $\nu_{(OH)}$ vibration; respectively.

The IR spectra of the formed ion associate shows a band corresponding to ν_{CH} (aliphatic) at nearly the same frequency (2853-2928cm^{-1}) as that of OXBr. The band corresponding to the stretching vibrations of C=O shifted to 1734 cm^{-1}. In addition, the peak due to $\nu_{sym\ (P=O)}$ appears at 1625 cm^{-1}. A small broad peak appears at 3500 cm^{-1} which might be attributed to stretching vibration of H-bonded hydroxyl group formed via self association of OXBr or via pairing with PMA. The above arguments indicate that an ion associate has been formed between OXBr and PMA.

3.6. ^{1}H-NMR Spectra

When the ion pair is formed during titration of OXBr with PMA, oxyphenonium is rapidly exchanged between the ion pair sites and the bulk solution causing the NMR peak of

a set of equivalent protons to be a collapsed singlet [34,35], Table 3. The proposed structure of OXBr-PMA ion pair is shown in Scheme 2.



$.H_2\,(Mo\,O_3)_{12}PO_4$

Scheme 2. Suggested Structure of Oxyphenonium phosphomolybdate (OXBr-PMA) Ion associate with NMR numbering

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

OXBr	**OXBr-PMA**
δ1.55 (3H, m, H6e, H2a, H3a)	δ 1.55 (3H, s, H6e, H2a, H3a)
δ 2.14 (1H, m, H1a)	δ 2.13 (1H, s, H1a)
δ2.50 (4H, m, He)	δ 2.46 (4H, s, He)

3.7. Analytical Applications

OXBr was determined in its formulation using the proposed titrants (Figure 6). As shown in Tables 4 and 5, the mean recovery values of OXBr from its formulation were the same as the pure drug, indicating the high selectivity of the proposed procedure and show that presence of excipients in the studied formulation doesn't affect the results. The results obtained were in good agreement with the labeled values for OXBr formulation.

The accuracy and reproducibility with respect to the reference method [19] 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.

Table 4. Quantitative determination of OXBr using the proposed PMA and $AgNO_3$ methods compared to the reference method [19]

Proposed Method						**Reference Method [19]***
PMA			**$AgNO_3$**			
Taken mg	Found mg	Recovery %	Taken mg	Found mg	Recovery %	
1	1.006	100.67	1	1.006	100.67	
3	3.02	100.66	3	2.99	99.66	
5	4.96	99.20	7	7.02	100.28	
10	10.067	100.67	10	10.02	100.2	
15	14.99	99.96	20	20.13	100.65	
Mean ± SD=100.23± 0.65			Mean ± SD = 100.29 ± 0.41			Mean ± SD = 100.11± 0.63
n=5			n=5			n=5
RSD=0.64			RSD=0.41			RSD=0.62
V=0.42			V=0.16			V=0.39
SE=0.29			SE=0.18			SE=0.28
t =1.36 (1.86)[a]			*t*=1.51 (1.86)[a]			
F=3.8 (6.39)[b]			*F*=1.45 (6.39)[b]			

*Conductometric titration with ammonium reineckate.

[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)

PMA			**$AgNO_3$**		
Taken, mg	Found, mg	Recovery %*	Taken, mg	Found, mg	Recovery %*
1	1.006	100.6	1	0.985	98.53
3	2.99	99.66	3	2.97	99.24
5	4.99	99.81	7	6.96	99.45
10	9.96	99.60	10	9.91	99.17
15	15.20	101.33	20	20.02	100.14
Mean ± SD = 100.20 ± 0.74			Mean ± SD = 99.30 ± 0.57		
n = 5			n = 5		
RSD = 0.73			RSD = 0.57		
V = 0.54			V = 0.32		
SE = 0.33			SE = 0.25		

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

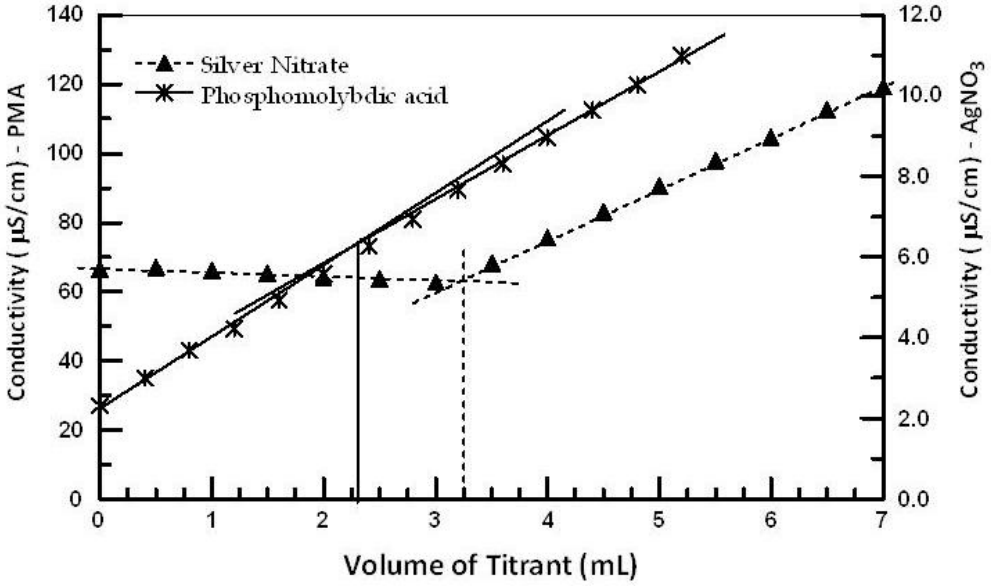


Fig. 6. Conductometric titration of 20 mg OXBr with 0.005 M $AgNO_3$ and 5 mg OXBr using PMA in Spasmodine® tablets

4. CONCLUSION

A simple, accurate and reproducible (RSD=0.41 – 0.73%) conductometric procedure has been shown throughout this paper. Application of the proposed procedure to OXBr in its dosage forms was successful without interference from concomitants usually present in these formulations. Reaction of both titrants with OXBr resulted in formation of an insoluble 1:1 ion associate. The obtained conductance values were utilized for the calculation of solubility product of this ion pair and so the equilibrium constant of the ion pairing reaction.

In addition, a comparison between four processing schemes for locating the equivalence point was held. Though the process of data manipulation resulted in some faulty results, having a methodical procedure that avoids human's partiality is more adequate.

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