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Conductometric Determination of Dropropizine and Tizanidine Hydrochloride in their Pharmaceutical Formulations

Hanan M. Elwy*, Mona M. Abdel-Moaty and Safaa M. Abdel-Hamid

National Organization for Drug Control and Research (NODCAR), Pyramids Ave. Giza, P.O. Box 29 Cairo, Egypt

* Corresponding Author, Tel.: +202-01203699982; Fax: +202-35855582

E-Mail: hanan18s@yahoo.com

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Abstract- A simple, accurate and sensitive conductometric method for the determination of dropropizine and tizanidine hydrochloride is developed. The presented method is based on its ion association of drug with phosphotungstic and phosphomolybdic acids. The effects of solvent, reagent concentration, temperature and molar ratio were studied and the solubility products of the formed ion associates were calculated. The method was successfully applied for the determination of two drugs in their pure state and pharmaceutical formulations with mean recovery values of 99.91-100.11 and 99.92-100.04% and relative standard deviations (RSD) were 0.57-0.63 and 0.60-0.66% for dropropizine and tizanidine hydrochloride, respectively. Statistical comparison of the results with reported methods showed excellent agreement.

Keywords- Dropropizine, Tizanidine hydrochloride, Phosphotungstic acid, Phosphomolybdic acid, Conductometric titration

1. INTRODUCTION

Dropropizine (DRO), 3-(4-phenyl -1-piperazinyl)-1,2-propanediol (Scheme1) is a cough suppressant reported to have a peripheral action in non-productive cough[1].The drug is listed

in Clark`s, Analysis of Drug and Poisons [2]. Studies of the human metabolism and toxicological detection of the cough suppressant DRO in urine [3,4] and plasma [5] using gas chromatographic-mass spectrometric methods are described. Recently, some spectrophotometric methods have been reported for determination of DRO in pure form and in pharmaceutical preparations [6-8]. Potentiometric titration method [9] is also used for determination of DRO with N-bromoccinimide (NBS) in sulphuric acid medium and the end point is determined using a Platinum indicator electrode.

Tizanidine hydrochloride (TIZ), 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole hydrochloride(Scheme1), is α 2- adrenergic agonist and centrally active myotonolytic skeletal muscle relaxant intended for the symptomatic treatment of acute muscle spasms and of chronic spasticity [1]. Some methods have been reported, including spectrophotometry [9-19] spectrofluorimetry [20], voltammetry [21,22] chromatography [23-29] and potentiometry using ion selective electrodes[30].

Conductance measurements are used successfully in quantitative titration of systems in which the conductance of the solution varies before and after the equivalence point. One of the valuable features of the conductance method of titration is that it permits the analysis of the components of precipitation reactions. Some conductometric titration methods have been reported for determination of some drugs [31-35], some of them using phosphotungstic and phosphomolybdic acids [32,33].

The present work aims to introduce new conductometric titration method for the determination of DRO and TIZ. This method is very simple in application and of low expense in comparison to the previously mentioned techniques and at the same time offer a high degree of accuracy and precision. The proposed conductometric titration method through the reaction of drug with PTA and PMA yields accurate and reproducible results, and has also been applied to the assay of pharmaceutical preparations.

2. EXPERIMENTAL

2.1. Apparatus

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

2.2. Chemicals and Reagents

All chemicals were of analytical grade and all solutions were prepared with deionized water. Pure- grade dropropizine (DRO) and its pharmaceutical preparation (Tussipine Lozenges, 20 mg DRO/Lozenge) were provided by EVA Pharma, Egypt. Tizanidine hydrochloride (TIZ) and its tablets (Sirdalud, 4 mg TIZ/ tablet) were obtained by Novartis Pharma AG. Basle, Switzerland.

Phosphotungstic acid (PTA) and phosphomolybdic acid (PMA) were obtained from Merck (USA) and their solutions (10^{-2} mol L^{-1}) were prepared in bidistilled water and standardized by the reference method [36]. Another solutions of 5×10^{-3} and 2×10^{-3} mol L^{-1} were also prepared freshly.

2.3. Preparation of standard drug solutions

Stock solutions (10^{-2} mol L^{-1}) were prepared by dissolving the accurate weights of pure solid of DRO (236.30 mg/100 mL) and TIZ (290.17 mg/100 mL) in bidistilled water. The solutions were kept in the refrigerator for no more than one week. Dilute solutions whenever required were obtained by appropriate dilution with water.

2.4. General procedure

Volumes (1.5-7.5 mL of 5×10^{-3} mol L^{-1} for each drug) containing 1.77-8.85 mg of DRO and 2.17-10.87 mg of TIZ were transferred to 50 mL volumetric flask and made to the mark with bidistilled water. The contents of the volumetric flask were transferred to a beaker and the conductivity cell was immersed. Then 5×10^{-3} mol L^{-1} PTA or PMA solution was added from a micro-burette (capacity of 5 mL with division of 0.05 mL) and the conductance was measured subsequent to each addition of the reagent solution after stirring. The conductance reading, taken 1-2 min, after each addition of reagent. The conductance reading was corrected for dilution by means of the following equation, assuming that conductivity is a linear function of dilution:

$$\Omega_{corr.} = \Omega_{obs.} [(V_1+V_2)/V_1)] \quad (1)$$

Where Ω is the electrolytic conductivity, V_1 is the initial volume of drug and V_2 is the volume of the added reagent (corr.=corrected, obs.=observed).

A graph of corrected conductivity versus the volume of titrant added was constructed and the end point was determined. One mL of 5×10^{-3} mol L^{-1} PTA or PMA is theoretically equivalent to 3.54 mg of DRO or 4.35 mg of TIZ.

2.5. Procedure for pharmaceutical preparations

Contents of 20 tablets or lozenges containing TIZ or DRO, respectively, were accurately weighed and powdered, a quantity of powder equivalent to prepare 50 mL of 5×10^{-3} mol L^{-1} solution of the pure drug (59.07 mg of DRO and 72.54 mg of TIZ) were taken and dissolved in 40 mL of water. The solutions were shaken in a mechanical shaker for about 30 min, and then filtered into a 50 mL volumetric flask and completed to the volume with water. Different volumes of the solutions (1.5-7.5 mL) were taken and subjected to the conductometric titration as mentioned above.

2.6. Conductometric determination of the solubility product of the ion associates

A series of solutions of different concentrations (C) was prepared for DRO, TIZ, PTA and PMA. The conductivities of these solutions were measured at 25°C and the specific conductivities (K_s), were calculated and are used to obtain the equivalent conductivities (λ) of the solutions. Straight-line plots of λ versus $\sqrt{c}$ were constructed and $\lambda_{o\ DRO}$, λ_{oTIZ}, λ_{oPTA}, and λ_{oPMA} were determined from the intercept of the respective line with λ axis. The activities coefficients of the ions employed were taken as unity because all the solutions were sufficiently dilute (5×10^{-4}-5×10^{-3}mol L^{-1}). The values of $\lambda_{o\ (DRO\text{-}PTA)}$, $\lambda_{o\ (TIZ\text{-}PTA)}$, $\lambda_{o\ (DRO\text{-}PMA)}$ and $\lambda_{o\ (TIZ\text{-}PMA)}$ were calculated using Kohlrausch law of independent migration of ions [37]. The solubility(S) and solubility product (K_{sp}) of a particular ion associate were calculated using the following equations:

$$S=Ks\times \frac{1000}{\lambda o} \quad \text{(ion associate)} \qquad (2)$$

$$K_{sp}=(n)^{n}\,(S)^{n+1} \quad \text{(in general)} \qquad (3)$$

$$K_{sp}=27\,S^{4} \quad \text{for 1:3 ion associates} \qquad (4)$$

Where Ks; is the specific conductivity of the saturated solution, of the ion associate, determined at 25°C and n is the stoichiometric of the reactant species. The saturated solution was made by stirring a suspension of the solid precipitate in distilled water for 15 min at 25°C.

2.7. Procedure for determination the drug-titrant ratio

One milliliter of 5×10^{-3} mol L^{-1} PTA and PMA were transferred to a 50 ml volumetric flask and made up to the mark with bidistilled water. The contents were quantitatively transferred to a beaker and the conductivity cell was measured. Then 5×10^{-3} mol L^{-1} solution of DRO or TIZ was added from a microburette and the conductance was measured subsequent to each addition of the drug solution after through stirring for 1-2 min.

3. RESULTS AND DISCUSSION

Conductance measurements are used successfully in quantitative titration of systems in which the conductance of the solution varies before and after the equivalenc point. In these cases, the titration curve can be represented by two lines intersecting at 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. The cationic drugs, DRO and TIZ are able to form precipitates with heteropoly acids as phosphotungstic acid (PTA) and phosphomolybdic acid (PMA), so the applicability of conductometric titration of these drugs with PTA and PMA was tested. The different parameters affecting the end point, such as the solvent, temperature, concentration of both drugs and PTA or PMA, were tested.

A **B**

Scheme 1. Chemical structures of dropropizine (A) and tizanidine hydrochloride (B)

3.1. Factors affecting the end point of titration

3.1.1. Effect of solvent

Conductometric titration of DRO and TIZ against PTA or PMA in different media (aqueous solution, 50% ethanol-H_2O, 50% methanol-H_2O and 50% acetone-H_2O) was carried out to establish the best solvent medium for these conductometric titrations. The results obtained in all media with exception of the aqueous medium show that shape of titration curves is not suitable for the conductometric determination as the conductance points are scattered and exhibit non-linearly around the end-point, and in addition, the conductance values were found to be much lower than in case of aqueous medium. Thus the aqueous medium is the suitable one to be chosen throughout the conductometric titrations. The dilution of drug solution to 50 mL with bidistilled water gave the best results. These the dilution of drug solution to 50 mL will be used for all experiment processes.

3.1.2. Effect of temperature

The effect of temperature on the evaluation of the end point of the conductometric titration of DRO and TIZ against PTA or PMA was studied by carrying out titrations at 25, 35 and 45°C. The results showed that as the temperature increases, the conductivity of the solution increases and no effect was observed on the shape of the titration curve and the position of the end point. Then room temperature (25±2°C) was chosen.

3.1.3. Effect of concentration of PTA and PMA

Certain amount of DRO and TIZ (0.6-3.0 ml of 10^{-2} mol L^{-1} in 50 ml water) was titrated against 2×10^{-3}, 5×10^{-3}, and 1×10^{-2} mol L^{-1} solutions of PTA and PMA. The reagent concentration in each titration must not be 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 the reagents is 5×10^{-3} mol L^{-1} to achieve a constant and highly stable reading within 1-2 min of mixing. Concentration less than 5×10^{-3} mol L^{-1} led to unstable reading and more time was needed to obtain constant conductance values. The

system under investigation showed a regular rise in conductance up to the equivalence point where a sudden change in the slope occurs. This behavior is probably related to the formation of RNH^+ and OH^- by hydrolysis. On adding PTA or PMA, the ion associate is formed by replacing the RNH^+ ions by mobile H^+ and the conductivity increases, [32]. After the end point, more reagent acid is added and the conductivity increases more rapidly.

3.1.4. Molar ratio

It is confirmed that 1.0 mole of PTA or PMA was required for complete precipitation of 3.0 mole of DRO or TIZ. A graph of corrected conductivity versus mole of drug/mole of reagent was constructed (Fig. 1).

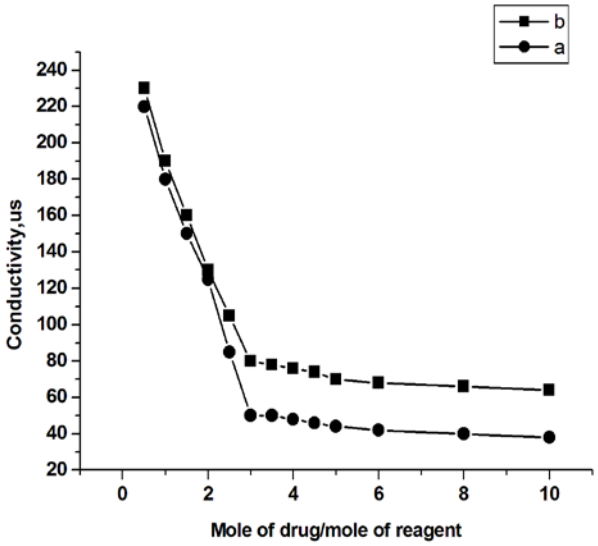

Fig. 1. Molar ratio of dropropizine with a (PTA) and b (PMA)

3.2. Analytical results

The results of the drug determination presented in Table1 showed that good recoveries and low standard deviations were obtained. The optimum concentration ranges for determination are 1.77-8.85 mg of dropropizine and 2.17-10.87 mg of tizanidine with mean recovery values of 99.91-100.11 and 99.92-100.04% and relative standard deviations (RSD) 0.57-0.63 and 0.60-0.66% for dropropizine and tizanidine, respectively, at which sharp inflections and stable conductance reading are obtained. Figs. 2&3(as examples) represent the titration curves for 1.77-8.85 mg of dropropizine and 2.17-10.87 mg of tizanidine against 5×10^{-3} mol L^{-1} PTA and PMA, respectively. In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression [38] of observed drug concentration against the theoretical values (five points) was illustrated. The calculated t-values are between 0.271-2.033 which are lower than the tabulated value at 95% confidence

level and four degrees of freedom (2.776). The slope of the curve was showed that it did not differ significantly from the ideal value of unit. Thus there are no systematic differences between the determined and the true concentration over a wide range (1.77-8.85 mg for DRO and 2.17-10.87 mg for TIZ). The results of different statistical treatments of the data are presented in Table 2.

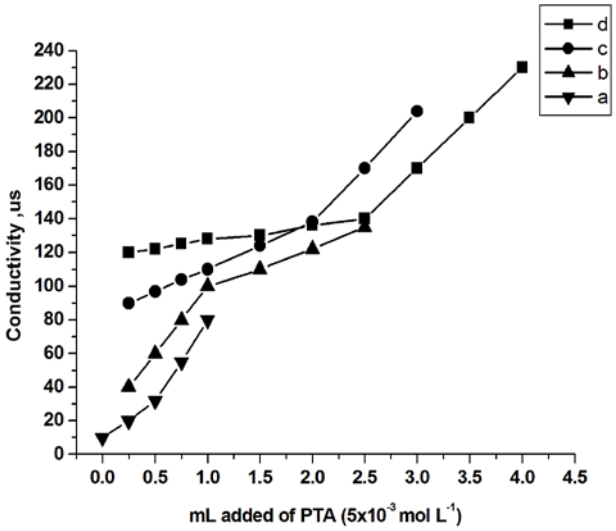

Fig. 2. Conductometric titration curves of dropropizine *vs.* 5×10^{-3} mol L^{-1} PTA

a. 1.77 b. 3.54 c. 7.08 d. 8.85 mg of dropropizine

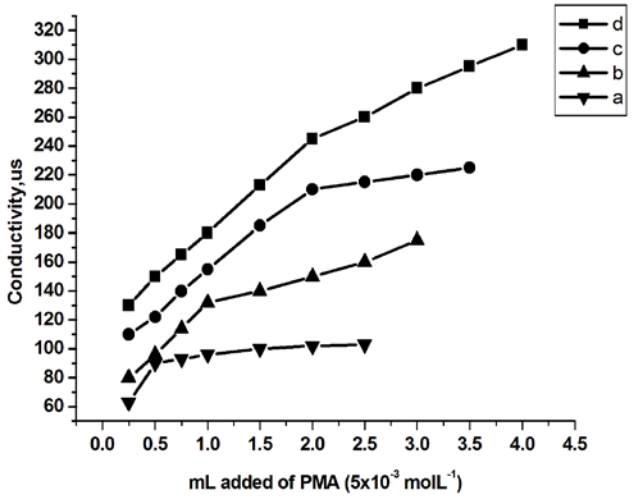

Fig. 3. Conductometric titration Curves *vs.* 5×10^{-3} mol L^{-1} PMA

a. 2.17 c. 8.7

b. 4.35 d. 10.57 mg of tizanidine.HCl

Table1. Conductometric determination of dropropizine and tizanidine in pure solutions

Taken (mg)	**PTA (5×10^{-3} mol L^{-1})**			**PMA (5×10^{-3} mol L^{-1})**		
	Found[a](mg)	**Recovery** (%)	**RSD (%)**	**Found**[a] (mg)	**Recovery (%)**	**RSD (%)**
Dropropizine						
1.77	1.76	99.44	0.80	1.77	100.00	0.86
3.54	3.56	100.56	0.63	3.53	99.71	0.62
5.31	5.32	100.19	0.76	5.30	99.81	0.69
7.08	7.09	100.14	0.31	7.10	100.28	0.57
8.85	8.87	100.22	0.37	8.83	99.77	0.40
Mean		100.11	0.57		99.91	0.63
Tizanidine.HCl						
2.17	2.16	99.54	0.65	2.18	100.46	0.99
4.35	4.38	100.69	0.72	4.38	99.54	0.65
6.52	6.50	99.69	0.68	6.55	100.46	0.73
8.70	8.74	100.46	0.43	8.65	99.43	0.49
10.87	10.85	99.82	0.52	10.84	99.72	0.45
Mean		100.04	0.60		99.92	0.66

[a] Average of four determinations

Table 2. Linear regression of data obtained from determination of the investigated drugs using PTA and PMA

Ion associate	**Slope of the regression line** [a]	**Intercept of the regression line** [a]	**Correlation coefficient (r)**	**SD (mg)**	**t-test (2.776)**[b]
Dropropizine PTA	1.0028	-0.005	0.9999	0.011	2.033
Tizanidine PTA	0.9995	0.007	0.9999	0.033	0.271
Dropropizine PMA	0.9994	-0.001	0.9999	0.017	0.526
Tizanidine PMA	0.9949	0.020	1.0000	0.031	1.081

[a] Observed versus theoretical values (5points)
[b] Tabulated 95% confidence limit at 4 degrees of freedom

3.3. Analytical applications

The validity of the proposed method was assessed by its application to the determination of dropropizine and tizanidine in their pharmaceutical preparations. The mean recovery values were 99.95-100.40 and 99.89-99.97% with RSD 0.53-0.59 and 0.62-0.68% for dropropizine lozenges and tizanidine tablets, respectively, (Table 3). This is nearly the same as in the case of determining pure drug samples, indicate the high selectivity of the method towards the studied drugs. Thus, the excipients such as: starch, lactose, glucose, magnesium stearate, talc and cellulose, in the formulations didi not interfere in the determination.

The results of the formulations determination are compared with those obtained from the reference methods [8,17] applying the Student's t-test and F-test values of 95% confidence level did not exceed the theoretical values of 2.306 and 6.39 for t- and F-tests respectively, (Table 3). This comparison indicated that the proposed methods is not only as accurate as the reference methods, but it use simple reagents and apparatus; it is also applicable to a wide range of concentration besides being time saving (20 min are required for each complete titration). Thereby encouraging its application in quality control of these drugs, in their pure form and pharmaceutical preparations.

Table 3. Conductometric titration for determination of dropropizine and tizanidine in some pharmaceutical preparations

		Recovery ±SD(%)[a]		
Pharmaceutical	**Drug**	**PTA**	**PMA**	**Reference method**
Tussipine Lozenges (20mg of DRO/loz)	Dropropizine	100.40±0.53 t=0.88 F=3.27	99.95±0.59 t=0.04 F=3.29	99.93±1.07 [8] (2.306) [b] (6.39) [b]
Sirdalud tablets (4mg of TIZ/tab.)	Tizanidine	99.97±0.62 t=0.66 F=2.81	99.89±0.68 t=0.79 F=2.34	100.33±1.04 [17]

[a] Mean± standard deviation of five determinations.
[b] The tabulated values of t- and F- tests at 95% confidence limit.
Ref.[8] DRO with TCNQ and ref.[17] TIZ with eosin y.

3.4. Solubility of ion associates [39]

Chemical compounds have different solubility values depending on their nature and at a given temperature only a limited amount of them could be dissolved in a given solvent. The solid phase and the solution saturated with the solute are in dynamic equilibrium that is the amount dissolved per unit time is equal to the amount precipitated in this time. The equilibrium characterized by the concentration of the saturated solution. In general, analytical

precipitates are salts or other ionic compounds with low solubility, which dissociate in their solutions. Clearly, a precipitate for gravimetric work must have a sufficiently low solubility so that the soluble amount does not seriously affect the outcome of the analysis. Where the quantity of substance being determined is small and where the demands for accuracy are high, the soluble amount could be of real concern.

The solubilities of the ion- associate complexes of dropropizine or tizanidine with PTA and PMA can be determined and tabulated in Table 4. The solubility of the ion associate complexes with PTA are 1.0×10^{-4} and 8.13×10^{-5} g.mol L^{-1} or with PMA are 3.31×10^{-4} and 2.88×10^{-4} g.mol L^{-1} for dropropizine and tizanidine, respectively, i.e. the solubility of the ion associate with PTA is less than with PMA.

Table 4. Values of solubility, solubility product and equilibrium constant for each ion associate of drug with PTA or PMA at 25°C

Ion associate	**$K_s\times10^6$(s)**	**λo (s.l.mol^{-1})**	**pS[a]**	**pK_{sp}[b]**	**K**
Dropropizine PTA	180	1810	4.00	14.57	3.72×10^{14}
Tizanidine PTA	154	1920	4.93	14.93	8.55×10^{14}
Dropropizine PMA	449	1370	3.48	12.49	3.10×10^{14}
Tizanidine PMA	430	1480	3.54	12.82	6.62×10^{14}

[a] $S = K_s \times 1000/\lambda o$ (ion associate).

[b] $K_{sp} = 27\ S^4$.

3.5. Solubility products of 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 (Ksp) of the formed ion-associates were determined conductometrically as described under the experimental part. The equilibrium constant of the precipitation reaction is inversely proportional to the solubility product, whereas the smaller the solubility product of the formed ion-associate, the sharper the end point. The solubility product of the ion associate of drug-PTA is lower than that of drug-PMA, so it is most stable and the solubility product of TIZ ion-associates, so they are relatively more stable than that DRO ion- associates.

The solubility products of the ion associates were found to be 2.69×10^{-15}, 1.17×10^{-15}, 3.23×10^{-13} and 1.51×10^{-13} for DOR_3PTA, TIZ_3PTA, DOR_3PMA and TIZ_3PMA, respectively. Consequently, the equilibrium constants of the ion-associate formation reactions can be calculated as follows: (where $K=\frac{1}{Ksp}$)

$3DRO + H_3PTA \longrightarrow DRO_3PTA + 3H^+$, $K=3.72\times10^{14}$

$3TIZ + H_3PTA \longrightarrow TIZ_3PTA + 3H^+$, $K=8.55\times10^{14}$

$3DRO + H_3PMA \longrightarrow DRO_3PMA + 3H^+$, $K=3.10\times10^{14}$

$3TIZ + H_3PTA \longrightarrow TIZ_3PMA + 3H^+$, $K=6.62\times10^{14}$

The results are grouped in Table 4.

These equilibrium constant values are very high; indicating that the degree of completeness of the ion associate formation reaction is about 99.99%. In this equilibrium, the solubility product of the undissociated ion associate in water (i.e. 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 its saturated solution is, therefore very dilute [40,41].

4. CONCLUSION

The conductometric determination method has the advantage of being simple, accurate, and reproducible (RSD=0.57-0.66% and 0.53-0.68% for pure and dosage forms, respectively). The proposed method was compared with the reference methods [8,17], indicating the absence of any systematic error and no significant difference between the compared methods. The proposed method showed more accuracy, reproducibility, precise results, inexpensive technique and does not require any sophisticated instruments or unavailable reagents. The proposed method is suitable for the determination of the studied drugs in dosage forms without interferences from excipients which are present in the dosage forms, suggesting application in drug substances and drug formulations.

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