Conductometric determination of Dextromethorphan hydrobromide

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ABSTRACT

Simple and accurate conductometric titration has been used for determination of the antitussive drug dextromethorphan (Dex), where sodium tetraphenylborate (NaTPB), silicotungstic acid (STA), phosphotungstic acid (PTA), phosphomolybdic acid (PMA) and reineckate ammonium salt (RAS) were used as titrants. The formed ion-associates were studied conductomterically for the assignment of stoichiometric ratios and solubility products. The suggested procedure has been applied to the determination of Dex in pure state and pharmaceutical preparations with high accuracy and precision.   © 2011 Trade Science Inc. - INDIA

INTRODUCTION

Dextromethorphan (Dex, ent-3-methoxy-17-methylmorphinan, $C_{18}H_{25}NO$) is a nonnarcotic antitussive drug, acts through depression of the medullary centers of the brain to decrease the involuntary urge to cough[1].
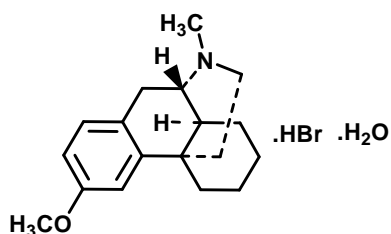
High performance liquid chromatography (HPLC)[2], gas chromatography[3] and liquid chromatography techniques[4] are the most popular techniques for Dex quantification. Moreover, the derivative spectrophotometry[5,6], ion pair complex formation[7,8], pro-

ton nuclear magnetic resonance (^{1}HNMR)[9] and capillary electrophoresis (CE)[10] have also been reported. Nevertheless, most of the aforementioned methods are laborious and usually require extraction and complicated pretreatment procedures prior to analysis. In contrast, the electrochemical techniques particularly conductometric measurements possess analytical and economic advantages including; low cost and simplicity, since no reference electrodes are needed. Moreover, conductometric analysis is performed in both concentrated and dilute solutions with accuracy depends on the system; in binary solutions it is as high as 0.1%, but in multi-component systems it is much lower[11,12].

Although potentiometric methods have been reported for Dex determination[13,14], conductometric titration, in which the analyte is converted to non-ionic form by neutralization or precipitation, is of more value[15]. Conductometric titrations are especially useful for very dilute solutions as the percentage change in

conductance is independent of concentration. Unlike potentiometric methods, measurements need not be made close to the equivalence point so that there is an advantage in conductometric methods when the chemical reactions involved are relatively incomplete. Conductometric titration rests on the marked changes that occur near the titration endpoint in the relation between conductivity and the amount of titrant added (an extreme or inflection point). It is used in particular for the titration of acid-base in colored and turbid solutions or solutions containing reducing and oxidizing agents where the usual color change of acid–base indicators cannot be seen[12,16,17].

This study aims to apply the conductometric measurements to Dex quantification in pure form and pharmaceutical preparations as well as determination of the stoichiometric ratios and solubility products of Dex ion-associates.

EXPERIMENTAL

Reagents and materials

Authentic Dex ($C_{18}H_{26}BrNO.H_2O$, 370.3) sample was kindly provided from the National Organization of Drug Control and Research, Cairo, Egypt. The purity of the active ingredient was assigned to be 99%. Ion pairing agents including; sodium tetraphenylborate (NaTPB, $Na[C_{24}H_{20}B]$, Fluka), silicotungstic acid (STA, $H_4[SiW_{12}O_{40}.xH_2O]$, Fluka), phosphotungstic acid (PTA, $H_3[PW_{12}O_{40}.xH_2O]$, Fluka), phosphomolybdic acid (PMA, $H_3[PMo_{12}O_{40}.xH_2O]$, Fluka) and reineckate ammonium salt (RAS, $[NH_4(Cr(NH_3)_2(SCN)_4).H_2O]$, Fluka) were used cation-exchangers for precipitation of different Dex-ion pairs.

Pharmaceutical preparations

Tussilar tablets and drops (Kahira Pharm. and Chem. Ind. Co. Cairo, Egypt, 10mg/tablet and 1g/100 ml solution, respectively) were purchased from local drug stores. Ten tablets were weighed, grinded and an accurate weight of the powder assigned to contain 100mg DXM was dissolved in bidistilled water, filtered and completed to 50 ml with bidistilled water.

Apparatus

Conductivity meter 4310 Jenway (UK) was used

in conductance measurements with a dip type conductivity cell of two Pt (non-polarized) electrodes of 1.0 cm^2 in area, rigidly fixed at 1.0 cm apart (cell constant K=1.0). Elementar-Vario El (Germany) was used for elemental analysis (C, H, N, and S) of the ion pairs. All measurements were performed under ambient conditions. Water distiller of Hamilton Laboratory Glass Ltd., WSC/4D (UK) was used for bidistilled water preparation. Microcal Origin 6.0 (Microcal Software Inc., version 1.0.0.1) computer program was applied in data treatment for graphical and statistical treatments and calculations.

Working procedure

(1) Ion-associates preparation

Ion-associates synthesis protocol included drop wise addition of 10^{-2} M aqueous solution of ion pairing agents (TPB, RAS, PTA, PMA, and STA) to 50 ml of 10^{-2} M Dex solution. The mixture was left to react for 5min under stirring at room temperature. The resulting precipitate was then filtered off on Whatman filter paper and washed several times with bidistilled water. The compound was left to dry for 24h at 60ºC, washed with petroleum ether to remove any residual moisture, and then grinded to fine powder[18,19]. Small sample portions were sent for elemental analysis.

(2) Stoichiometric ratios determination

A definite volume (5 ml) of 10^{-2} M Dex was transferred to a 50 ml volumetric flask and made up to the mark with bidistilled water. The drug solution was placed in a suitable titrating vessel and the conductivity cell was immersed, then a titrant of 10^{-2}M of TPB, RAS; 2.5×10^{-3} M of PMA, PTA or 3×10^{-3}M STA was added from a digital burette. After each addition (0.2 ml), the solution was stirred for 1-2min and allowed to attain equilibrium; the conductance (µS) was measured. The electrolytic conductivity of the intervening solution was determined by passing an alternating current (AC) between the cell electrodes (5-10 V at 50-10,000 Hz) where direct current (DC) potential cannot be used as the current flow would lead to electrolysis (polarization of electrodes) and hence changes in solution composition. The cell temperature should be held constant to within ± 0.1 K throughout a series of measurements to give

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high precision. The cell is washed with bidistilled water, immersed in 0.5 M H_2SO_4, electrolyzed with DC voltage using repeated polarity reversal to remove impurities, and finally washed and stored in bidistilled water.

To eliminate the effect of dilution on the increase in conductance, the measured values were corrected for volume change by means of the following equation, assuming that conductivity is a linear function of dilution:

$k_{corr} = k_{obs}[(v_o + v_{added}) / v_o]$

Where, k_{obs}, the observed specific conductivity, v_o, the initial volume, and v_{added}, the added volume. The corrected conductivity was then plotted against the volume added of titrant and the first derivative was used to estimate the end point and the stoichiometric ratios[10-13].

(3) Solubility products determination

Series of solutions of different concentrations ($C = 10^{-4}$-10^{-2} M) were prepared for each of Dex, TPB, RAS, PMA, PTA, and STA. The conductivities of these solutions were measured at 25°C and the specific conductivities (k), corrected for the effect of dilution were calculated and used to obtain the equivalent conductivities (λ) of these solutions.

$\lambda = 1000 \ k / C$

λ (at a finite concentration) and λ_o (at infinite dilution) can be related by Onsanger equation[16]:

$\lambda = \lambda_o - (a + b \lambda_o) \ C^{1/2}$

where, (a) and (b) are constants related to the interionic forces (accounting for the electrophoretic and the time of relaxation effect, respectively). Straight line plots of λ versus $C^{1/2}$, were constructed and the equivalent conductance values at infinite dilution (λ_{oDex}, λ_{oTPB}, λ_{oRAS}, λ_{oPMA}, λ_{oPTA}, and λ_{oSTA}) were determined from the intercept of the respective line with the λ axis. The activity coefficients were taken as unity since the solutions were sufficiently dilute. The equivalent conductance values of the IPs under complete dissociation condition (λ_{oIP}) were calculated from Kohlrausch's law of independent migration of the ions[16,17].

$\lambda_{oIP} = n \ \lambda_{oDex} + \lambda_{o(ion pairing agent)}$

Where; n is the stoichiometric ratio.

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

$S = k_s \times 1000 / \lambda_{oIP}$

$K_{sp} = S^2$ **for 1: 1 ion associate**

$K_{sp} = 4S^3$ **for 1: 2 ion associate**

$K_{sp} = 27S^4$ **for 1: 3 ion associate**

$K_{sp} = 256S^5$ **for 1: 4 ion associate**

Where k_s, is the specific conductivity of a saturated solution of IP at 25°C and corrected for the effect of dilution. The saturated IP solutions were prepared by stirring the IP suspensions in bidistilled water for 3h and then left for 24h before measurement[20-23].

RESULTS AND DISCUSSION

Conductivity is a measure of the ability of a solution to conduct electricity when subjected to a potential gradient and equals the reciprocal of resistivity (Siemens = Ω^{-1}). The conductometric methods are fundamentally non-selective, where conductivity is related to the ionic strength of the solution and the contributions of the individual types cannot be distinguished in the values measured. Hence, conductometry is primarily useful when determining the concentrations in binary electrolyte solutions (for determining the solubilities of poorly soluble compounds). In the case of multicomponent systems, conductometry is used when the qualitative composition of the solution is known and invariant in the continuous or batch analysis of solutions in process streams[12]. Straightforward, conductometry is used extensively as the basis for sensors and biosensors construction[24, 25].

Preliminary IP identification studies

(1) Determination of the stoichiometric ratios of the ion-associates

Dex ($C_{18}H_{25}NO$, 271.4) is a tertiary amine cation having a high affinity towards the formation of water insoluble ion pair (IP) complexes with the oppositely charged anions such as TPB, RAS, PTA, PMA, and STA.

Elemental analysis revealed that Dex form ion association with TPB and RAS in stoichiometric ratio of 1: 1 (drug: titrant). Complexes of ratio 3: 1 are formed with both PTA and PMA, while STA formed complex of 4: 1 ratio with Dex (TABLE 1).

TABLE 1: Elemental analysis data for various Dex-IPs

IP	MWt_{cal}	C%		H%		N%		S%		Tentative formula
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found	
Dex-TPB	590.64	85.3	84.7	7.6	7.5	2.4	2.3	-	-	$[C_{18}H_{25}NO][C_{24}H_{20}B]$
Dex-RAS	607.82	43.4	43.9	5.8	6.4	18.4	16.3	21.1	21.09	$[C_{18}H_{25}NO][C_4H_{10}CrN_7S_4]$
Dex-PMA	2636.43	24.6	25.3	2.8	3.1	1.6	1.3	-	-	$[C_{18}H_{25}NO]_3[PMo_{12}O_{40}]$
Dex-PTA	3691.35	17.6	18.3	2.0	2.3	1.1	0.9	-	-	$[C_{18}H_{25}NO]_3[PW_{12}O_{40}]$
Dex-STA	3959.86	21.8	21.6	2.5	2.5	1.4	1.2	-	-	$[C_{18}H_{25}NO]_4[SiW_{12}O_{40}]$

Conductance measurements has been successfully in quantitative titration systems where the conductance of the solution varied prior to and after the equivalence point. The titration curve, obtained by plotting the change in conductance versus volume of titrant added, represented two straight lines intersecting at the end point. The system showed a regular rise in conductance up to the equivalence point where a sudden change in the conductance observed as obviously shown from the first derivative plots sustaining the elemental analysis data (Figure 1 and 2). Results obtained sustained the elemental analysis data for ion pair stoichiometric ratios.
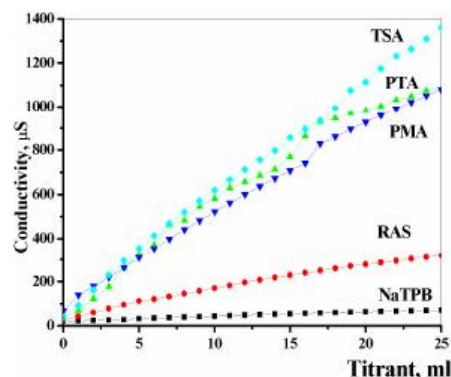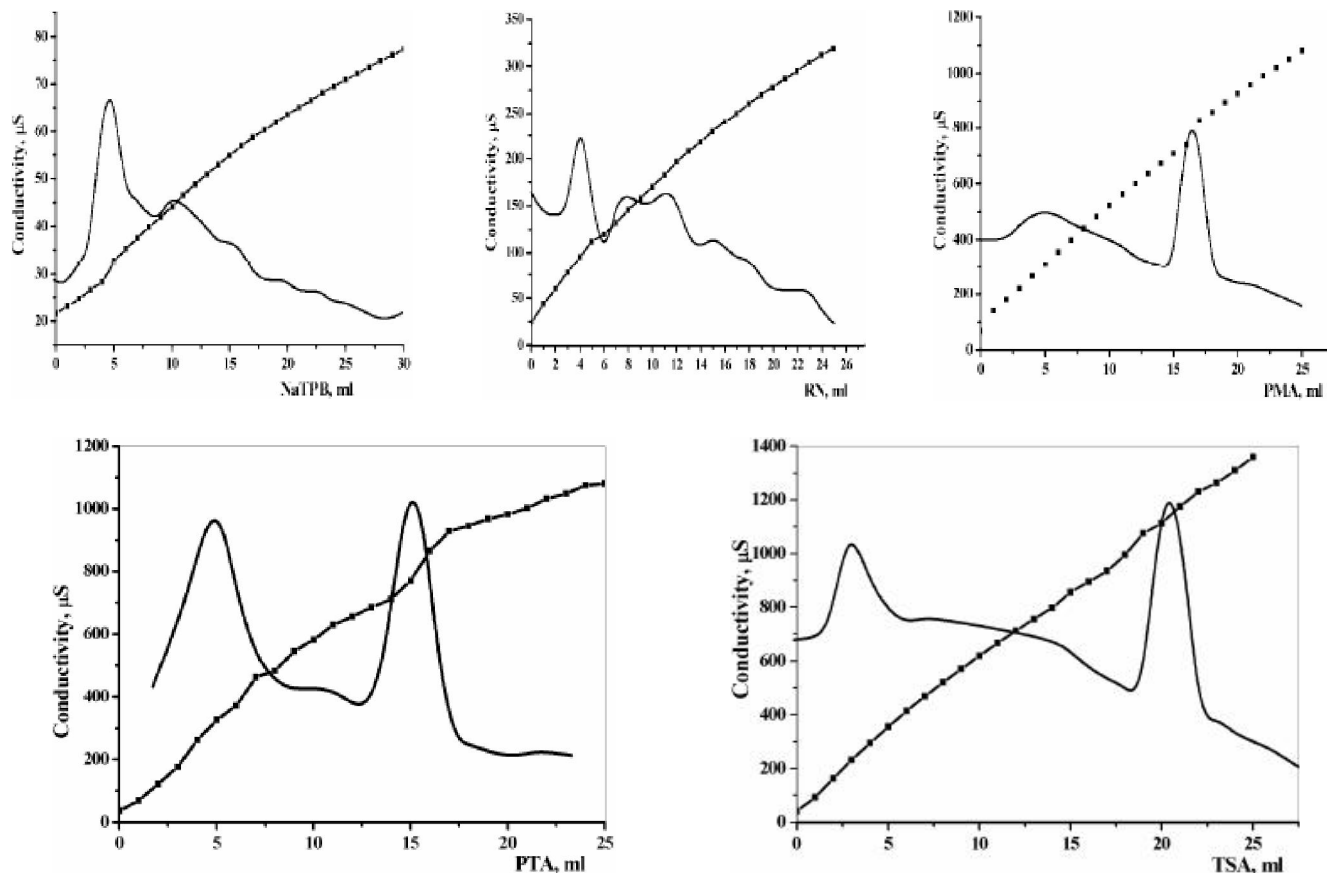

Figure 1 : Conductometric titration of Dex with different ion pairing agents

Figure 2 : Conductometric titration of 5 ml of 10^{-2} M Dex with 10^{-2} M NaTPB and RAS, 3×10^{-3} M PMA and PTA, and 2.5×10^{-3} M STA

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Determination of solubility products of the ion-associates

The solubility of an ion-exchanger is one of the main factors controlling the life-span of the sensor incorporating it as a sensing material. Determination of the solubility product of an ion-pair is very important since its reciprocal is approximately equal to the formation constant, which in turns is tightly related to the degree of hydrophobicity of the ion-exchanger. Since, as the hydrophobicity of the IP increases, the leaching rate into the aqueous bathing solution decreases.

The solubility of a sparingly soluble salt is expressed by the equilibrium constant for the reaction:

$$AB \text{ (solid)} + Solvent = A^+ + B^-$$

$$K = [AS^+][B^-] / [AB][S]^n$$

Both [AB] and [S] are unchanged in solubility reactions of sparingly soluble salts, hence the equation can be rewritten thus, known as the solubility product (K_{SP}), is widely used as a measure of the solubility of sparingly soluble salts[15-17].

$$K_{SP} = [A^+][B^-]$$

Determination of the solubility product of the IP is very important since as the hydrophobicity of the IP increases, the leaching rate into the aqueous bathing solution decreases. The solubility of an ion-exchanger is one of the main factors controlling the life span of the sensor which incorporate it as electroactive material[23,27,28].

According to Kohlrausch's law of independent migration of the ions, the molar conductivity of an electrolyte equals the sum of the molar conductivities of the cations and the anions[18,29];

$$\Lambda = n^+\Lambda^+ + n^-\Lambda^-$$

Where n, number of anions or cations.

The equivalent conductance (λ) of an ion is the conductance of a solution of unspecified volume containing one gram-equivalent and measured between electrodes 1 cm apart. Due to interionic effects, (λ) is concentration dependent, and the limiting ionic equivalent conductance (λ_o) at infinite dilution (no disturbing effect on the motilities of ions other than solvent and temperature) reaches its maximum value and used for comparison purposes. The magnitude of (λ_o) is determined by the charge, size, the solvent viscosity, and the magnitude of the applied poten-tial. Hence, the equivalent conductance of the solvated IPs (λ_{oIP}) at infinite dilution could be calculated as follow:

$$\lambda_{oDex-TPB} = \lambda_{oDex} + \lambda_{oTPB}$$
$$\lambda_{oDex-RAS} = \lambda_{oDex} + \lambda_{oRAS}$$
$$\lambda_{oDex-PMA} = 3\lambda_{oDex} + \lambda_{oPMA}$$
$$\lambda_{oDex-PTA} = 3\lambda_{oDex} + \lambda_{oPTA}$$
$$\lambda_{oDex-STA} = 4\lambda_{oDex} + \lambda_{oSTA}$$

The solubility products (K_{sp}) of the ion associates were determined conductometrically and found to be 3.48×10^{-9}, 1.92×10^{-9}, 9.90×10^{-20}, 2.15×10^{-18}, and 2.28×10^{-22} for Dex-TPB, Dex-RAS, Dex-PMA, Dex-PTA and Dex-STA, respectively (TABLE 2).

TABLE 2 : Conductometrically measured solubility (S), solubility products (K_{SP}), and formation constants (k) of various ion-associates

Ion-associate	λ_{oIP}	K_s	S	K_{sp}	$K = 1/K_{sp}$
Dex-TPB	1.19×10^9	7.02	5.89×10^{-5}	3.48×10^{-9}	2.87×10^8
Dex-RAS	1.50×10^9	6.58	4.38×10^{-5}	1.92×10^{-9}	5.21×10^8
Dex-PMA	7.80×10^9	6.07	7.78×10^{-6}	9.90×10^{-20}	1.01×10^{19}
Dex-PTA	6.30×10^9	10.58	1.68×10^{-5}	2.15×10^{-18}	4.66×10^{17}
Dex-STA	5.20×10^9	8.05	1.55×10^{-5}	2.28×10^{-22}	4.39×10^{21}

The very low solubility of Dex-TPB IP (S = 5.89×10^{-5} M) and consequently, the high formation constant value (k = 2.87×10^8), revealed that the degree of completeness of the reaction was more than 99.9%. At equilibrium, the solubility product of the undissociated IP in water (the intrinsic solubility) was omitted as this term makes a negligible contribution to the total solubility because the IPs were sparingly soluble in water and their saturated solutions were, therefore, very dilute[26-28].

Determination of Dex in pure state and pharmaceutical preparations

From figure 2, it can be concluded that, TPB forms only 1:1 IP with well defined stoichiometric ratio, while PTA, PMA or TSA form 1:1 ion pairs and via addition of excess titrant, 1:3 or 1:4 were formed suggesting using TPB as titrant. Aliquots solutions containing 2.71-18.99 mg Dex were titrated conductometrically against 10^{-2} M TPB, standardized solution[30]. Graphs of the corrected conductivity against the volume of titrant were constructed (Figure 3) and the end points were determined.
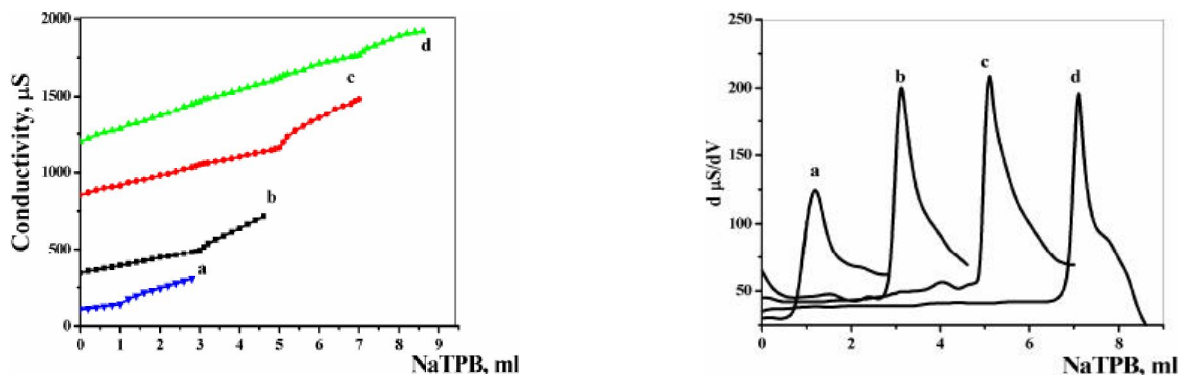
Figure 3 : Conductometric titration of Dex with 10^{-2} M NaTPB: a) 2.71mg, b) 8.13 mg, c) 13.5 mg, d) 18.97Dex

The proposed procedures were successfully employed for the assay of DXM in their authentic samples as well as pharmaceutical formulations. The results (TABLE 3) clearly indicated satisfactory agreement between the Dex contents in different samples determined by the developed sensor and official method. The average recovery ranged between 96.73 to 102.60%.

TABLE 3: Conductometric quantification of Dex in pure state and pharmaceutical preparations

Sample	Taken	Official method		Developed Sensors	
		Recovery %	R.S.D*	Recovery %	R.S.D
Pure DXM	2.71	96.52	3.4	98.50	0.78
	8.13	99.65	2.5	98.32	0.65
	13.5	99.50	2.2	99.10	0.89
	18.99	97.25	2.8	98.40	1.10
Tussilar tablets	2.71	94.30	1.8	96.54	3.50
Tussilar drops	2.71	98.56	1.65	102.60	2.10
	8.13	101.52	1.45	96.73	1.80

*Average of five titration process

CONCLUSION

The conductometric methods are characterized by low cost and simplicity, conductometric titrations are especially useful for very dilute solutions as the percentage change in conductance is independent of concentration and measurements need not be made close to the equivalence point. The proposed method has been successfully applied for stoichiometric ratios detection besides, solubility product and formation constant determination of various ion-associate complexes. Moreover, conductometric titrations have been applied for Dex quantification in authentic samples with high accu-racy and precision approving their applicability to drug quality control tests.

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