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RESEARCH ARTICLE

Conductimetric Determination of the Antidepressants Amitriptyline and Dothiepin Hydrochlorides and Tranylcypromine Hemisulphate in Their Pharmaceutical Formulations

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Conductimetric determination of the antidepressants amitriptyline and dothiepin hydrochlorides and tranylcypromine hemisulphate in their pharmaceutical formulations

Summary

Simple and sensitive conductimetric methods for the determination of amitriptyline hydrochloride, dothiepin hydrochloride and tranylcypromine hemisulphate are presented based on their ion associates with phosphotungstic and phosphomolybdic acids. The effects of solvent, molar ratio, reagent concentration and temperature were studied, and the solubility products of the formed ion associates were calculated. The method was applied to the determination of the drugs in pure state and their pharmaceutical preparations with mean recovery values of 96.25-104.90, 95.75-103.12 and 97.90-102.30%, and coefficients of variation of 0.23-1.62, 0.22-0.63 and 0.25-1.35 for amitriptyline, dothiepin hydrochlorides and tranylcypromine hemisulphate, respectively. The mean recovery values were 97.28-101.77, 97.60-104.50, 102.30-104.50 and 99.2-103.40 with coefficients of variation of 0.20-1.05, 0.24-0.91, 0.26-0.65 and 0.43-1.19 for tryptizol tablets, prothiaden tablets, prothiaden capsule and parnetil tablets, respectively. This is nearly the same as in the case of determining pure drug samples, indicating the high selectivity of the method towards the studied drugs.

Key Words : *Antidepressants, amitriptyline HCl, dothiepin HCl, tranylcypromine hemi-sulphate, conductimetry.*

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Farmasötik Formülasyonlarında Antidepresan Amitriptilin ve Dotiepin Hidroklorürlerin ve Tranilsipromin Hemisülfatın Kondüktimetrik Tayini

Özet

Amitriptilin hidroklorür, dotipin hidroklorür ve tranilsipromin hemisülfatın tayini için, fosfotungistik ve fosfomolibdik asit ile iyon birleşmesine dayanan basit ve duyarlı konduktimetrik yöntemler sunulmaktadır. Çözücü, molar oran, reaktif konsantrasyonu ve sıcaklığın etkisi çalışılmış ve oluşan iyon birleşimlerinin çözünme ürünleri hesaplanmıştır. Yöntem, amitriptilin hidroklorür, dotipin hidroklorür ve tranilsipromin hemisülfatın saf haldeki ve farmasötik preparatlardan tayininde sırasıyla % 96,25- 104,90, % 95,75- 103,12 ve % 97,90- 102,30 ortalama geri kazanım değerleri ve 0,23- 1.62, 0.22- 0.63 ve 0.25- 1.35 vryasyon katsayıları ile uygulanmıştır: Triptizol tablet, protiaden tablet, protiaden kapsül ve parnetil tablet için ortalama geri kazanım değerleri sırasıyla 97.28- 101.77; 97.60- 104.50; 102.30- 104.50 ve 99.2- 103.40, varyasyon katsayıları 0.2- 1.05; 0.24- 0.91; 0.26- 0.65 ve 0.43- 1.19'dur. Bu değerler, çalışılan ilaçlar açısından yöntemin yüksek selektivitesini gösterir şekilde, saf ilaç örneklerinin tayin edilmesi durumunda da hemen hemen aynıdır.

Anahtar Kelimeler : *Antidepresanlar, amitriptilin HCl, dotiepin HCl, tranilsipromin hemisülfat, kondüktimetri*

INTRODUCTION

The investigated drugs are very important antidepressants indicated in the treatment of depression and anxiety frequently associated with depressive illness. Several techniques have been adopted for the determination of amitriptyline, including spectrophotometry[1,2], high-performance liquid chromatography[3,4], gas chromatography[5], capillary electrophoresis[6] and voltammetry[7]. Amitriptyline has

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been also determined potentiometrically using ion-selective electrodes[8,9]. Dothiepin has been determined using liquid chromatography[10-12], kinetic[13] spectrophotometry, conductimetry[14] and also by using ion-selective electrodes[15]. Tranylcypromine was determined by spectrophotometry[16-18], gas chromatography-mass spectrometry[19,20], gas chromatography[21,22], high-performance liquid chromatography[23,24], thin layer liquid chromatography[25] and ion-selective electrodes[26].

The present work aims to introduce new conductimetric methods for the determination of amitriptyline and dothiepin hydrochlorides and tranylcypromine hemisulphate. These methods are 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 when compared to the reference methods[2,13,17] of their determination.

EXPERIMENTAL

A JENWAY 4330 pH and conductivity meter (England) was used for conductance measurements. The cell constant, Kcell, was 1.0. A temperature measurement sensor was provided with the conductivity bridge.

Reagents

Doubly distilled water and analytical grade reagents were used to prepare all solutions. Pure-grade amitriptyline hydrochloride (AmCl) and its pharmaceutical preparation (tryptizol tablets 25 mg/tablet), dothiepin hydrochloride (DpCl) (prothiaden tablets 75 mg/tablet; and prothiaden capsule 25 mg/capsule) and tranylcypromine hemisulphate ($Tc1/2SO_4$) (parnetil tablets 10 mg/tablet) were provided by El Kahira for pharmaceuticals and chemical industry company, Cairo, Egypt, under license of Merck, USA and Knoll AG, Ludwigshafen, Germany. Ethyl alcohol, acetone and dioxane were supplied by BDH.

Stock solutions were prepared by dissolving the accurate weights of pure solid in bi-distilled water and adding a few drops of acid (HCl or H_2SO_4) to prevent fungi formation before completing to the required volume, and the solutions were kept in the refrigerator for no more than one week to avoid any degradation, if it occurred. Working solutions of lower concentrations were invariably prepared by appropriate dilution.

General procedure

Volumes containing 9.41- 47.08 mg AmCl, 9.95 – 49.78 mg DpCl or 5.46 – 27.33 mg Tc1/2SO4 were transferred to a 50 ml volumetric flask and made to the mark with bi-distilled water. The contents of the volumetric flask were transferred to a beaker and the conductivity cell was immersed. Then 10^{-2} M PTA or PMA was added from a graduated microburette (0.01 ml) and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring. The conductance reading, taken after 1-2 min after each addition, was corrected for dilution[27] by means of the following equation, assuming that conductivity is a linear function of dilution:

$$\Omega_{corr} = \Omega_{obs} [(\vartheta_1 + \vartheta_2)/ \vartheta_1]$$

Where Ω is the electrolytic conductivity, ϑ_1 is the initial volume and ϑ_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 milliliter of 10^{-2} M PTA or PMA is theoretically equivalent to 9.41 mg AmCl, 9.95 mg DpCl or 5.46 mg $Tc1/2SO_4$.

Procedure for determining the drug – titrant ratio

Six milliliters of 10^{-2} M AmCl, DpCl or $Tc1/2SO_4$ were transferred to a 50 ml volumetric flask and made up to the mark with bi-distilled water. The contents were quantitatively transferred to a beaker and the conductivity cell was immersed. Then 10^{-2} M so-

lution of PTA or PMA was added from a microburette and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring for 1-2 min. A graph of corrected conductivity versus volume was constructed.

Procedure for tablets

Twenty tablets containing amitriptyline, dothiepin or tranylcypromine were weighed and powdered. A quantity of powder equivalent to prepare 10^{-2} M solution of the drug was transferred to a 100 ml volumetric flask and made up to the mark with distilled water. The general procedure was then followed in the concentration ranges already mentioned.

Procedure for capsules

Contents of 20 capsules containing dothiepin were weighed and a quantity of powder equivalent to prepare 10^{-2} M solution of the drug was transferred to a 100 ml volumetric flask and made up to the mark with distilled water. The general procedure was then followed in the above-mentioned concentrations.

Conductimetric determination of the solubility product of the ion associates

A series of solutions of different concentrations (c) was prepared for amitriptyline; dothiepin, tranylcypromine, PTA, or PMA. The conductivities of these solutions were measured at 25°C and the specific conductivities (λ_0), corrected for the effect of solvent, were calculated and used to obtain the equivalent conductivities (λ) of the solutions. Straight-line plots of λ versus λc were constructed and λ_0AmCl, λ_0DpCl; λ_0Tc1/2SO4, λ_0PTA or λ_0PMA was determined from the intercept of the respective line with λ axis. The activity coefficients of the ions employed were taken as unity because all the solutions were sufficiently dilute (5x10-5 to 5x10-3 M). The values of λ_0(Am-PTA), λ_0(Am-PMA), λ_0(Dp-PTA), λ_0(Dp-PMA), λ_0(Tc-PTA) and λ_0(Tc-PMA) were calculated using Kohlrausch's law of independent migration of ions[28].

The solubility (s) and solubility product (KSp) of a particular ion associate were calculated using the following equations:

$$S = Ks \times 1000/\lambda_{0(\text{ion-associate})}$$
$$K_{Sp} = 27S^4 \text{ for 1:3 ion-associates}$$

Where Ks is the specific conductivity of a saturated solution of the ion associate, determined at 25°C and corrected for the effect of solvent. The saturated solution was made by stirring a suspension of the solid precipitate in distilled water for 15 min at 25°C[29].

RESULTS AND DISCUSSION

Conductance measurements are used successfully in quantitative conductimetric titration of systems in which the conductance of the solution varies before and after the equivalence point. In these cases, the titration curve can be represented by two lines intersecting at the end point. Titrations in different media were attempted to obtain the best results. Preliminary experiment in aqueous, ethanol, 50% ethanol-water, 50% acetone-water and 50% dioxane-water mixtures showed that the aqueous medium is the most suitable for obtaining stable conductimetric readings.

The reagent concentration in each titration must not be less than 10 times that of the drug solution in order to minimize the dilution effect on the conductivity throughout the titration. The optimum concentration of PTA or PMA as titrant is 10^{-2} M to achieve a constant and highly stable reading within 1-2 min after mixing. Concentrations less than this led to unstable readings and required more time to obtain constant conductance values. Temperatures up to 50°C showed no effect on the end point.

The systems 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_x^+ and OH^- by hydrolysis. On adding PTA or PMA, the ion associate is formed by replacing the RNHions by mobile H+ and the conductivity increases[30]. After the end point, a curve break is observed at a drug-reagent molar ratio of 3:1 in all cases - amitriptyline,

dothiepin and tranylcypromine. Figure 1 shows the conductimetric titration curves of dothiepin versus PTA or PMA as a representative example of the pure drug to calculate the molar ratio of the drug reagent.

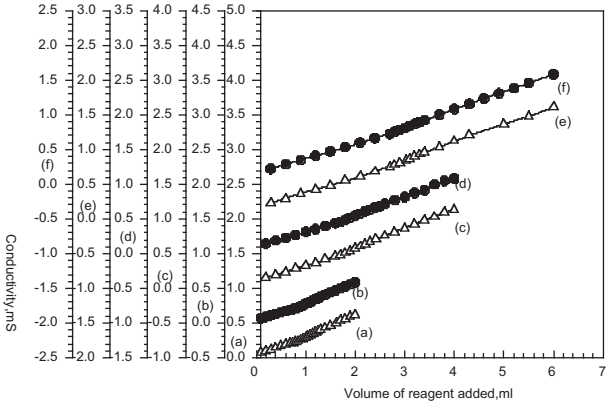

Figure 1. Conductimetric titration of 9.95 (a,b),19.90 (c,d) and 29.87 mg (e,f) DpCl against 10^{-2} M PTA (a,c&e) or 10^{-2} M PMA (b,d&f).

Analytical results

The results of the drug determination presented in Table 1 showed that good recoveries and low standard deviations were obtained. The optimum concentration ranges for determination are 9.41-47.08, 9.95-49.78 or 5.46-27.33 mg with mean recovery values of 96.25-104.90, 95.75-103.12 and 97.90-102.30% and coefficients of variation of 0.23-1.62, 0.22-0.63 and 0.25-1.35 for amitriptyline HCl, dothiepin HCl and tranylcypromine hemisulphate, respectively, at which sharp inflections and stable conductance readings are obtained. Limit of detection was 9.41, 9.95 or 5.46 mg for amitriptyline HCl, dothiepin HCl and tranylcypromine hemisulphate, respectively.

Table 1. Conductimetric determination of the investigated drugs in pure solution

Taken (mg)	PTA			PMA		
	Found[a] (mg)	Recovery (%)*	RSD (%)*	Found[a] (mg)	Recovery (%)*	RSD (%)*
Amitriptyline hydrochloride						
9.41	9.05	96.25	0.52	9.80	104.25	0.23
18.80	18.09	96.25	0.69	18.14	96.50	0.63
28.20	27.92	99.00	0.63	29.58	104.90	0.33
37.66	39.35	104.50	1.62	37.58	99.80	0.54
47.08	49.19	104.50	0.63	45.95	97.60	0.63
Dothiepin hydrochloride						
9.95	9.99	100.50	0.34	9.52	95.75	0.60
19.90	19.95	100.30	0.22	19.39	97.45	0.63
29.87	30.54	102.26	0.48	29.07	97.33	0.26
39.82	40.31	101.25	0.30	41.06	103.12	0.39
49.78	50.92	102.30	0.36	50.97	97.66	0.31
Tranylcypromine hemisulphate						
5.46	5.58	102.30	0.25	5.34	97.9	1.35
10.93	11.12	101.75	0.38	11.06	101.20	0.78
16.39	16.22	99.01	0.43	16.22	99.00	0.74
21.86	22.24	101.75	0.38	21.99	100.62	0.25
27.33	26.75	97.90	0.98	27.91	97.90	0.95

RSD: Relative standard deviation.
* Five determinations

The Student's t-test (at 99.9% confidence level) and F-test were applied[31]. The calculated t values ranged from 1.91 to 3.06, which is lower than the tabulated values at the 99.9% confidence level (4.03), while the F values were found to range from 0.16 to 1.20, which is lower than the tabulated value (6.61 for five determinations) at the 95% confidence limit. This means that there are no systematic differences between the determined and true concentrations; thus, the proposed method is of the same accuracy as the reference methods[2,13,17]. The results of validation of the proposed methods are presented in Table 2.

Table 2. Validation of data for investigated drugs in pure solution comparative with the official methods.

	Official method	PTA	PMA
Amitriptyline hydrochloride			
X±SE	95.40±0.91	100.10±0.82	100.61±0.47
Probability		>0.05	<0.05
Relative error (%)		0.09	0.60
$F^{(5,5)}$value(5.05)		0.82	0.27
Dothiepin hydrochloride			
X±SE	100.00±0.85	101.32±0.34	98.25±0.43
Probability		<0.05	<0.05
Relative error (%)		1.30	1.78
$F^{(5,5)}$value(5.05)		0.16	0.25
Tranylcypromine hemisulphate			
X±SE	101.40±0.91	100.54±0.48	99.32±1.00
Probability		>0.05	>0.05
Relative error (%)		0.53	0.68
$F^{(5,5)}$value(5.05)		0.27	1.20

X: Mean value. SE: Standard error.

Analytical applications

The validity of the proposed method was assessed by its application to the determination of AmCl, DpCl and Tc1/2SO_4 in their pharmaceutical preparations (tablets and capsules) (Table 3). The mean recovery values were 97.28-101.77, 97.60-104.50, 102.30-104.50 and 99.2-103.40 with coefficients of variation of 0.20-1.05, 0.24-0.91, 0.26-0.65 and 0.43-1.19 for tryptizol tablets, prothiaden tablets, prothiaden capsule and parnetil tablets, respectively. This is nearly the same as in the case of determining pure drug samples, indicating the high selectivity of the method towards the studied drugs. Figure 2 (a, b & c) represents the titration curves for 9.41-47.08 mg tryptizol tablets, 9.95 – 49.08 mg prothiaden capsules and 5.46 – 27.33 mg parnetil tablets against PTA as a representative figure.

Table 3. Conductimetric determination of amitriptyline and dothiepin hydrochlorides and tranylcypromine hemisulphate in their pharmaceutical preparations.

Taken (mg)	PTA			PMA		
	Found (mg)	Recovery (%)*	RSD (%)*	Found (mg)	Recovery (%)*	RSD (%)*
Amitriptyline hydrochloride						
Tryptizol tablets (25mg/tablet)						
9.41	9.43	100.30	0.20	9.43	100.30	1.15
18.80	18.28	97.28	0.54	18.55	98.72	0.43
28.20	27.89	98.92	0.36	28.63	101.56	0.73
37.66	38.32	101.77	0.87	36.76	97.62	0.71
47.08	47.22	100.30	1.05	47.22	100.30	1.30
Dothiepin hydrochloride						
Prothiaden tablets (75mg/tablet)						
9.95	10.26	103.20	0.63	9.88	99.30	0.57
19.90	20.79	104.50	0.24	19.66	98.80	0.69
29.87	29.95	100.30	0.91	29.84	99.90	0.20
39.82	38.86	97.60	0.42	39.89	100.20	0.23
49.78	49.18	98.80	0.36	50.12	100.70	0.35
Prothiaden capsules (25mg/capsule)						
9.95	10.39	104.50	0.58	9.63	96.80	0.27
19.90	20.35	102.30	0.65	19.50	98.01	0.52
29.87	31.21	104.50	0.26	31.21	104.50	0.63
39.82	41.36	103.87	0.50	41.61	104.50	0.19
49.78	50.92	102.30	0.34	49.28	99.00	0.63
Tranylcypromine hemisulphate						
Parnetil tablets (10mg/tablet)						
5.46	5.58	102.30	0.70	5.36	98.22	1.40
10.93	11.30	103.40	0.44	11.22	102.66	0.64
16.39	16.25	99.20	0.67	16.34	99.70	0.53
21.86	22.54	103.12	1.19	22.14	101.30	0.52
27.33	27.06	99.02	0.43	28.27	103.45	0.34

RSD: Relative standard deviation.
* Five determinations.

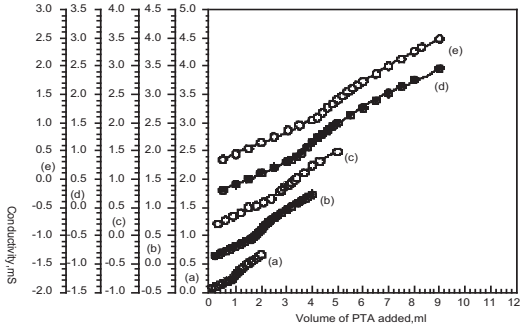

Figure 2a. Conductimetric titration of 9.41 (a), 18.8 (b), 28.2 (c), 37.66 (d) and 47.08 mg (e) tryptizol tablet against 10^{-2} mol dm^{-3} PTA.

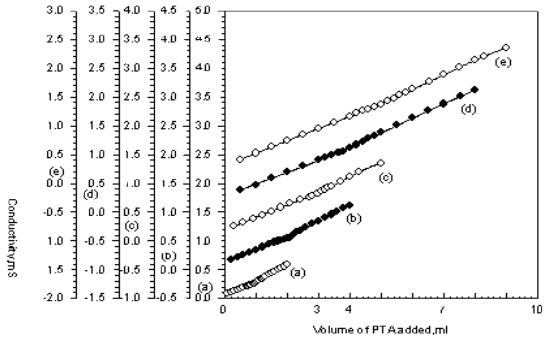

Figure 2b. Conductimetric titration of 9.95(a),19.90(b),29.87(c), 39.82 (d) and 49.78 mg (e) prothiaden capsule against 10^{-2} mol dm^{-3} PTA

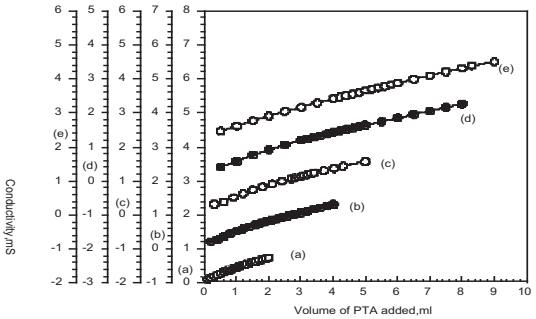

Figure 2c. Conductimetric titration of 5.46 (a) ,10.93 (b), 16.39 (c) ,21.86 (d) and 27.33 mg (e) parnetil tablet against 10^{-2} mol dm^{-3} PTA.

The results of the formulation determinations were compared with those obtained from reference methods[1,13,17] applying the F-test and the t-test (Table 4). In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression of observed drug concentration against the theoretical values obtained using the reference method was calculated (Table 5).

Table 4. Validation of data for investigated drugs in pharmaceutical preparations compared with the reference methods.

	Reference method	PTA	PMA
Amitriptyline hydrochloride			
Tryptizol tablets			
X±SE	101.40±0.91	99.71±0.60	99.70±0.86
Probability		>0.05	>0.05
Relative error (%)		0.29	0.30
$F^{(5,5)}$value(5.05)		0.43	0.89
Dothiepin hydrochloride			
Prothiaden tablets			
X±SE	100.00±0.85	100.88±0.51	99.78±0.40
Probability		>0.05	>0.05
Relative error (%)		0.87	0.22
$F^{(5,5)}$value(5.05)		0.36	0.22
Prothiaden capsule			
X±SE	100.00±0.85	103.49±0.48	100.56±0.45
Probability		<0.05	<0.05
Relative error (%)		3.37	0.55
$F^{(5,5)}$value(5.05)		0.32	0.28
Tranylcypromine hemisulphate			
Parnetil tablets			
X±SE	96.60±0.91	101.40±0.69	101.06±0.69
Probability		>0.05	>0.05
Relative error (%)		1.38	1.04
$F^{(5,5)}$value(5.05)		0.57	0.57

X: Mean value. SE: Standard error

Table 5. Linear regression analysis of data obtained from determination of the investigated drugs in pure and pharmaceutical preparations using PTA and PMA

Ion associate	Slope of the regression line[a]	Intercept of the regression line	Correlation of the regression line	t value (4.03)[b]	F value (6.61)[c]
Am_3-PTA					
(pure)	1.077	-1.716	0.999	2.74	0.82
tablets	0.999	-0.130	0.999	2.45	0.43
Am_3-PMA					
(pure)	0.973	0.718	0.998	2.24	0.27
tablets	0.980	0.292	0.999	3.05	0.89
Dp_3-PTA					
(pure)	1.026	-0.313	0.999	1.91	0.16
tablets	0.963	1.044	0.999	2.60	0.36
capsules	1.025	0.235	0.999	2.29	0.32
Dp_3-PMA					
(pure)	1.050	-1.358	0.999	2.00	0.25
tablets	1.011	-0.324	0.999	2.64	0.22
capsules	1.018	-0.167	0.997	2.63	0.28
Tc_3-PTA					
(pure)	0.977	0.350	0.999	2.39	0.27
tablets	0.991	0.292	0.999	2.72	0.57
Tc_3-PMA					
(pure)	1.025	-0.309	0.999	3.06	1.20
tablets	1.037	-0.348	0.999	2.67	0.57

[a]Observed versus theoretical.
[b]Tabulated 99.9% confidence limit at five degrees of freedom.
[c]Tabulated 95.0% confidence limit at five degrees of freedom.

The regression equation of calibration curves can be represented as:

Y= Slope of regression line (a) X mean value (x) + intercept of regression line (b)

The slopes of the regression lines did not differ significantly from the ideal value of unity, while the intercepts of the lines were very small, indicating that there are no systematic differences between determined and expected concentrations within the investigated range using the presented methods.

Solubility products of ion associates

Ion-associate formation is the main controlling factor in many chemical reactions, where the degree of feasibility of titration depends on the degree of completeness of the precipitation reaction. The equilibrium constant of the precipitation reaction is inversely proportional to the solubility products, whereas the smaller the solubility product of the formed ion associates, the sharper is the end point. It is noteworthy to mention also that the solubility of ion associates is one of the main factors controlling the life span of solid-state ion-selective electrodes built up from these ion associates, and which are widely used as an analytical tool for determining those drugs under investigation.

The solubility products of the ion associates were found to be $9.93x10^{-32}$, 1.49x10-39, $5.10x10^{-31}$, $9.94x10^{-38}$, $1.18x10^{-24}$ and $3.16x10^{-31}$ for Am_3-PTA, Am_3-PMA, Dp_3-PTA, Dp_3-PMA, Tc_3-PTA and Tc_3-PMA, respectively. Consequently, the equilibrium constants of the ion-associate formation reaction can be calculated as follows:

$3Am^{++}PTA \rightarrow Am_3PTA$	K= 1.00x1031
$3Am^{++}PMA \rightarrow Am_3PMA$	K= 6.71x1038
$3Dp^{++}PTA \rightarrow Dp_3PTA$	K= 1.96x1030
$3Dp^{++}PMA \rightarrow Dp_3PMA$	K= 1.00x1037
$3Tc^{++}PTA \rightarrow Tc_3PTA$	K= 8.47x1023
$3Tc^{++}PMA \rightarrow Tc_3PMA$	K=3.16x1030

These equilibrium constant values are very high, indicating that the degree of completeness of the ion-associate formation reaction is about 99.0%. In the equilibria, 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[35].

CONCLUSION

The application of the proposed method to determination of the investigated drugs in pure solution and pharmaceutical preparations is characterized by a high degree of precision and accuracy when compared with the reference method. Also, the present method is a simple, rapid, highly sensitive, selective, inexpensive technique and does not require any sophisticated instruments or unavailable reagents. Thus, it can be applied for routine analysis and verification in quality control and quality assurance during manufacture of these drugs.

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