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AAS and AES determination of furaltadone, methadone and trazodone in pharmaceutical formulations

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Abstract

Ion-associate complexes of furaltadone, methadone and trazodone hydrochlorides with $[Cd(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ were precipitated and the excess unreacted cadmium or zinc complex was determined. A new method using atomic emission and atomic absorption spectrometry for the determination of the above drugs in pure solutions and in pharmaceutical preparations is given. The drugs can be determined by the affort method in the ranges 7.2–72.16, 6.9–69.18 and 8.1–81.6 μg/ml solutions of the three drugs, respectively. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Furaltadone (FD), methadone (MD) and trazodone (TD) hydro-chlorides are very important pharmaceutical compounds. Therefore, we found it important to prepare new ion-associates containing these drugs and to study and elucidate their chemical structures. Also the work present a new rapid method for the determination of these drugs after transformation into the ion-associates.

Furaltadone (+)-5-morpholinomethyl-3-(5-nitro-furfurylidene amino) oxazolidin-2-one hydrochloride, FD is the active ingredient of many pharmaceutical preparations. It was formerly administered by mouth as an antibacterial agent and has been used in veterinary medicine. Methadone is a powerful narcotic analgesic resembling morphine in its action and used. Trazodone is a triazolo pyridine derivative. The distinguishing property of trazodone is its capacity to act selectively on the system of emotional integration, correcting the two main mechanisms responsible for depression: (a) an excessive input of unpleasant information as for example in secondary depression and (b) an intrinsic defect in integration, as in endogenous depression. TD also act as selectively on the serotoninergic system both at

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the central level, where its antiserotonin effect prevails since serotonin is involved in cerebral ischemia; this latter effect may prove to be useful in pathological conditions accompanied by a diminished cerebral blood flow.

Several methods were previously reported for the determination of FD [1–15], MD [16–31] and TD [32–42]. Although, Direct coupled plasma-atomic emission spectrometry (DCP-AES) and atomic absorption spectrometry (AAS) are rapid methods and have a very low detection limits which cannot be reached by most of other methods, they have not been applied yet to the determination of these drugs. The present work include new DCP-AES and AAS methods for the determination of the investigated drugs. The method is based on precipitating the ion-associates formed from the combination of these drugs with an excess of $[Cd(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$. The equilibrium concentration of the metal ion present as the soluble inorganic complex ion in the supernatant solution was determined using atomic emission and absorption.

2. Experimental

2.1. Reagent and materials

Doubly-distilled water and analytical grade reagents were used to prepare all solutions. FD and TD were purchased from Misr Company for Pharmaceutical Industries, Egypt. MD was purchased from Sigma. Cadmium nitrate, zinc acetate and potassium thiocyanate were supplied by Aldrich. The pharmaceutical formulations of FD were from Zambon, Ital. (Anauran tablets, 25 mg FD/tablet) and Uriach, Spain (Furantoina tablets, 40 mg FD/tablet 25), of MD were from Esteve, Spain (Metasedin tablets, 25 mg MD/tablet), Simes, Ital. (Eptadone tablets, 10 mg MD/tablet) and Wellcome, Austral (Physeptone tablets, 20 mg MD/tablet) and of TD were from Farma Lepori, Spain (Deprax tablets, 25 mg TD/tablet), Searle, Netherlands (Trazolan tablets, 50 mg TD/tablet) and Egyptian International Pharmaceutical Industries Co., Tenth of Ramadan City A.R.E. (Trittico tablets, 50 mg TD/tablet).

2.2. Apparatus

The pH of the solutions was measured using an Orion Research Model 701A digital pH-meter. Direct coupled plasma atomic emission measurements were carried out using a Beckman spectra span III emission spectrometer and atomic absorption measurements were made on Hitachi atomic absorption Z-6100 polarized Zeeman spectrometer. Conductometric measurements were carried out using YSI model 32M conductance meter with YSI 3417 dip type cell ($K_{1cell} = 1$).

2.3. Preparation of the standard solutions

The standard solutions of Cd(II) and Zn(II) were prepared by weighing 1.0 g of high purity cadmium shot or zinc metal and transferring to a 1-l volumetric flask and then adding 50 ml of concentrated HNO_3. After complete dissolution, the solution was filled to the mark with distilled water. The 1000 μg Cd or Zn/ml solutions were stored in plastic bottles, which had been presoaked in dilute HNO_3. The solutions were stable for ≈ 1 year.

2.4. Emission and absorption measurements

The cadmium and zinc were measured at wavelengths 214.43 and 206.20 nm, order 105 and 109, plasma position 0.0, detection limit 0.005 and 0.01 μg/ml, linear dynamic ranges 0.05–300 and 0.1–1000 μg/ml, background equivalent concentration 0.4 and 0.3 mg, entrance slits 50×300 μm^2 and exit slits 100×300 μm^2. Using AAS the Cd(II) and Zn(II) were measured at wavelengths 228.8 and 213.9 nm, slit 0.7 nm, relative noise 1.0, sensitivity 0.028 and 0.018 μg/ml and linear ranges 2.0 and 1.0 μg/ml. The instruments were equally adequate for present purposes (see below) and were used according to availability. The atomic spectrometry was calibrated as in the previously reported work [43].

2.5. Determination of solubility of the ion-associates

The solid ion-associate was added in excess to a

Table 1
Elemental analysis, composition and some physical properties of the drug ion-associates

Drug	Ion-associate composition	m.p. (°C)	Molar ratio	Color	% Found (calculated)			
					C	H	N	Metal
Furaltadone	$(C_{13}H_{17}N_4O_6)_2[Cd(SCN)_4]$	352	2:1	White	36.18 (36.20)	3.42 (3.41)	16.88 (16.89)	11.27 (11.30)
	$(C_{13}H_{17}N_4O_6)_2[Zn(SCN)_4]$	329	2:1	White	38.01 (37.99)	3.60 (3.58)	17.70 (17.73)	6.86 (6.90)
Methadone	$(C_{21}H_{28}NO)_2[Cd(SCN)_4]$	287	2:1	White	57.25 (57.23)	5.81 (5.80)	8.72 (8.70)	11.67 (11.65)
	$(C_{21}H_{28}NO)_2[Zn(SCN)_4]$	255	2:1	White	60.14 (60.17)	6.05 (6.10)	9.13 (9.15)	7.10 (7.12)
Trazodone	$(C_{19}H_{23}ClN_5O)_2[Cd(SCN)_4]$	272	2:1	White	47.50 (47.48)	4.29 (4.33)	15.83 (15.82)	10.61 (10.59)
	$(C_{19}H_{23}ClN_5O)_2[Zn(SCN)_4]$	236	2:1	White	49.70 (49.68)	4.51 (4.53)	16.52 (16.52)	6.45 (6.44)

solution of the optimum pH and ionic strength. The solution was shaken for 4–6 h and left to stand for a weak to attain equilibrium, then the saturated solution was filtered into a dry-beaker (rejecting the first few ml of filtrate). The equilibrium concentration of the metal ion present in the form of a soluble inorganic complex was measured using atomic spectrometry, and hence the solubility (S) of the precipitate was evaluated, from which the solubility product of the ion-associate was calculated.

2.6. Conductometric measurements

The stoichiometry of the ion-associates was elucidated also by conductometric titrations [44] of the drugs with $[Cd(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ solutions.

2.7. Determination of the drugs

Aliquots (0.5–5.0 ml) of 0.001 M drug solutions were quantitatively transferred into 25 ml volumetric flasks. To each flask 1.0 ml of 0.01 M standard solution of $[Cd(SCN)_4]^{2-}$ or $[Zn(SCN)_4]^{2-}$ was added and the volume was completed to the mark with the aqueous solutions of the optimum pH and ionic strength (prepared from HCl and NaOH). The solutions were shaken well and left to stand for 15 min then filtered through Whatman P/S paper (12.5 cm) and the equilibrium metal ion concentration in the filtrate was determined using AES or AAS. The consumed metal ion in the formation of ion-associates was calculated and the drug concentration was thus determined indirectly.

2.8. Determination of drugs in pharmaceutical preparations

For analysis of FD, sampling was made by grinding up 20 tablets of both Anauran and Furantoina tablets then taking 8.65–65.34 and 9.75–70.15 μg of Anauran and Furantoina, re-

Table 2
Solubility and solubility product of the ion-associates at their optimum conditions of pH and ionic strength (μ) values ate 25 °C

Ion-associate	pH	μ	p^s	$^{pk}_{sp}$
Furaltadone Cd-thiocyanate	6.0	0.4	5.17	14.90
Methadone Cd-thiocyanate	5.0	0.3	5.12	14.76
Trazodone Cd-thiocyanate	8.0	0.5	5.23	15.11
Furaltadone Zn-thiocyanate	5.0	0.7	5.06	14.59
Methadone Zn-thiocyanate	4.0	0.6	5.07	14.62
Trazodone Zn-thiocyanate	7.0	0.2	5.25	15.17

p^s: $-\log$ solubility; $^{pk}_{sp}$: $-\log$ solubility product.

Table 3
Determination of the investigated drugs in pure solutions and in pharmaceutical preparations by AES and AAS

Sample	Taken (μg)	Mean recovery (%)	Mean RSD (%)
*Using $[Cd(SCN)_4]^{2-}$**			
Furaltadone solution	7.20–72.16	99.85	1.5
Anauran tablets[a]	8.65–65.34	101.04	1.3
Furantoina tablets[b]	9.75–70.15	101.12	1.2
Methadone solution	6.90–69.18	101.25	0.8
Eptadone tablets[c]	7.50–65.25	101.14	1.2
Metasedin tablets[d]	8.45–71.20	101.12	1.1
Physeptone tablets[e]	9.50–70.65	101.10	0.9
Trazodone solution	8.10–81.60	101.48	0.4
Deprax tablets[f]	9.75–75.26	101.16	0.7
Trazolan tablets[g]	11.50–80.50	101.09	0.6
Trittico tablets[h]	10.15–79.25	101.12	0.8
*Using $[Zn(SCN)_4]^{2-}$***			
Furaltadone solution	7.20–72.16	98.42	1.5
Anauran tablets[a]	8.65–65.34	100.10	1.0
Furantoina tablets[b]	9.75–70.15	100.16	1.1
Methadone solution	6.90–69.18	101.03	0.8
Eptadone tablets[c]	7.50–65.25	100.08	1.0
Metasedin tablets[d]	8.45–71.20	100.05	1.3
Physeptone tablets[e]	9.50–70.65	100.09	0.4
Trazodone solution	8.10–81.60	101.15	0.6
Deprax tablets[f]	9.75–75.26	101.02	0.8
Trazolan tablets[g]	11.50–80.50	101.12	0.7
Trittico tablets[h]	10.15–79.25	101.07	0.5

RSD: Relative standard deviation (five determinations).
* By AES.
** By AAS.
[a] Zambon, Ital.
[b] Uriach, Spain
[c] Simes, Ital.
[d] Esteve, Spain
[e] Wellcome, Austral
[f] Farma Lepori, Spain
[g] Searle, Netherlands
[h] Egyptian Inter. Pharm. Indust. Co., Tenth of Ramadan City, A.R.E.

spectively. For analysis of MD, sampling was mad by grinding up 12, 8 and 10 tablets of Eptadone, Metasedin and Physeptone tablets then taking 7.5–65.25, 8.45–71.20 and 9.50–70.65 μg of Eptadone, Metasedin and Physeptone, respectively. In case of analysis TZ, sampling was made by grinding up 15, 12 and 20 tablets of Deprax, Trazolan and Trittico tablets then taking 9.75–75.26, 11.50–80.50 and 10.15–79.25 μg of the three tablets, respectively. In all cases the analysis was completed as in the general procedure.

3. Results and discussion

Elemental analysis for C, H, N and metal of the solid ion-associates (Table 1) revealed that in all cases two drug cations form ion-associates with one $[Cd(SCN)_4]^{2-}$ or $[Zn(SCN)_4]^{2-}$ ion. These results are comparable to the previously reported results [45].

Conductometric titrations of the investigated drugs with $[Cd(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ were performed to give as insight into the stoichiometric compositions of the ion-associates formed in solution. With all ion-associates, the characteristics curve-breaks are observed at a cation/anion mol ratio of about 2, confirming the formation of 2:1 (drug: X^{2-}) ion-associates. The results obtained coincide with the elemental analysis of the precipitated ion-associates. The optimum pH and ionic strength values (Table 2) have been elucidated by determining the solubility of the ion-associates in HCl–NaOH solutions of different pH values and ionic strengths. The best were those exhibiting lowest solubility values.

3.1. Determination of drugs in pure solutions and pharmaceutical preparations

Furaltadone HCl, methadone HCl and trazodone HCl were determined precisely and accurately in aqueous solutions at their optimum conditions of pH and ionic strength (Table 2) and in pharmaceutical preparations using the present methods. The results given in Table 3 reveal that recoveries were in the range 99.85–101.48% and 98.42–101.15%, reflecting the high accuracy in addition to the high precision indicated by the very low values of the relative standard deviation.

Generally, the present method is as good as those reported in the United States Pharmacopoeia [46]. In the present method, 7.2–72.16, 6.9–69.18 and 8.1–81.6 μg/ml solutions of FD, MD and TD using $[Cd(SCN)_4]^{2-}$ and $[Zn(SCN)_4]^{2-}$ were determined, respectively, which means that

Table 4
Linear regression analysis for furaltadone, methadone and trazodone using cadmium and zinc thiocyanate

Parameters	Cadmium thiocyanate			Zinc thiocyanate		
	FD	MD	TZ	FD	MD	TZ
Optimum concentration range (μg/ml)	7.20–72.16	6.90–69.18	8.10–81.60	7.20–72.16	6.90–69.18	8.10–81.60
Shift or intercept of the regression line[a]	0.035	0.028	0.032	0.029	0.034	0.036
Slope of regression line	0.9983	0.9965	1.0037	0.9996	1.0048	1.0025
Student's/(2.310)[b]	2.15	2.23	2.07	2.12	2.11	2.09
Range of error (%)	100.0 ± 1.2	100.0 ± 1.3	99.7 ± 1.5	99.8 ± 1.6	100.0 ± 1.4	99.7 ± 1.3

[a] Observed versus theoretical.
[b] Tabulated 95% confidence limit (for slope).

this method is applicable over wider concentration ranges than previously reported methods for FD [8,11] in which FD was determined polarography by Guibeteau et al. and Berzas et al. up to 3.2 and 14.44 μg/ml, respectively, for MD [22,23] in which MD was determined using HPLC by Wilson and Chiarotti in the ranges 0.1–10 and up to 50 μg/ml, respectively and in case of TD [38,39] in which TD was determined using HP—TLC and HPLC by Roy and Beaulieu in the ranges 0.2–2 mg/ml and 25–100 μg/ml, respectively.

In pharmaceutical analysis, it is important to test the selectivity toward the excipiences and the fillers added to the pharmaceutical preparations. Fortunately, such materials mostly do not interfere. This is clear from the results obtained for the pharmaceutical preparations (Table 3) that these excipiences do not interfere.

Although the present method is more time consuming (20–25 min) in comparison to other methods such as (15 min for HPLC), it exhibits the advantages of simplicity, precision, higher sensitivity, accuracy and convenience. Moreover, the reproducibility of the results are superior to those obtained from other methods such as chromatography [14] for FD [16,19,20,22,23] for MD and [37–39] for TD. Therefore, the method should be useful for routine analytical and quality control assay of the investigated drugs in dosage forms.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression [47] of observed drug concentration against the theoretical values (five points) was calculated. Student's *t*-test [48] (at 95% confidence level) was applied to slope of the regression line (Table 4) and showed that it didn't differ significantly from the ideal value of unity. Hence, it can be concluded that there are no systematic differences between the determination and true concentration over a wide range. The standard deviations (S.D.) can be considered satisfactory at least for he level of concentrations examined.

Although the present method is more time consuming than some other methods, it exhibits fair sensitivity and accuracy. Moreover, the reproducibility of the results is superior to that obtained from other methods.

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