ISSN : 0974-7419 Volume 14 Issue 11

Analytical CHEMISTRY
An Indian Journal

Full Paper

ACAIJ, 14(11) 2014 [409-414]

New analytical method for the determination of pethidine in pharmaceutical formulations and urine samples

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ABSTRACT

Ion – associate complexes of pethidine hydrochloride with zinc (II) thiocyanate, potassium ferricyanide and ammonium reineckate were precipitated and the excess unreacted metal complex was determined. A new method was given for the determination of pethidine drug in pure solutions, in pharmaceutical formulations and urine samples using atomic emission and atomic absorption spectrometry. The drug can be determined by the affort method in the range 0.57 - 62.43 μg mL^{-1}.

KEYWORDS

Atomic emission;
Atomic absorption;
Ion-associate complexes;
Pharmaceutical analysis.

INTRODUCTION

Pethidine;(Pd) is a potent opiate analgesics, which has been employed in the treatment of a variety of medical conditions[1]. Pethidine hydrochloride; (PdCl) is also used as an illicit drug and therefore it is placed on the substances list drugs that have acceptable medical use and have high potential for abuse in the United States and many other countries. Pethidine is also prescribed as a substitute for heroin[2], and often used medically as postoperative analgesia. In sports, athletes often take far higher doses of drugs than have been given for therapeutic use or in clinical studies to excel in competition. They have been barred to use by the International Olympic Committee and other sports organizations[3]. Therefore, determination of pethidine has important practical meanings. To the best of our knowledge few reports have been published on the analysis of pethidine in pharmaceutical preparations, these methods are sophisticated such as high performance liquid chromatography (HPLC)[4,5], gas chromatography[6], gas chromatography in combination with mass spectrometry (GC-MS)[7,8], spectrophotometry[9, 10], potentiometric analysis[11-16] and colorimetry[17]. Many of these methods involve several time-consuming manipulations, extraction steps, derivatization reactions that are liable to various interferences, and are not applicable to colored and turbid solutions either.

Pethidine; (Pd) is a very important pharmaceutical compound. Therefore, we found it important to prepare new ion-associates containing this drug and to study and elucidate their chemical structures. Also the work present a new rapid method for the determination of this drug after transformation into the ion-associates.

Pethidine (Meperidine hydrochloride, Dolantin) (Ethyl, 1-methyl-4-phenylpiperidine-4-carboxylate hy-

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drochloride). The chemical structure of pethidine drug is shown in Figure 1.

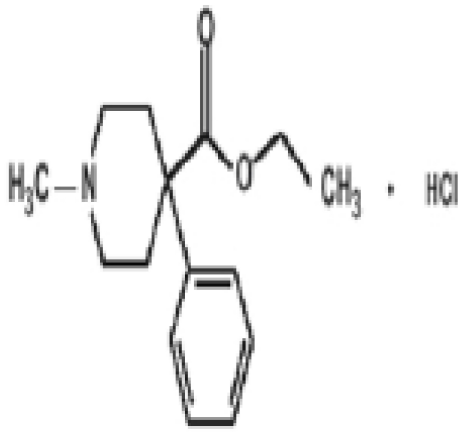

Figure 1 : Chemical structure of pethidine hydrochloride

The use of simpler, faster, less expensive and sensitive method is desirable.

Although, Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES) and Atomic Absorption Spectrometry (AAS) are rapid methods and have a very low detection limits which can not be reached by most of other methods. The present study includes new ICP-AES and AAS methods for the determination of the investigated drug. The method is based on the precipitating the ion-associates formed as a result of the combination of this drug with an excess of $[Zn(SCN)_4]^{2-}$, $[Fe(CN)_6]^{3-}$ and $[Cr(NH_3)_2(SCN)_4]^{1-}$. 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.

MATERIALS AND METHODS

Doubly-distilled water and analytical grade reagents were used in the preparation of all solutions. Pethidine was obtained from General Administration of Pharmacy, Ministry of Health (Cairo, Egypt). Demerol tablets containing (50 and 100 mg pethidine hydrochloride / tablet) as Pharmazeutische Produkte Althofstrasse Neuenhof / AG (Switzerland company) were purchased from local market. Zinc sulfate, potassium thiocyanate, potassium ferricyanide and ammonium reineckate were from Aldrich (www.sigmaaldrich.com).

Apparatus

The pH of the solutions was measured using an Orion Research Model 701A digital pH-meter. Inductively coupled plasma atomic emission measurements were carried out using ICPE- 9000 Shimadzu plasma atomic emission spectrometer and atomic absorption measurements were made on AA-6650 Shimadzu atomic absorption spectrophotometer. Conductimetric measurements were carried out using conductivity measuring bridge type M.C.3 model EBB/10 (K_{cell} = 1); [Chertsey, Surry, England]. The IR absorption spectra were obtained by applying the KBr disk technique using a Pye Unicam SP – 300 infrared spectrometer.

Preparation of the standard solutions

Standard solutions of chromium and zinc were prepared by weighing 1.0 g of a high-purity sample (chromium shot and zinc metal, respectively), transferring it to a 1-liter measuring flask and then adding 50 ml of concentrated HNO3. After complete dissolution, the solution was filled to the mark with distilled water. The 1000 μg mL-1 solution was stored in plastic bottles which had been presoaked in dilute HNO3. The solutions were stable for approximately one year. Standard solution of iron was obtained from Aldrich

Emission and absorption measurements

Analytical Parameters for the Measurement of Cr,Zn and Fe Using ICP-AES are listed in TABLE 1. Using AAS the Zn (II) was measured at wavelength 213.9 nm, slit 0.7 nm, relative noise 1.0, sensitivity 0.018 μg $mL^{-1}$and linear range 1.0 μg mL^{-1}. The instruments were equally adequate for present purposes and were used according to availability. The atomic spectrometry was calibrated as in the previously reported work[18-20].

Determination of solubility of the Ion – associates

The solid ion-associate was added in excess to a 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. Hence, the solubility (S) of the precipitate was evaluated, from which the solubility product of the ion-associate was calculated.

TABLE 1 : Analytical Parameters for the Emission Measurement of Cr, Zn and Fe Using ICP-AES

Element	Wavelength (nm)	Order	Plasma position	DL (mg/L)	LDR (mg/L)	BEC (mg)	RSD x BEC (%)
Cr	267.71	84	0	0.01	0.1-1000	0.4	7 x 0.7
Zn	206.20	109	0	0.01	0.1-1000	0.3	10 x 0.9
Fe	248.30	90	0	0.01	0.1-1000	0.2	1 x 0.7

Note. DL, detection limit; LDR, linear dynamic range; BEC, background equivalent concentration; RSD, relative standard deviation. For all elements: state, ion; entrance slits, 50 x 300 µm; exit slits, 100 x 300 µm.

Conductometric measurements

The stoichiometry of the ion-associates was elucidated also by conductometric titrations[21] of the drugs with $[Zn(SCN)_4]^{2-}$, $[Fe(CN)_6]^{3-}$ and $[Cr(NH_3)_2(SCN)_4]^{1-}$ solutions.

Analytical determination of pethidine in aqueous solutions

Aliquots (0.05 - 5.5 mL) of 0.001 mol L^{-1} drug solutions were quantitatively transferred to 25 mL volumetric flasks. To each flask 1.0 mL of 0.01 mol L^{-1} standard solution of $[Zn(SCN)_4]^{2-}$, $[Fe(CN)_6]^{3-}$ and $[Cr(NH_3)_2(SCN)_4]^{1-}$ 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). The equilibrium metal ion concentration in the filtrate was determined using ICP-AES or AAS. The consumed metal ion (Cr, Fe or Zn) in the formation of ion-associates was calculated, and the drug concentration was determined indirectly.

Analytical determination of pethidine in pharmaceutical preparations and urine samples

The Pethidine - containing pharmaceutical preparations (Demerol 50 and 100 mg tablets) were successfully assayed using the present method. Sampling were made by grinding (20 and 10 tablets), respectively then taking 0.65 - 60.25 and 1.25 - 58.45 µg / ml of Demerol 50 and 100 mg tablets, respectively. Urine samples were obtained from 20 patients after 2 – 8 hours of taking dose. In all cases the tablets and urine samples were analyzed at the optimum condition solution applying the above described procedure.

RESULTS AND DISCUSSION

The results of elemental analysis (TABLE 2) of the produced solid ion associates reveal that two pethidinium cations form ion associates with one $[Zn(SCN)_4]^{2-}$ and three $[Fe(CN)_6]^{3-}$, while only one pethidinium cation combines with $[Cr(NH_3)_2(SCN)_4]^{1-}$ to form a 1:1 ion associate. These results are comparable to the previously reported results[22-24].

Conductometric titrations of the investigated inorganic complexes with Pd HCl were performed to give insight into the stoichiometric compositions of the ion-associates formed in solutions. In case of ion associates with $[Zn(SCN)_4]^{2-}$, the characteristic curves break at a molecular ratio ([Pd] / $[x]^{n-}$) of about 2, confirming the formation of 2:1 (Pd : x^{2-}) ion associates but in the case of the reineckate anion where the curve exhibits a sharp break at the 1:1 molecular ratio and in the case of $[Fe(CN)_6]^{3-}$ anion the curve exhibits a sharp break at the 3 :1 molecular ratio. The results obtained coincide with the elemental analysis of the precipitated ion- associates.

TABLE 2 : Elemental analysis, composition and some physical properties of pethidine ion - associates

Drug	Ion-associate composition	m. p. ^{0}c	Molar ratio	Color	% Found (calculated) C	H	N	Metal (Zn, Cr or Fe)
Pethidine	$(C_{15}H_{21}NO_2)_2[Zn(SCN)_4]$	285	2 : 1	white	56.11 (56.15)	5.73 (5.78)	11.51 (11.56)	8.94 (8.99)
	$(C_{15}H_{21}NO_2)[Cr(NH_3)_2(SCN)_4]$	344	1 : 1	pink	40.26 (40.33)	4.73 (4.78)	17.29 (17.34)	9.15 (9.20)
	$(C_{15}H_{21}NO_2)_3[Fe(CN)_6]$	273	3 : 1	white	64.09 (64.16)	6.56 (6.60)	13.18 (13.21)	5.84 (5.87)

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The optimum pH and ionic strength values (TABLE 3) 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.

TABLE 3 : Solubility and solubility product of pethidine ion-associates at their optimum conditions of pH and ionic strength (μ) values ate 25° C

Pd- Ion – associate	pH	μ	p^s	pk_{sp}
$(C_{15}H_{21}NO_2)[Cr(NH_3)_2(SCN)_4]$	5.0	0.7	9.45	18.90
$(C_{15}H_{21}NO_2)_2[Zn(SCN)_4]$	4.0	0.4	7.12	20.75
$(C_{15}H_{21}NO_2)_3[Fe(CN)_6]$	3.0	0.6	8.26	31.61

p^s : -log solubility; $p^k sp$: -log solubility product

Analytical determination of pethidine in aqueous solutions, pharmaceutical preparations and urine samples

Pethidine HCl was determined precisely and accurately in aqueous solutions at their optimum conditions of pH and ionic strength (TABLE 4), in pharmaceutical preparations and urine samples using the present method. The results given in TABLE 4 reveal that recoveries were in the range 98.92 - 100.07 %, 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 before where, 0.57 - 62.43 μg mL^{-1} solutions

TABLE 4 : Determination of Pethidine in aqueous solutions, pharmaceutical preparations and urine samples by ICP-AES and AAS

Sample	Amount taken (μg)	Mean recovery (%)	Mean RSD (%)
Using $[Zn(SCN)_4]^{2-*}$			
Pure Pd solution	0.57 - 62.43	99.92	0. 7
Demerol tablets [a] (50 mg Pd / tablet)	0.65 - 60.25	99.93	0.5
Demerol tablets [a] (100 mg Pd / tablet)	1.25 - 58.45	99.93	0. 6
Urine after 2 hs	5.75 - 45.25	99.94	0.7
Urine after 6 hs	9.45 - 35.35	99.93	0.6
Urine after 8 hs	15.25 - 25.15	99.95	0.5
Using $[Zn(SCN)_4]^{2-**}$			
Pure Pd solution	0.57 - 62.43	99.96	0. 6
Demerol tablets [a] (50 mg Pd / tablet)	0.65 - 60.25	99.95	0.7
Demerol tablets [a] (100 mg Pd / tablet)	1.25 - 58.45	99.96	0. 7
Urine after 2 hs	5.75 - 45.25	99.95	0.8
Urine after 6 hs	9.45 - 35.35	99.95	0.9
Urine after 8 hs	15.25 - 25.15	99.94	0.6
Using $[Cr(NH_3)_2(SCN)_4]^{1-*}$			
Pure Pd solution	0.57 - 62.43	100.01	0.6
Demerol tablets [a] (50 mg Pd / tablet)	0.65 - 60.25	100.03	0.5
Demerol tablets [a] (100 mg Pd / tablet)	1.25 - 58.45	100.03	0. 7
Urine after 2 hs	5.75 - 45.25	100.07	0.6
Urine after 6 hs	9.45 - 35.35	100.05	0. 7
Urine after 8 hs	15.25 - 25.15	100.02	0.8
Using $[Fe(CN)_6]^{3-*}$			
Pure Pd solution	0.57 - 62.43	98.95	0.7
Demerol tablets [a] (50 mg Pd / tablet)	0.65 - 60.25	98.96	0.8
Demerol tablets [a] (100 mg Pd / tablet)	1.25 - 58.45	98.94	0.9
Urine after 2 hs	5.75 - 45.25	98.93	0. 7
Urine after 6 hs	9.45 - 35.35	98.92	0.8
Urine after 8 hs	15.25 - 25.15	98.97	0.6

RSD : Relative Standard Deviation (five determinations); * By ICP-AES; ** By AAS; [a] Althofstrasse Neuenhof / AG (Switzerland company)

of pethidine using $[Zn(SCN)_4]^{2-}$, $[Fe(CN)_6]^{3-}$ and $[Cr(NH_3)_2(SCN)_4]^{1-}$ was determined, respectively, which means that this method is applicable over a wider concentration range than that of the previously published colorimetric method [17] in which pethidine was determined in the ranges 5 – 45 μg mL^{-1}.

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. It is clear from the results obtained for the pharmaceutical preparations (TABLE 4) that these excipiences do not interfere.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression[25] of observed drug concentration against the theoretical values (five points) was calculated. The student's *t-test*[25] (at 95% confidence level) was applied to the slope of the regression line which showed that it did not differ significantly from the ideal value of unity. Hence, it can be concluded that there are no systematic differences between the determination and the true concentration over a wide range. The standard deviations (SD) can be considered satisfactory at least for the level of concentrations examined.

CONCLUSION

The present method is as good as those reported before where, 0.57 - 62.43 μg mL^{-1} solution of pethidine using $[Zn(SCN)_4]^{2-}$, $[Fe(CN)_6]^{3-}$ and $[Cr(NH_3)_2(SCN)_4]^{1-}$ were determined, respectively, which means that this method is applicable over a wider concentration range than previously published method [17] in which pethidine was determined in the ranges 5 – 45 μg mL^{-1}.

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 those obtained with other methods.

ACKNOWLEDGEMENTS

The Authors wish to thank College of Applied Medical Sciences - Taif University for supporting this work.

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