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Il Farmaco 54 (1999) 835–837

IL FARMACO

Short communication

The use of 7,7,8,8-tetracyanoquinodimethane for the determination of nortriptyline and desipramine in tablets

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Received 25 March 1998; accepted 2 August 1999

Abstract

A sensitive and selective spectrophotometric method is described for the assay of nortriptyline and desipramine. The method is based on the interaction of these drugs as electron donors with 7,7,8,8-tetracyanoquinodimethane (TCNQ) as a π-acceptor in acetonitrile at 80°C, to give highly coloured chromogens which exhibit maximum absorption at 567 nm. The proposed method was successfully applied to the determination of these drugs (as salts) in sugar-coated tablets.

Keywords: Nortriptyline; Desipramine; 7,7,8,8-Tetracyanoquinodimethane; Spectrophotometric determination

1. Introduction

Nortriptyline **1** and desipramine **2** are tricyclic antidepressants and published spectrophotometric methods for their determination are based on different reactions such as oxidation [1], ion pair [2,3] or dithiocarbamic acid formation [4]. 7,7,8,8-Tetracyanoquinodimethane (TCNQ) as a π-acceptor, interacts with *n*-electron donors and some drugs such as alkaloids [5], penicillins [6], antihistamines [7], terfenadine [8] and some others [9–11] have been determined spectrophotometrically reading the absorbance of the resulting radical anion $TCNQ^{\bullet -}$. This paper describes a new spectrophotometric method for the determination of **1** and **2** (as salts) in tablets using TCNQ as reagent.

2. Experimental

2.1. Apparatus and chemicals

Shimadzu 160A UV–Vis and Zeiss PMQ II spectrophotometers were used. Pharmaceutical grade nortriptyline and desipramine as hydrochloride salts and sugar-coated tablets were generous gifts from Troponwerke, Köln, Germany and Ciba-Geigy, Basel, Switzerland, respectively. TCNQ was from Riedel-de-Haen, Germany. All chemicals and solvents were of analytical or spectroscopic grade.

2.2. Procedure

2.2.1. Preparation of calibration graphs

Transfer a 10 ml aliquot of stock solution (aqueous solutions of 1.25 mg ml^{-1} calculated as base) into a separating funnel, add 5 ml of water and 1 g of NaCl and dissolve the NaCl. Alkalize the solution with 1 ml concentrated ammonia and extract the free base with three 15-ml portions of $CHCl_3$. Filter the combined extract through a phase separating filter paper damped with $CHCl_3$ to a 50-ml volumetric flask and dilute to volume with $CHCl_3$. Pipette 2 ml of the solution into a 10-ml volumetric flask, remove the solvent in a stream of nitrogen and dissolve the residue completely in acetonitrile using an ultrasound bath. Add acetonitrile up to the mark to provide a solution of 50 μg ml^{-1}. Transfer serial volumes of standard base solution in the ranges 0.2–2.0 ml for **1**, and 0.2–1.6 ml for **2** into a series of 10-ml volumetric flasks. Bring the volume to 2

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0014-827X/99/$ - see front matter
PII: S0014-827X(99)00089-0

ml with acetonitrile. Add 2 ml of TCNQ reagent (0.02% in acetonitrile) and mix. Place the flask in a water bath at 80°C for 10 min for **1** and 20 min for **2**. Cool, add acetonitrile to the mark, mix and measure the absorbance at 567 nm against a reagent blank similarly prepared.

2.2.2. Assay procedure for tablets

Place ten tablets (as limited material was available, ten tablets were used) in a 250-ml beaker, add 200 ml of water, sonicate and shake occasionally to disintegrate the tablets. Then shake mechanically for 15 min and transfer the supernatant solution. Add another 200 ml of water into the beaker, shake and sonicate again for 15 min. Filter the combined supernatant solution into a 500-ml volumetric flask, wash the residue with small portions of water and add water up to the mark. Transfer 10 ml of the solution into a separating funnel and then extract the base and dilute the solution to 50 ml, as described in Section 2.2.1. Pipette 0.5 ml of the solution into a 10-ml volumetric flask and remove the chloroform. Add 2 ml of acetonitrile, dissolve the base and then analyse the solution by the procedure described in Section 2.2.1. The amount of **1** and **2** in the tablets was calculated from the regression equations.

*2.3. Synthesis of the chromophore of **1***

To a solution of excess TCNQ in acetonitrile was added notriptyline base in a small amount of $CHCl_3$ ($CHCl_3$ was evaporated during the heating process) and the mixture was heated at 80°C for 10 min. The purple chromophore was easily purified on preparative silica gel plates using 1:1 petrol–ethylacetate as the mobile phase. The compound was eluted from silica by $CHCl_3$ and the solvent was evaporated. ^{1}H NMR in $CDCl_3$ (200 MHz, J in Hz) δ 2.58 (s, 3H, N–CH_3); 5.81(t, $J = 7.07$ vinyl hydrogen); 6.86 (d, $J = 8.73$, one quinonoid hydrogen); 6.96–7.24 (m, 10 hydrogens); 7.72 (d, $J = 8.66$, one quinonoid hydrogen).

3. Results and discussion

Among the π-acceptors, TCNQ gives the predominant chromogen of the highest molar absorptivity with n-electron donors (ε between 30 000–45 000) and therefore it is the reagent of choice [5,7,10,11]. Most spectrophotometric methods with TCNQ [5–10] are based on the resulting intense blue-coloured radical anion $TCNQ^{\bullet -}$ (reading at 815 or 750 nm) formed in acetonitrile at room temperature. Hovewer, reactions in aqueous acetonitrile solution at pH 9.0–9.5 have also been reported [11,12]. Under these conditions, chromophores were either $TCNQ^{\bullet -}$ [11] or an unidentified product [12] with a λ_{max} of 578 nm.

As TCNQ reacts with n-electron donors, first bases of **1** and **2** were obtained from salts by liquid–liquid extraction of the alkalized aqueous solutions with $CHCl_3$. In our work, TCNQ formed intense purple chromophores with **1** and **2** (bases) when heated at 80°C in acetonitrile, whereas at room temperature only a pale green colour appeared. Both chromophores exhibit very similar absorption spectra with the same λ_{max} of 567 nm. The spectrum of the chromophore formed with desipramine is shown in Fig. 1. It is known that [13] TCNQ reacts with certain primary or secondary amines to give products in which one or two cyano groups are replaced by the amine. As an example, TCNQ reacts with pyrrolidine to give 7-pyrrolidino-7,8,8-tricyanoquinodimethane with the same λ_{max} of 567 nm. To confirm the structures, the chromogen formed with **1** was obtained. Its NMR spectrum in $CDCl_3$ (see Section 2) revealed that the chromogen was formed by replacing one cyano group at TCNQ with the amine.

Acetonitrile, chloroform, dioxane, methanol, ethanol, acetone and dimethyl formamide were tested as solvents. Acetonitrile afforded maximum colour intensity and stability. In addition, it is a good solvent for the reagent. Fig. 2 shows that at 60°C the colour increased relatively slowly for desipramine. At 80°C, maximum absorption was reached after 20 min. For nortriptyline heating at 80°C for 10 min is recommended. The colour remains stable for 12 h when kept in the dark. A four-fold amount of reagent was found to be sufficient for maximum and reproducible colour intensity and a concentration of 0.02% is recommended. No interference was observed from tablet excipients. By this method, amitriptiline, diazepam, nitrazepam, medazepame, oxazepame, chlordiazepoxide, promazin and perfenazine, if present, do not interfere the determination. Application of Job's method of continuous variation [14] indicated a molar ratio of donor to acceptor of 1:1 for **2** as a representative example.

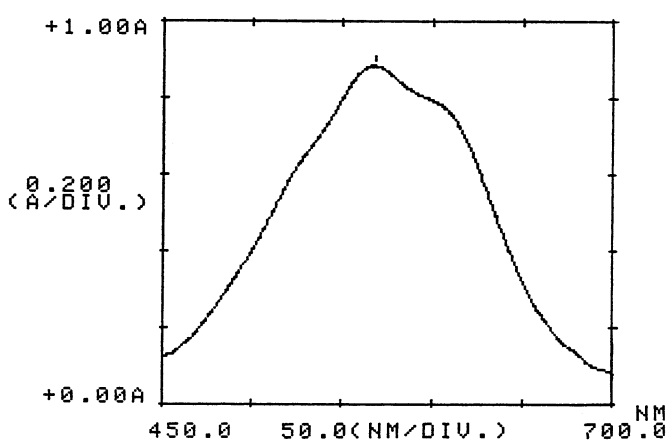

Fig. 1. Absorption spectrum of desipramine–TCNQ reaction product in acetonitrile (8 μg ml^{-1} as base).

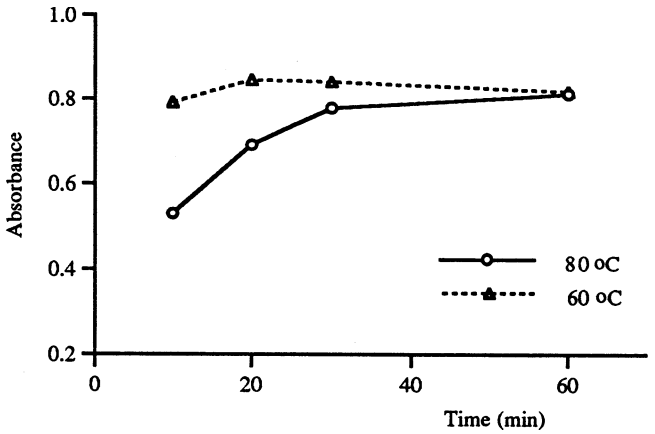

Fig. 2. Effect of temperature and reaction time on the colour intensity of the reaction product of desipramine with TCNQ.

Calibration graphs were linear over the concentration range 1–10 μg ml^{-1} ($A = 0.1266C - 0.014$) for **1**, and 1–8 μg ml^{-1} ($A = 0.1126C - 0.025$) for **2** ($r = 0.9999$ for both). The value of molar absorptivities were 3.33×10^4 and 3.00×10^4 l mol^{-1} cm^{-1} for **1** and **2**, respectively.

Commercial tablets containing **1** and **2** as hydrochlorides were analysed by this method. The results were compared by using the student's *t*- and *F*-tests with those of official reference methods [15,16], which are based on extraction procedures followed by UV-spectrophotometric measurement. At the 95% confidence level there was no significant difference (Table 1).

Compared with the reference UV-spectrophotometric methods [15,16], the proposed method is more selective and sensitive. It is also more selective than the colorimetric methods [1–3], because in these methods the reagents used given colours with primary, secondary and tertiary amines while TCNQ only produces chromophores with certain amines. This is especially important when an analysis is performed in biological fluids. Concerning the sensitivity, only the method in [1] is more sensitive (linearity range is 0.2–2.5 μg ml^{-1}) than the recommended method. But in this procedure a very strong acidic medium (85–90% H_3PO_4) is necessary for reaction.

In conclusion, the proposed method is sensitive and selective. Analysis in urine is now under investigation.

Table 1
Assay results for **1** and **2** in tablets [a]

	Recovery ± SD [b] (%)		
	Proposed method		Reference method [15,16]
1	100.14 ± 0.89		98.78 ± 1.03
		$t = 2.24$	
		$F = 1.26$	
2	98.80 ± 0.85		99.80 ± 1.12
		$t = 1.60$	
		$F = 1.31$	

[a] Each tablet contained 25 mg of **1** or **2** hydrochloride salts.
[b] $n = 5$, $P = 0.05$, $t = 2.31$, $F = 6.39$.

References

[1] H. Fenner, Redox reactions of tricyclic psycopharmaceuticals, II. Spectrophotometric determination of very small amounts of thymoleptic drugs of the diphenylamine series, Fresenius Z. Anal. Chem. 249 (1970) 124–127.
[2] J. Lemli, I. Knockkaert, Determination of organic bases in pharmaceuticals by cobalt thiocyanate, Pharm. Weekb. Sci. Ed. 5 (1983) 142–144.
[3] B. Pitarch, J. Manes, F. Bosch, Extractive colorimetric determination of mono-, bi, tri, and tetracyclic antidepressants using ion pairs, An. R. Acad. Farm. 52 (1986) 279–289.
[4] G.L. Corona, R.M. Facino, Identification and evaluation of amitriptyline and its basic metabolites in rabbit urine, Biochem. Pharm. 17 (1968) 2045–2050.
[5] A. Taha, G. Rücker, Utility of π-acceptors in alkaloid assay, Arch. Pharm. 310 (1977) 485–494.
[6] H.F. Askal, G.A. Saleh, N.M. Omar, Utility of certain π-acceptors for the spectrophotometric determination of some penicillines, Analyst 116 (1991) 387–390.
[7] M.M. Abdel-Khalek, M.E. Abdel-Hamid, M.S. Mahrous, Use of 7,7,8,8-tetracyanoquinodimethane in the colorimetric determination of some antihistamines, J. Assoc. Off. Anal. Chem. 68 (1985) 1057–1059.
[8] M.E. Abdel-Hamid, M.A. Abuirjeie, Utility of iodine and 7,7,8,8-tetracyanoquinomethane for determination of terfenadine, Talanta 35 (1988) 242–244.
[9] K.-A. Kovar, W. Mayer, H. Auterhoff, Molecular complexes and radicals of procaine, Arch. Pharm. 314 (1981) 447–458.
[10] K.-A. Kovar, M.E. Abdel-Hamid, Charge-transfer complexes formation in drug analysis, II: Molecular complexes and radicals of drugs containing the imidazoline ring, Arch. Pharm. 317 (1984) 246–256.
[11] S.A. Hussein, A.M. Mohamed, M. Abdel-Alim, Utility of certain π-acceptors for the spectrophotometric determination of gliclazide and tolazamide, Analyst 114 (1989) 1129–1131.
[12] A.M.I. Mohamed, Spectrophotometric determination of some benzothiadiazine diuretics with 7,7,8,8-tetracyanoquinodimethane, Talanta 35 (1988) 621–624.
[13] W.R. Hertler, H.D. Hartzler, D.S. Acker, R.E. Benson, Substituted quinodimethanes. III. Displacement reactions of 7,7,8,8-tetracyanoquinodimethane, J. Am. Chem. Soc. 84 (1962) 3387–3393.
[14] P. Job, Formation and stability of inorganic complexes in solution, Ann. Chim. 9 (1928) 113–203.
[15] Nortriptyline tablets, The British Pharmacopoeia, British Pharmacopoeia Commission, London, 1980, p. 795.
[16] Desipramine tablets, The United States Pharmacopeia, XXI, The United States Pharmacopeial Convention, Rockville, 1985, p. 283.