Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 168 (2016) 235–243

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

A novel strategy for spectrophotometric simultaneous determination of amitriptyline and nortriptyline based on derivation with a quinonoid compound in serum samples

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ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form 3 June 2016
Accepted 6 June 2016
Available online 7 June 2016

Keywords:
Amitriptyline
Nortriptyline
Magnetic solid phase extraction
Chloranil
Spectrophotometry
Simultaneous determination

ABSTRACT

A novel and efficient strategy for the simultaneous determination of two tricyclic antidepressant (TCA) drugs [amitriptyline (AT), and its main metabolite (nortriptyline; NT)] *via* a combination of magnetic solid phase extraction (MSPE), and spectrophotometric techniques in serum is suggested. For this purpose, the imidazolium ionic liquid (Imz)-modified Fe_3O_4@SiO_2 nanoparticles (Fe_3O_4@SiO_2-Imz) was employed as an adsorbent for the MSPE. Preconcentration (loading–desorption) studies were performed under optimized conditions including pH, adsorbent amount, contact time, eluent volume, and desorption time. Afterward, determination of each drug was carried out by specific strategy. Acetaldehyde (AC), and 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil; CL) were used as chemical reagents for reaction with NT, while AT did not react with these reagents. This method is based on the condensation reaction between secondary amine group of NT and AC to afford an enamine, and subsequently reaction with CL to produce a chlorinated quinone-substituted enamine. The final product exhibited maximum absorption at 556 nm, while the AT was determined at 240 nm. The limits of detections (LODs) for NT and AT in serum sample were obtained as 0.19 and 0.90 ng mL^{-1}, respectively. The limits of quantifications (LOQs) were obtained to be 0.63 and 2.93 ng mL^{-1} for NT and AT, respectively. A linear range was obtained to be 1 to 5 ng mL^{-1}. Results indicated that the suggested method is applicable for simultaneous determination of NT and AT in serum samples.

1. Introduction

Since the introduction of amitriptyline (AT) [{3-(10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptan-5-ylidene) propyldimethylamine hydrochloride}] in 1960 this drug still is an important drug in the treatment of depression, especially in developing countries [1,2]. AT is metabolized mainly by demethylation forming nortriptyline (NT) [3-(10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)propyl-(methyl)-amine hydrochloride], and by hydroxylation, lead to the formation of E-10-hydroxy(EHAT) and Z-10-hydroxyamitriptyline (ZHAT). The NT is further demethylated to desmethylnortriptyline (NNT), and hydroxylated to E-10-hydroxy (EHNT) and Z-10 hydroxynortriptyline (ZHNT). The demethylation of AT and NT is mainly catalyzed by CYP2C19, with the participation of other CYP enzymes that formed in higher drug concentrations. The formation of the E-10-hydroxy metabolites is dependent on the activity of CYP2D6, with stereospecificity to the (−)-EHAT and (−)-EHNT metabolites. The main metabolic pathways of AT and NT in blood are shown in Scheme 1 [3].

The most commonly used methods for determination of AT, NT, and other tricyclic antidepressant (TCA) drugs are spectrophotometric method [4–7], micellar liquid chromatography (MLC) [8], voltammetry [9], capillary gas-liquid chromatography (CGLC) [10], capillary zone electrophoresis (CZE) [11], high-performance liquid chromatography (HPLC) [12–14], electron-capture gas chromatography (ECGC) [15], thin layer chromatography (TLC) [16], LC-MS [17], GC [18], liquid-liquid microextraction (LLE)-GC [19], GC–MS [20], gas-liquid chromatography (GLC) [21], and chemometric methods [22].

It is an unquestionable fact that the development of new and efficient approach for extraction, preconcentration, and isolation of real samples are required to enhance sensitivity, and selectivity of the analytical method. In this respect, solid phase extraction (SPE) can be considered as a versatile approach, mainly due to its improvements in automation, reproducibility and high-throughput capability [23–25]. In the last decade, a great deal of research effort has focused on the improvement of SPE systems. A relatively new development in this field is the use of magnetic nanoparticles (MNPs), which is the so-called magnetic solid phase extraction (MSPE). The MSPE has some advantages such as excellent adsorption efficiency, rapid separation from the matrix through external magnetic field without retaining residual

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http://dx.doi.org/10.1016/j.saa.2016.06.013
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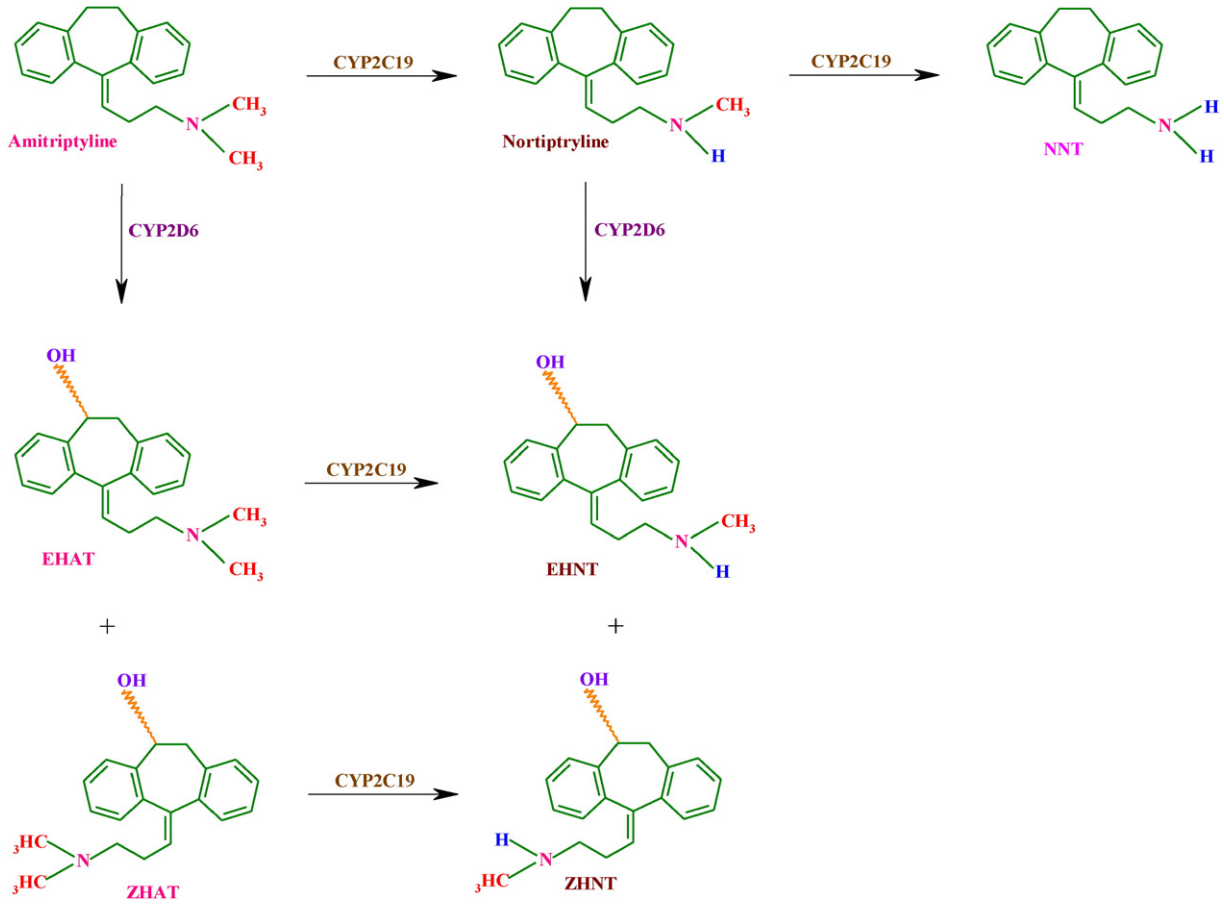


Scheme 1. Main metabolic pathways of amitriptyline and nortriptyline in blood.

magnetization after its removal, and has recently exhibited significant advantages in separation science [26–28]. The Fe_3O_4@SiO_2-ionic liquid (Fe_3O_4@SiO_2-IL) is composed of a core-shell structure with a core of dense and globular magnetic nanoparticles, and a SiO_2-IL shell that the magnetic property of the core solved the separation difficulty, while the shell-type mesoporous structure shortens the diffusion path, and increases the effective area for adsorption [29,30].

This paper describes the development and validation of an efficient analytical method by a combination of MSPE, and spectrophotometric techniques for the simultaneous determination of AT and NT in the serum sample. This method is based on the condensation of free secondary amine group of NT and AC to afford an enamine, and subsequently reaction with CL to produce a chlorinated quinone-substituted enamine which was measured spectrophotometrically. Meanwhile, it should be mentioned that NT is a secondary amine and AT is a ternary amine and both of them have the same maximum absorption at 240 nm in UV–vis spectroscopy (overlapping) before reaction. Since AC reacted with the primary or secondary amines, thus AT remains as not reacted species in solution with maximum absorption at 240 nm (without shift). This matter is the base of the selective simultaneous determination of AT and NT drugs.

2. Experimental

2.1. Chemicals and reagents

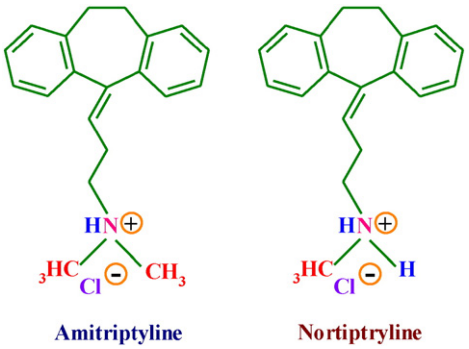
Amitriptyline hydrochloride (Hetero Drugs Ltd., Hyderabad, India), and nortriptyline hydrochloride (Pfizer Egypt, S.A.E., Cairo, Egypt) were used as received. The chemical structures of these drugs are shown in Scheme 2. Acetaldehyde (AC), and chloranil (CL) were provided from Sigma-Aldrich (USA), and were used without purification. All chemicals including sodium hydroxide, potassium hydroxide, methanol, and acetonitrile were of analytical grade or the highest purity available from Merck (Darmstadt, Germany), and were used as received. All organic solvents used throughout this study were analytical grade, and double distilled water (DDW) was used throughout the study.

2.2. Synthesis of adsorbent

The imidazolium ionic liquid (Imz)-modified Fe_3O_4@SiO_2 nanoparticles (Fe_3O_4@SiO_2-Imz) as adsorbent was synthesized in our laboratory as illustrated in Scheme 3 [31].

2.3. Drug loading experiments

It should be mentioned that, since both drugs have relatively similar chemical structures (Scheme 2), all of loading and desorption processes



Scheme 2. Chemical structures of amitriptyline and nortriptyline hydrochlorides.