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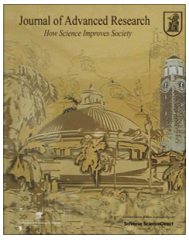

ORIGINAL ARTICLE

Selective determination of dimenhydrinate in presence of six of its related substances and potential impurities using a direct GC/MS method

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ABSTRACT

A novel simple, direct and selective gas chromatography–mass spectrometry (GC/MS) procedure was developed for the determination of the antihistamine drug dimenhydrinate (DMH) in presence of six of its related substances and potential impurities, namely, diphenylmethane, diphenylmethanol, benzophenone, orphenadrine, caffeine and 8-chlorocaffeine. The method involved resolution of the underivatized compounds using a trifluoropropylmethyl polysiloxane (Rtx-200) capillary column and the mass spectrometric detection was carried out in the electron-impact (EI) mode. Excellent baseline separation of DMH and the cited related substances was achieved in less than 15 min. Quantification of the parent drug DMH was based on measuring its peak area. The reliability and analytical performance of the proposed method were validated with respect to linearity, range, precision, accuracy, specificity, robustness, detection and quantification limits. Calibration curve of DMH was linear over the range 50–500 μg/mL with determination coefficient (R^2) = 0.9982. The proposed method was successfully applied for the assay of DMH in tablets dosage form with recoveries >96.80%.

Introduction

Dimenhydrinate (DMH) is the diphenhydramine salt of 8-chlorotheophylline. It is chemically known as a (1:1) compound of 8-chloro-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione with 2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine [1]. DMH is an antihistamine with antimuscarinic and significant sedative effects [2]. It is mainly used as an antiemetic in the prevention and treatment of motion sickness [2]. It is also used for the symptomatic treatment of nausea and vertigo caused by

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Ménière's disease and other vestibular disturbances [2]. The quantification of DMH in various drug formulations and/or biological samples was addressed in several reports. Analytical methodology in these reports involved the use of spectrophotometry [3,4], adsorptive stripping voltammetry [5], capillary electrophoresis [6], liquid chromatography–tandem mass spectrometry (LC/MS/MS) [7], high performance liquid chromatography (HPLC) with fluorescence detection [8], HPLC with UV detection [9] and high performance thin layer chromatography (HPTLC) [10,11]. Recently, an electrochemical method based on batch injection analysis with multiple pulsed amperometric detection was reported for stoichiometric determination of DMH [12].

Few GC/MS methods could be found in the scientific literature for the analysis of DMH merely for toxicological and forensic purposes [13,14]. Furthermore, few articles described the application of gas chromatography (GC) in analysis of diphenhydramine which is one of the two components of DMH. The simultaneous determination of diphenhydramine and pseudoephedrine in cough syrup was carried out using GC with flame ionization detector (FID) [15]. On the other hand, GC coupled with either nitrogen–phosphorus detection (NPD) or mass selective detection (MSD) was exploited for the determination of diphenhydramine in several biological samples [16,17]. Finally, GC/MS was applied for the identification of diphenhydramine and its metabolites along with other drugs commonly detected in clinical toxicology laboratories [18].

Although not widely used in pharmaceutical analysis, GC/MS can be considered one of the powerful techniques for separation and analysis of complex mixtures. We previously published the selective determination of some pharmaceutical compounds in presence of their related substances using direct GC/MS methods [19,20]. Reviewing the literature revealed the use of gradient elution RP-HPLC with UV detection methods for the separation of DMH together with its related substances and impurities [21,22]. DMH related substances which are involved in this study are diphenylmethane, diphenylmethanol (benzhydrol), benzophenone, orphenadrine, caffeine and 8-chlorocaffeine [21–23]. Chemical structures of the parent drug and the related substances are shown in Fig. 1. To the best of our knowledge, there were no reports for the application of GC/MS in the analysis of DMH in pharmaceutical preparations. Additionally, there were no GC reports for the selective determination of DMH in presence of its related substances, degradation products or impurities. This work describes a simple, direct and selective capillary GC/MS method for the separation of DMH together with the above-mentioned related substances. The described method proved to be suitable for the quality assessment of DMH in its tablets.

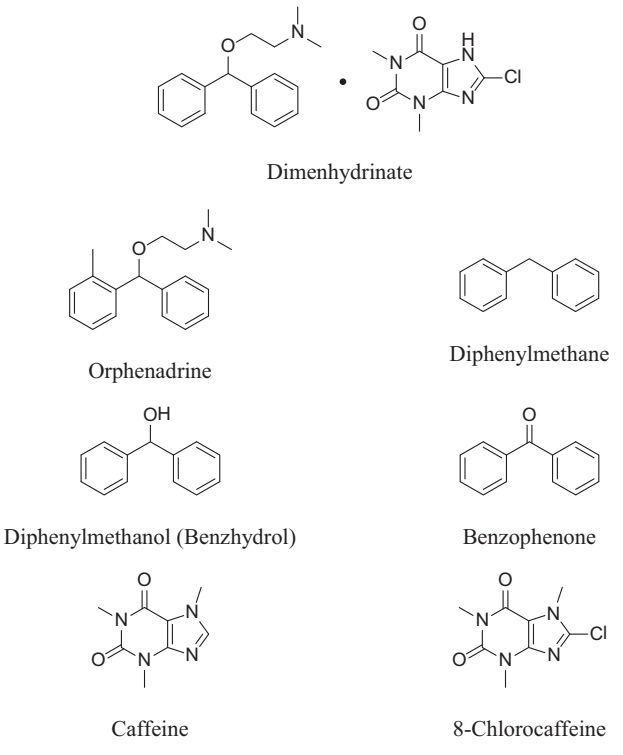

Fig. 1 Structures of the parent compound dimenhydrinate and the related substances involved in the study.

Experimental

Materials

Dimenhydrinate, diphenylmethane, diphenylmethanol (benzhydrol), diphenylmethanone (benzophenone), orphenadrine hydrochloride, caffeine and 8-chlorocaffeine were purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). HPLC-grade acetonitrile was purchased from Fisher Scientific (Fair Lawn, NJ, USA). Pharmaceutical preparation examined in this study is Dramamine® tablets (Batch No. 133542, Prestige Brands, Inc., Tarrytown, NY, USA) labeled to contain 50 mg DMH per tablet.

General procedure and construction of calibration graph

DMH and its related substances are all readily soluble in acetonitrile. DMH (1000 μg/mL) stock solution was prepared in acetonitrile. DMH working solutions were prepared by dilution of aliquots of the stock solution with acetonitrile to reach the concentration range 50–500 μg/mL. The prepared working solutions were analyzed under the described GC/MS conditions under Instrumentation. The peak areas were plotted against the corresponding concentrations to construct the calibration graph.

Stock solutions of the six related substances (1000 μg/mL) were separately prepared in acetonitrile. Aliquots of these stock solutions were added to an aliquot of the parent compound stock solution and the mixture was diluted with acetonitrile. This mixture was analyzed under the described GC conditions.

Assay of tablets dosage form

A total of 10 tablets were weighed and finely powdered. Acetonitrile (30 mL) was added to an accurately weighed quantity of the powdered tablets equivalent to 50 mg DMH, stirred for 10 min then filtered into a 50-mL calibrated flask. The residue was washed with 2×5 mL acetonitrile and washings were