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Analysis of pharmaceutical preparations containing antihistamine drugs by micellar liquid chromatography

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Abstract

Rapid chromatographic procedures for analytical quality control of pharmaceutical preparations containing antihistamine drugs, alone or together with other kind of compounds are proposed. The method uses C_{18} stationary phases and micellar mobile phases of cetyltrimethylammonium bromide (CTAB) with either 1-propanol or 1-butanol as organic modifier. The proposed procedures allow the determination of the antihistamines: brompheniramine, chlorcyclizine, chlorpheniramine, diphenhydramine, doxylamine, flunarizine, hydroxyzine, promethazine, terfenadine, tripelennamine and triprolidine, in addition to caffeine, dextromethorphan, guaifenesin, paracetamol and pyridoxine in different pharmaceutical presentations (tablets, capsules, suppositories, syrups and ointments). The methods require minimum handling sample and are rapid (between 3 and 12 min at 1 mL min^{-1} flow rate) and reproducible (R.S.D. values < 5%). Limits of detection are lower than 1 μg mL^{-1} and the recoveries of the analytes in the pharmaceutical preparations are in the range 100 ± 10%.

Keywords: Micellar liquid chromatography; Antihistamine drugs; Pharmaceutical preparations; Cetyltrimethylammonium bromide

1. Introduction

Organisms produce histamine as a consequence of the decarboxylation of the histidine amino acid, which produces activation of the called histamine receptors. The major allergic responses are mediated through the called H_1 receptor. Effects on the called H_2 receptors include esophageal contraction, gastric acid secretion and increased lower airway secretion. In addition, histamine activates the specific receptors that are present in the nose, eyes, respiratory conducts and skin provoking allergic reactions [1].

Antihistaminic drugs act by competitive inhibition of the H_1 or H_2 histamine receptors reducing the allergic symptoms. Despite these beneficial effects, antihistamines provoke adverse reactions like somnolence, confusion, lack of coordination, etc. However, with the development of the called second generation of antihistamines, some of these problems are being solved [1].

The determination of antihistamines in pharmaceutical preparations for its quality control has been performed using several analytical techniques, such as volumetric analysis [2,3], voltametria [4], atomic absorption [5], fluorimetry [6,7], spectrophotometry [8–12], gas chromatography [13] liquid chromatography [14–17], capillary electrophoresis [18] and micellar electrokinetic chromatography [19,20].

The *United States Pharmacopeia* (USP) [21] recommends spectrophotometric and chromatographic methods. The spectrophotometric methods in the UV region require previous extractions with hexane, ether or chloroform, retroextractions using acid media, evaporation and reconstitution [21]. Liquid chromatography methods use alkylsylane, phenyl, cyano or porous silica columns and hydro-organic mobile phases with high organic solvent content (acetonitrile, methanol and tetrahydrofuran) [21]. Frequently, an ion-pair reagent such as sodium hexanesulfonate, octanesulfonate or lauryl sulphate and an alkyl-amine, i.e.

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N,*N*-dimethyloctylamine, triethylamine, trimethylamine are added to the mobile phase in RP-HPLC in order to improve the chromatographic peak characteristics (retention time and peak shape) [21].

Micellar liquid chromatography (MLC) is a mode of reversed phase liquid chromatography, which uses aqueous solutions of surfactants above the critical micellar concentration. This chromatographic system presents some differences with respect to the classical reversed phase chromatography because the stationary phase is modified by the absorption of surfactant and the mobile phase presents surfactant micelles. This system provides hydrophobic, electronic and steric sites of interaction for solutes that allows the effective separation of compounds of different nature [22,23]. In addition, the solubilization capability of the micellar solutions simplifies the sample preparation step and reduces the consumption of organic solvents. MLC analytical procedures to determine different kinds of drugs in pharmaceutical preparations have been reported [24–33].

The aim of this work was to develop simple and rapid methods for the analysis of pharmaceutical preparations containing the most used antihistamines (brompheniramine, chlorcyclizine, chlorpheniramine, diphenhydramine, doxylamine, flunarizine, hydroxyzine, promethazine, terfenadine, tripelennamine and triprolidine) and other active components such as caffeine, dextromethorphan, guaifenesin, paracetamol and pyridoxine in several pharmaceutical preparations (tablets, capsules, syrups and creams). In order to adjust the eluent strength of the micellar mobile phase and reduce the analysis time cetyltrimethylammonium bromide (CTAB) was used.

2. Experimental

2.1. Reagents and standards

Micellar mobile phases were prepared using cetyltrimethylammonium bromide (99%, Acros Organics, Geel, Belgium) as surfactant. CTAB was dissolved in different buffered solutions depending on the required working pH for the analysis: (i) for pHs 3, 6 and 7, aqueous solutions of 0.05 M phosphate buffer were prepared with sodium dihydrogen phosphate (analytical reagent, Panreac, Barcelona, Spain) and (ii) for pH 5, aqueous solutions of 0.05 M citric buffer were prepared with trisodium citrate (analytical reagent, Guinama, Valencia, Spain). Appropriate amount of 2 M solutions of sodium hydroxide (for analysis, Panreac) or hydrochloric acid (for analysis, Merck, Darmstadt, Germany) were added to adjust the pH. After that, adequate volumes of 1-propanol or 1-butanol (both HPLC grade, Scharlab, Barcelona, Spain) were added to obtain the working concentration.

The antihistamine drugs and the other compounds involved in this work were obtained from several sources: brompheniramine, chlorcyclizine, chlorpheniramine, doxylamine, flunarizine, guaifenesin, promethazine, terfenadine and triprolidine from Sigma–Aldrich, S.A. (Madrid, Spain); caffeine, dextromethorphan, diphenhydramine, hydroxyzine, paracetamol, pyridoxine and tripelennamine from Guinama.

Stock standard solutions of the antihistamine drugs were prepared by dissolving the compounds in 0.02 or 0.04 M CTAB solutions, depending on the surfactant concentration in the mobile phase. Working solutions were prepared by dilution of the stock standard solutions with mobile phase.

Barnstead E-pure, deionized water (Sybron, Boston, MA) was used throughout. The mobile phases and the solutions injected into the chromatograph were vacuum-filtered through 0.45 μm nylon membranes (Micron Separations, Westboro, MA, USA). The solutions were stored in the refrigerator at 4 °C.

2.2. Instrumental and measurement

An Agilent 1100 chromatograph with an isocratic pump, an UV–vis detector was used (Palo Alto, CA, USA). Data acquisition and processing were performed on a HP Vectra XM computer (Amsterdam, The Netherlands) equipped with HP-Chemstation software from Agilent (A0402, 1996).

The solutions were injected into the chromatograph through a Rheodyne valve (Cotati, CA, USA) with a 20 μL loop. A Spherisorb octadecyl-silane column (5 μm, 250 mm × 4.6 mm i.d.) from Scharlau (Barcelona, Spain) was used. The mobile phase flow rate was 1.0 mL min^{-1}. UV detection was performed using wavelength values close to the maximum absorption ones of the compounds. All the assays were carried out at room temperature.

In order to obtain the absorption spectra of the compounds, an Agilent 8452A Spectrophotometer with diode array and equipped with Hewlett-Packard computer, model Vectra ES/12 (Palo Alto, CA, USA) was used.

A microph 2000 pH-meter (Crison, Barcelona, Spain) was used for pH adjustment and an ultrasonic bath (Ultrasons Selecta, Barcelona, Spain) was used to remove the air from the mobile phases.

2.3. Sample preparation

Pharmaceuticals of antihistamines are commercialized under different presentations, such as tablets, capsules, ointments, suppositories and syrups.

For the analysis of tablets, 10 units were weighed, ground in a mortar and finally, an adequate amount of the solid (50 mg) was taken and dissolved in 0.02 M CTAB solution, buffered at pH 3, using an ultrasonic bath (10 min). In the case of the pharmaceutical presentations Ilvico and Delor, after grinding the tablets, the powder obtained was dissolved in methanol. After that, an adequate volume of aliquot was taken and diluted with mobile phase. The resulting solution was centrifuged and finally, an aliquot of the clean solution was injected into the chromatograph. For the analysis of capsules, three units were taken and dissolved in 0.02 M