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Dedicated to the memory of
Professor Maria Brezeanu (1924–2005)

NON-MISCIBLE SOLVENT LARGE VOLUME INJECTION – HPLC/DAD METHOD FOR DETERMINATION OF BUTYLATED HYDROXYANISOLE IN LOVASTATIN AND SIMVASTATIN PHARMACEUTICAL FORMULATIONS

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A simple and sensitive RP-HPLC method for the determination of 2 and 3-tert-butyl 4- hydroxyanisole (BHA) as antioxidants in pharmaceutical formulations containing Lovastatin and Simvastatin is described. Sample preparation is based upon the selective extraction of BHA with i-octane followed by the direct injection of the extract onto the chromatographic column. High injection volumes of the samples containing the target analyte dissolved in i-octane are allowed, without observing any focusing phenomena, resulting in an enhanced sensitivity. The method was tested for precision (repeatability and intermediate reproducibility), sensitivity, accuracy and robustness. UV spectrometric detection at 291 nm was used, allowing identification and detection limits in the ppm range (BHA concentration with respect to the analysed solid material). The proposed method can be successfully used in routine assay of BHA in pharmaceutical formulations of Lovastatin or Simvastatin, as well as for monitoring the BHA content during stability studies.

INTRODUCTION

In many pharmaceutical products, the active drug may undergo oxidative degradation, resulting in serious limitations in terms of shelf-life. Antioxidants are chemical substances able to preclude or to significantly slow the oxidation reactions. Their action consists in the generation of stable radicals inhibiting the first step of the oxidative degradations.

Synthetic phenols such as 2 and 3-tert-butyl 4-hydroxyanisole (BHA) and tert-butyl hydroquinone (TBHQ) are widely used as antioxidants in both pharmaceutical and food industries.[1,2] The content of BHA, individually or combined with other antioxidants, in products for human use, is strictly regulated in the European Community (EU) by means of the 95/2/EC directive.

A literature survey shows that BHA has been determined in high variety of matrices (lard, margarines, edible oils, cosmetics, capsaicinoids, chewing gum, wine, vinegar, biscuits, plasma) using electrometric techniques,[3-10] fluorescence spectrometry,[12,13] gas chromatography with different detection systems, including mass spectrometry,[14-17] or micellar electrokinetic chromatography.[18] HPLC methods are often used, mainly with UV spectrometric detection[1,19-22] and electrometric detection.[23-25] In order to increase sample throughput at routine scale, flow injection methods for the assay of BHA have been also proposed.[26-31]

The action of BHA as antioxidant for hydroxymethylglutaryl coenzyme A reductase inhibitors namely Lovastatin and Simvastatin was already proved.[32] Until now, many pharmaceutical formulations with Lovastatin or Simvastatin containing BHA as antioxidant have been authorized on different markets.

However, when using HPLC for the assay of BHA, the real analytical challenge consists in the selection of an appropriate solvent selectively isolating the target analyte against the active drugs and a sensitive detection, rather than the chromatographic separation itself. Isolation of BHA against the active

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