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Original article

Development and validation of stability indicating HPLC and HPTLC methods for determination of sulpiride and mebeverine hydrochloride in combination

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ABSTRACT

Validated sensitive and highly selective stability indicating methods are adopted for simultaneous quantitative determination of sulpiride and mebeverine hydrochloride in presence of their reported impurities and hydrolytic degradates whether in pure forms or in pharmaceutical formulation.

The first method is High Performance Liquid Chromatography, where the mixture of sulpiride and mebeverine hydrochloride together with the reported interferents plus metopimazine as internal standard are separated on a reversed phase cyano column (5 μm ps, 250 mm × 4.6 id) using acetonitrile: water (70:30 v/v) adjusted to pH = 7 as a mobile phase. The drugs were detected at 221 nm over a concentration range of 5–40 μg ml^{-1} and 5–60 μg ml^{-1} with mean percentage recoveries 99.75% (S.D. 0.910) and 99.99% (S.D. 0.450) for sulpiride and mebeverine hydrochloride respectively.

The second method is High Performance Thin Layer Chromatography, where sulpiride and mebeverine hydrochloride are separated on silica gel HPTLC F_{254} plates using absolute ethanol:methylene chloride: triethyl amine (7:3:0.2 by volume) as mobile phase and scanning of the separated bands at 221 nm over a concentration range of 0.4–1.4 and 0.2–1.6 μg $band^{-1}$ with mean percentage recoveries 101.01% (S.D. 1.991) and 100.40% (S.D. 1.868) for sulpiride and mebeverine hydrochloride respectively.

1. Introduction

Sulpiride (SUL); N-(1-ethylpyrrolidin-2-ylmethyl)-2-methoxy-5-sulphamoylbenzamide, is a substituted benzamide used in the management of schizophrenia with antipsychotic, antidepressant and antiemetic activity [1]. Mebeverine hydrochloride (MEB); 3,4-dimethoxybenzoic acid 4-[ethyl [2-(4-methoxyphenyl)-1-methyl-ethyl] amino] butylester, is reported as an active antispasmodic drug [1]. The combination of the two drugs is used to treat gastrointestinal and colic spasms as a consequence of psychosomatic manifestation of nervous tension, mental stress or anxiety. The chemical structures, molecular weights and molecular formulae are shown in Fig. 1. SUL and MEB are determined by pharmacopoeial and non pharmacopoeial methods. Both SUL and MEB are assayed in the British pharmacopoeia via non-aqueous titration [2]. The non pharmacopoeial methods used for determination of SUL include spectrophotometry [3,4], electrochemistry [5–12], fluorimetry [13–16], TLC-densitometry [17,18], HPLC [19–35], LC-MS [36–41], radio-immuno assay [42,43], ion exchange chromatography [44] and capillary electrochromatography [45] while those mentioned for MEB include spectrophotometry [46–52], electrochemistry [53–55], HPTLC [56,57], HPLC [58–64] and LC-MS [65–68].

SUL and MEB were analyzed in their binary mixture via derivative spectrophotometry [69–71], TLC-densitometry [71], HPLC [71] and chemometric techniques (CLS) [72]. MEB is very liable to hydrolytic degradation [64] where it is degraded in the alkaline and acidic solutions into veratic acid and 4-(ethyl [2-(4-methoxyphenyl)-1-methylethyl] amino) butan-1-ol (mebOH) Fig. 2, while SUL has been analyzed before in presence of its major impurities [17]; 2-aminomethyl-1-ethylpyrrolidine (sulam) and 2-methoxy-5-sulfamoyl benzoic acid methyl ester (sules), Fig. 2. However, no analytical method has been published for the simultaneous analysis of this combination in presence of the reported degradation products and the impurities, whether in pure forms or in the pharmaceutical preparation, which became the aim of this work.

2. Results and discussion

2.1. HPLC results

A sensitive, accurate and highly selective isocratic HPLC method is implemented in our work for analysis of SUL and MEB in

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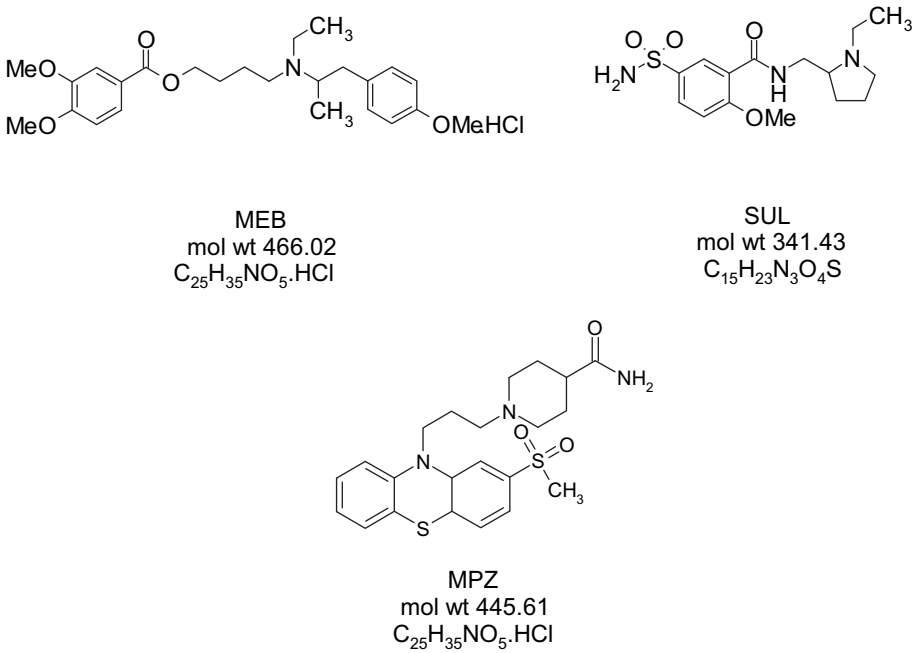

Fig. 1. Chemical structure, molecular weight and molecular formula of SUL, MEB and MPZ (internal standard).

combination and in presence of the reported impurities and degradation products, using acetonitrile: water (70:30 v/v) adjusted to pH = 7 as a mobile phase, with retention times of 1.52, 1.86, 4.41, 5.23, 5.74 and 6.62 min for veratic acid, sules, MPZ, SUL, mebOH and MEB respectively, Fig. 3. The retention times for SUL, MEB and MPZ come between 4 and 7 min which grants speed to the routine analysis of the main drugs with accuracy and extra selectivity compared to the previously published method [71]. Sulam is a non UV absorbing compound with no active chromophores (Fig. 2), hence couldn't be cited to the chromatogram, and is not expected to interfere with the peak area of any of the drugs of interest. Veratic acid and sules peaks elute very close to the solvent front and injection peak and no guarantee they could be quantifiable under the presented conditions. The method has the advantage of using an internal standard which compensates for any error that may occur due to baseline drift or fluctuations in the readings of the UV detector.

The calibration graphs for MEB and SUL were constructed by plotting the peak area ratio (drug peak area/internal standard peak area) for both MEB and SUL versus their corresponding concentrations respectively. Recording of peak area ratio of drugs of interest to the internal standard peak area compensates for errors that may occur due to baseline drift or fluctuations in the UV detector's readings. The regression equations were calculated as:

$$Y = 0.1596X + 0.2875,\ r = 0.9999 \text{ for SUL},$$

$$Y = 0.1439X + 0.4001,\ r = 0.9999 \text{ for MEB},$$

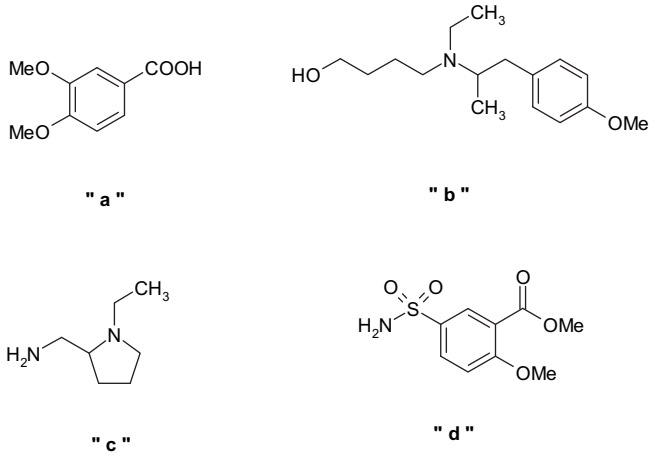

Fig. 2. The chemical structures of MEB degradation products [a – veratic acid (mol wt = 182), b – 4-(ethyl [2-(4-methoxyphenyl)-1-methylethyl] amino) butan-1-ol (mol wt = 265)] and the major impurities associated with SUL [c – 2-aminomethyl-1-ethyl pyrrloidine (mol wt = 128), d – 2-methoxy-5-sulfamoyl benzoic acid methyl ester (mol wt = 245)].

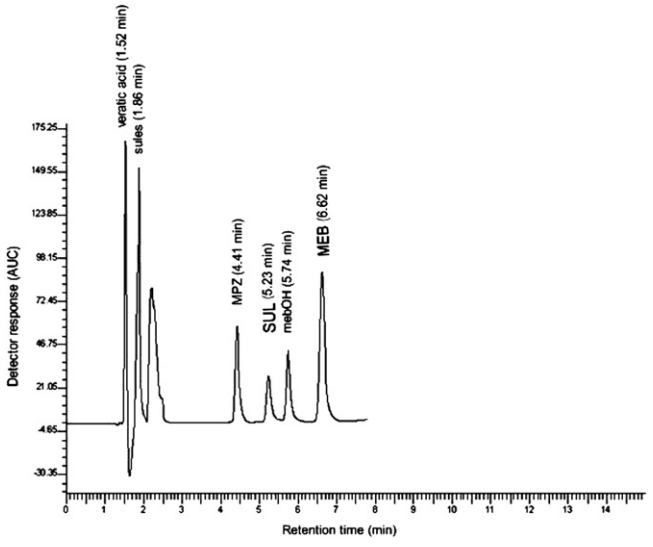

Fig. 3. HPLC chromatogram of 10 μg ml^{-1} of veratic acid, sules, MPZ, SUL, mebOH and MEB (1.52, 1.86, 4.41, 5.23, 5.74 and 6.62 min, respectively) Note: sulam shows no active chromphores, hence not detected at 221 nm.