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LIQUID CHROMATOGRAPHIC METHOD FOR THE DETERMINATION OF FESOTERODINE IN TABLET DOSAGE FORMS USING EXPERIMENTAL DESIGNS

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Introduction: Overactive bladder (OAB) syndrome is defined as urinary urgency, with or without urgency urinary incontinence, usually accompanied by increased micturition frequency and nocturia. The condition is chronic with an overall prevalence of approximately 12% in the general population. Fesoterodine fumarate (FESO) is a urinary antispasmodic, in a modified release preparation, licensed for the treatment of symptoms that may occur in patients with OAB syndrome. FESO is a novel nonselective oral antimuscarinic agent that acts functionally as a prodrug. It is rapidly and extensively hydrolyzed by nonspecific esterases to the active metabolite 5-hydroxymethyltolterodine (5-HMT), which is responsible for all antimuscarinic activity of FESO. FESO is commercially available, but at the moment is not included in any pharmacopoeia, and no analytical method is reported for the quantitative analysis of the drug in presence of its degradation products.
Objective: The aim of the present study was to develop and validate a high-throughput stability-indicating reversed-phase liquid chromatography (RP-LC) method for the determination of FESO in tablet dosage forms using experimental designs.
Method: Tablets were accurately weighed and crushed to a fine powder, appropriated amounts were transferred into volumetric flasks and diluted with methanol at final concentration of 200 µg/mL. The experiments were performed using a C_{18} column (100 x 4.6 mm i.d.). The Shimadzu LC system was operated isocratically at controlled temperature (45 ℃) using a mobile phase of acetonitrile-methanol-ammonium acetate (20 mM, pH 3.8) (30:15:55, v/v/v), run at a flow rate of 2.4 mL/min. The injection volume was 10 µL and PDA detection was set up at 208 nm. The peak areas were integrated automatically by computer using a Shimadzu Class VP software program. The mass spectrometry (MS) detection (Model Quattro LC, Micromass) was used do identify the degradation products produced during the forced degradation studies, determined by subjecting a tablet solution (200 µg/mL) to accelerated degradation by acidic, basic, thermal, oxidative, and photolytic conditions. Method validation investigated parameters such as the specificity, linearity, range, recovery, accuracy, precision, and limit of quantitation (LoQ) and limit of detection (LoD), according to the International Conference on Harmonization (ICH) guideline.
Results and discussion: Short column was incorporated for obtain high-throughput assays requested in industrial pharmaceutical analysis. Thus, the chromatographic separation was obtained within 2.5 min and it was linear in the concentration range of 5-150 µg/mL (r^2 = 0.9995). The specificity and stability-indicating capability of the method are proven through degradation studies, which also showed that there is no interference of the formulation excipients, showing that peak is free from any coeluting peak. The combination of LC with MS has become a powerful qualitative and quantitative analytical technique essential in various research fields, as quality control analysis. The six major degradation products were identified and namely as DP-1 to DP-6 and the degradation pathway of FESO has been proposed. Plackett-Burman experimental design and a 2^3 full factorial design were employed to estimate the robustness and intermediate precision, respectively. Moreover, method validation demonstrated acceptable results for accuracy, with a mean value of 99.46% (RSD=1.84%). The proposed method was successfully applied for the quantitative analysis of FESO in pharmaceutical dosage forms.
Conclusion: The results of the validation studies show that the stability-indicating RP-LC method is specific, accurate and has significant linearity, precision and robustness, without any interference from the excipients and degradation products. The major degradation products were analysed and identified by MS. Therefore, the proposed method was applied for the fast analysis of FESO in the tablet dosage forms, contributing to improve the quality control of pharmaceutical preparations containing this drug.

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