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Simultaneous Determination of Silymarin and Glibenclamide by HPLC—ESI—MS Technique; Method Development and Validation †

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Abstract: (1) Background: The aim of the study was to develop and validate a HPLC-ESI-MS method to determine simultaneously silymarin (Sil) and glibenclamide (Gly) in aqueous solutions, from chitosan-based microparticles. **(2) Methods:** Sil and Gly, in different concentrations, were loaded into chitosan microparticles using ionic gelation method [1]. Briefly, the drugs were dissolved in the minimum volume (0.5 mL) of proper solvent and then was added into 3 mL of 1% chitosan acetic acid solution. The mixture was stirred at room temperature for 2 h and then was dropped through a syringe needle into 20 mL of 2% TPP solution. After 12 h of stirring at room temperature, the formed beads were separated from the TPP solution and washed with distilled water and then dried at room temperature [2]. For identification and quantification of the loaded drugs, a HPLC-ESI-MS method using an Agilent 1200 Series HPLC system coupled to an Agilent 6520 accurate-mass quadrupole time-of-flight (Q-TOF) mass spectrometer, was developed. The separation was made on a Hypersil C18 column with 0.1% formic acid in MiliQ water (A) and acetonitrile (B) applied in gradient (% B: 0′–25; 5′–55; 9′–70; 12′–30; 15′–25). The DAD separation was monitored at 230, 280, 298, 300 nm, 0.1 mL/min of elute was directed to ESI/Q-TOF MS, operated at an ionization voltage of −4000 V, 325 °C, with ions' scan 50–1000 m/z in negative ion mode. The method was validated using recommended parameters [3] and Sil:Gly (1:1) standard solutions. **(3) Results:** By using M8 method, the SilA Rt was registered at 5.41 min, SilB at 5.66 min and Gly at 10.54 min. The loaded drugs were identified using MS-MS spectra and m/z characteristics for all compounds were found in the higher intensity for Rt presented above. The selectivity and precision of the methods are absolute because Rt for sample and standard have the same value, and blank solution proved no interference. The linearity of the answer function is absolute for SilA ($R^2 = 1$), and almost absolute for SilB ($R^2 = 0.9998$), and Gly ($R^2 = 0.9991$). S/N values for all compounds at all studied concentrations maintain similar values. For SilA we obtained a LOD = 0.285 mg/mL and LOQ = 0.95 mg/mL; for SilB we obtained a LOD = 0.045 mg/mL and LOQ = 0.15 mg/mL; and for Gly we obtained a LOD = 0.038 mg/mL and LOQ = 1.275 mg/mL. **(4) Conclusion:** We developed a high resolution HPLC-ESI-MS method to determine simultaneously Sil and Gly in a concentration range of 0.025–1 mg/mL.

Keywords: HPLC-ESI-MS method; silymarin; glibenclamide; chitosan microparticles

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