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LC-MS Analysis of Dimethyl Fumarate in Rat plasma with Measurement Uncertainty Estimation

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Abstract

Dimethyl fumarate (DMF) is the methyl ester of fumaric acid initially recognized as a very effective hypoxic cell radio sensitizer. Phase III clinical trials found that DMF successfully reduced relapse rate and increased time to progression of disability in multiple sclerosis. Small molecules like dimethyl fumarate pose particular difficulties when analyzing biological samples due to the increased possibility of matrix effects and in this scenario DMF immediately converts to its active metabolite MMF (Monomethyl fumarate) by oral route. It is for this reason that a sensitive liquid chromatography–tandem mass spectrometry method has now been developed for the analysis of DMF and for studying the pharmacokinetic profile in rats. Sample preparation was by rapid protein precipitation with acetonitrile. Analyte separation was achieved on a reversed-phase XTerra MS C18 column (100 x 3.9 mm, 3.5µ) with 0.01M ammonium formate and acetonitrile in gradient mode as the mobile phase at a flow rate of 1.0 mL/min and analyzed by a hybrid triplequadrupole linear ion trap mass spectrometer in positive electrospray ionization mode for both DMF and MMF. Limits of detection, and quantification were 20 and 50 ng/mL, for DMF and 1 and 10 ng/mL for MMF respectively. Calibration curve showed excellent linearity within the 50–2500 ng/mL range for DMF and 10–500 ng/mL range (r2 > 0.999) for MMF. Intraand inter-day precision defined by coefficient of variation was <10% and accuracy (bias %) was within 90–110%. Measurement uncertainty estimation was 8.6% for DMF and 11.6% for MMF. The method has been successfully used in the analysis of DMF and MMF in rat plasma following its administration to male wistar rats for pharmacokinetic studies.

Author Keywords

Dimethyl fumarate, Rat plasma, Pharmacokinetics, LC-MS, Measurement of Uncertainty, Monomethyl fumarate

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