

Title: Selective LC-MS/MS method for simultaneous plasma determination of imatinib, dasatinib, nilotinib, bosutinib, ponatinib and ibrutinib based on effective phospholipids removing clean-up method. Application to therapeutic drug monitoring.

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Abstract

Liquid chromatography-tandem mass spectrometry (LC–MS/MS) method has been developed and validated for simultaneous quantification of five tirosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) and one Bruton's tyrosine kinase inhibitor (ibrutinib) in human plasma. Stable isotope-labeled internal standards have been applied for each compound to minimize matrix effect which commonly occurs in MS analysis. The analytes and their internal standards were extracted from only 200 µL of human plasma using solid phase extraction (Versaplate-SCX). The compounds were eluted under gradient conditions using a Poroshell 120 EC-C18 column (2.1 x 75 mm, 2.7 mm) at flow rate of 0.5 mL/min and 60ºC. Analytical column was protected by a 0.2-µm on-line filter. The mobile phase consisted of 0.1% formic acid in MilliQ water, pH=2 (solution A) and 0.1% formic acid in acetonitrile (solution B) (80:20; v/v). Total run time was 9 minutes, including acquisition time of 6 minutes followed by a re-equilibration time of 3 minutes. Five µL of the sample was injected into the chromatographic system. All analytes were detected using the mode multiple reaction monitoring in the positive ionization mode. The method was validated according to the recommendations of regulatory agencies through tests of precision, accuracy, recovery, matrix effect, stability, sensitivity, and selectivity. Sample preparation method applied in the present assay removes more than 95% of main plasma phospholipids compared to protein precipitation. The method enables selective quantification of six compounds. Present assay is currently being applied to therapeutic drug monitoring of imatinib, dasatinib, nilotinib and ponatinib in clinical practice in order to individualize dose adjustment and manage adverse effect.

Biography

Dr. Aneta Wojnicz has completed her Master Degree in Environmental Biotechnology at Warminsko-Mazurski University (Poland)/Leibniz Hannover University (Germany) and her PhD in Clinical Pharmacology at Autonomous University Madrid (Spain). Currently, Aneta Wojnicz is working as Analytical and Pharmacokinetic Unit Responsible at Clinical Pharmacology Department, 'Hospital Universitario de la Princesa' (Madrid, Spain). The aim of the Unit is to develop and validate analytical LC-MS/MS methods for drug quantification in biological fluids. She has published more than 10 papers in reputed journals.

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