ABSTRACT

Dexrazoxane (DEX), a bisdioxopiperazine derivative, is the only clinically used drug effective against anthracycline-induced cardiotoxicity. First studies indicated that DEX is a pro-drug bioactivated in cardiomyocytes by enzymatic hydrolysis of piperazine rings to its active metabolite – ADR-925. However, further research revealed that effective cardioprotection induced by bisdioxopiperazine compounds is more likely related to topoisomerase IIβ depletion induced by DEX itself. The only bioanalytical method for simultaneous determination of DEX and its metabolite was developed using HPLC-MS/MS system. Nevertheless, the analysis requires 30 min for each run, which does not accomplish requirements for modern bioanalysis. The aim of this project is to develop and validate a fast UHPLC-MS/MS method for determination of DEX and ADR-925 in plasma. The analyses were performed using an UHPLC system coupled to triple quadrupole mass spectrometer with ESI source in positive ion mode (both Shimadzu). Following stationary phases were tested: ZORBAX Bonus-RP (100 mm × 3.0 mm, 1.8 μm), Luna Omega Polar C18 (100 mm × 2.1 mm, 1.6 μm) and Kinetex F5 column (100 mm × 2.1 mm, 1.7 μm). Mixtures of acetonitrile or methanol with different concentrations of ammonium formate or formic acid were tested as mobile phase with various isocratic and gradient elutions. The best results were achieved on the column Kinetex F5 with 1mM ammonium formate and methanol as a mobile phase in a gradient mode. Method was partially validated within the concentration range from 0,5 to 100 μM for both compounds in plasma.