Sequential liquid-liquid extraction coupled to LC-MS/MS for simultaneous determination of amlodipine, olmesartan and hydrochlorothiazide in plasma samples: Application to pharmacokinetic studies.

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Abstract

A recent fixed combination of amlodipine (AML) besylate, olmesartan (OLM) medoxomil and hydrochlorothiazide (HCT) has been marketed for the treatment of hypertension. The bioanalysis of this mixture is a
challenge due to the diverse physicochemical properties. The aim of this study is to develop a method using liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the simultaneous bioanalysis of the mixture
in human plasma.
A mobile phase of 10 mM ammonium formate containing 0.1% formic acid: methanol: acetonitrile (35:50:15,v/v/v) was recruited for the chromatographic separation of the mixture on a Zorbax SB-Aq (150ĭ4.6 mm, 5 εm)column. The deutrated analogues of AML, OLM and HCT were used as the internal standards (IS). Polarity switching SRM transitions in positive-mode for AML, OLM, and negative-mode for HCT were applied for detection.
Sequential double liquid-liquid extraction (SdLLE) was adopted for sample preparation. The developed method was fully validated and applied for the determination of AML, OLM and HCT following a single oral
administration of 5/20/12.5 mg of AML, OLM and HCT, respectively tablets to healthy volunteers (n = 30).
The developed method was linear (r2> 0.99), accurate (105 - 90%), precise (CV% <11.92) and specific for the determination of AML, OLM and HCT over the concentration range of 0.1ï15, 5ï1200 and 2ï150 ng/mL. The
adopted SdLLE resulted into reproducible extraction recoveries of 75%, 63% and 83% for AML, OLM and HCT,
respectively. The pharmacokinetic analysis revealed uniform profile in the subjects which were comparable to previously reported results in other populations.

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