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Simultaneous determination of irbesartan and hydrochlorothiazide in human plasma using HPLC coupled with tandem mass spectrometry: Application to a bioequivalence study

Lara F Tutunji, Maha F Tutunji, Mamoun I Alzoubi, Manal H Khabbas and **Adi I Arida**
University of Jordan, Jordan

Introduction: A combination dosage form of irbesartan and hydrochlorothiazide is indicated in the treatment of edema and hypertension. It provides consistent blood pressure lowering and tolerability regardless of age, obesity, and prevalence of type 2 diabetes and greater efficiency in patients with high cardiovascular risk.

Aim: Simultaneous determination of irbesartan and hydrochlorothiazide in plasma using a sensitive LC-MS/MS method and its application to a bioequivalence study under fasting conditions.

Materials & Methods: Plasma samples were prepared using protein precipitation with acetonitrile, the two analytes and the internal standard losartan were separated on a reverse phase C18 column (50 mm × 4 mm, 3 m) using water with 2.5% formic acid, methanol and acetonitrile (40:45:15, v/v/v (%)) as a mobile phase (flow rate of 0.70 mL/min). Irbesartan and hydrochlorothiazide were ionized using ESI source in negative ion mode, prior to detection by multiple reaction monitoring (MRM) mode while monitoring at the following transitions: m/z 296→269 and m/z 296→205 for hydrochlorothiazide, 427→175 for irbesartan.

Results: Linearity was demonstrated over the concentration range 0.06–6.00 g/ml for irbesartan and 1.00–112.00 ng/mL for hydrochlorothiazide (HCTZ). The calibration sensitivities were 0.2537±0.0055 and 0.0129±0.0002 for irbesartan and HCTZ, respectively. The lower limit of quantitation of Irbesartan and HCTZ were found to be 0.06 g/mL and 1.00 ng/ml, respectively. The limit of detection for irbesartan was 0.01 g/mL and for HCTZ was 0.51 ng/ml. The mean absolute recovery of irbesartan was 48.5, 59.6 and 60.7% for concentration levels of 0.18, 3.00 and 4.80 g/ml. The mean absolute recovery for HCTZ was 28.8, 33.0 and 34.1% for concentration levels of 3.00, 55.00 and 88.00 ng/ml. Both irbesartan and HCTZ were found to be stable under the mentioned test conditions.

Conclusion: An accurate and precise LC–MS/MS method for the simultaneous determination of irbesartan and HCTZ in human plasma has been developed and validated. The method demonstrated high selectivity and sensitivity which rendered the method fits for the purpose of its application to measure concentration–time profiles for bioavailability, pharmacokinetic and bioequivalence decision after dosing with two tablet formulations containing 300 mg irbesartan and 12.5 mg HCTZ tablet on healthy volunteers in a fasted state.

tutunji@ju.edu.jo

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