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Determination of sibutramine and its N-desmethyl metabolites in human plasma using HPLC coupled with tandem mass spectrometry: Application to bioequivalence studies

Lara Tutunji
Al-Ahliyya Amman University, Jordan

Spectrometry has been developed and validated for the determination of Sibutramine and its N-desmethyl metabolites in human plasma. The analytes sibutramine, N-mono desmethyl Sibutramine M1, N-N-dides methylsibutramine and Bisoprolol (internal standard) were separated on a reversed phase column (Merck, Purospher RP-C18, 30×4.0 (mm), 3µm) using a mobile phase consisting of an aqueous solution 20 20 mM ammonium acetate pH 4.0 in water and acetonitrile (67:33 v/v (%)), flow rate 0.40 (mL/min), after protein precipitation of plasma samples using tertiary butyl methyl ether. Detection utilized a tandem MS/MS. The analytes were ionized using an ESI source in the positive ion mode prior to detection by Multiple Reaction Monitoring (MRM) mode. The analytes were monitored at the following transitions (m/z) 280.20 → 125.20 for sibutramine, (m/z) 268.10 → 126.9 and 268.10 → 141.00 for N-monodesmethylsibutramine, (m/z) 254.10 → 126.9 and 254.10 → 141.00 for N-N-didesmethylsibutramine and (m/z) 2326.20 → 107.10 for Bisoprolol respectively. Sibutramine, N-monodesmethylsibutramine and N-N-didesmethyl sibutramine linearity was demonstrated over the concentrations ranging from 0.10 to 11.00 (ng/ ml). The developed method was fully validated prior to its application to a bioequivalence study involving sibutramine 15 mg/Capsule in healthy volunteers (N=37) under fasting conditions. Sibutramine was quickly absorbed from both the test and reference capsules in less than 1.5 hours reaching a C_{max} of about 1.3 ng/ml in the test formulation and 1.2 ng/ml in the reference formulation. Sibutramine exhibited a long half-life of about 24 hours in both test and reference formulations. Both metabolites had maximum concentrations after about 4 hours of capsule intake. Both metabolites showed slow excretion due to their long half-lives.

Biography

Lara Tutunji has completed her Bachelors in Pharmacy from the University of Jordan. She has completed her PhD from Temple University, USA. She has worked as an Assistant Professor at the Faculty of Pharmacy, University of Jordan between December 2005 and December 2017. She is currently working as an Assistant Professor at the Faculty of Pharmacy and Medical Sciences at Al-Ahliyya Amman University in Salt, Jordan. Her research interests include bioequivalence testing and evaluation of different drug delivery systems.

lara_tutunji@hotmail.com