Supplementary Material

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Development of a novel bilosomal system for improved oral bioavailability of Sertraline Hydrochloride: Formulation design, *In-vitro characterization*, *Ex-vivo* and *In-vivo studies*

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Methods

LC-MS/MS analysis for SER plasma levels

LC-MS/MS system

LC-MS/MS system was consisted of Shimadzu Prominence series LC system (Shimadzu Scientific Instruments, Kyoto, Japan) equipped with degasser (DGU-20A3) and conjugated with triple Quadrupole Mass spectrometer (API-4000 Model 1034067S, AB Sciex Instruments, Framingham, MA, USA).The mobile phase consisted of acetonitrile: 0.1% formic acid in water (80:20, %v/v) was pumped through ZORBAX Eclipse plus column C18 (4.6 x 50 mm, 5µm) in an isocratic manner at a flow rate of 0.88 ml/min under ambient temperature. The MS/MS detection was operated in electro spray positive ion mode (ES+) for both SER and internal standard (Loperamide hydrochloride).The system equipped with turbo ion spray with interface heater at Turbo heater temperature of 500 °C. The ion spray voltage was set to 5500 V. Curtain gas, Nebulizer gas, heater (auxillary) gas and Collision activation dissociation gas were set at 20, 20, 50 and 7 psi, respectively. The parameters, namely, declustering potential, entrance potential, collision energy and Collision cell exit potential were 46, 10, 15 and 28 V for SER, while 35, 10, 15 and 26 for the internal standard (Loperamide hydrochloride), respectively. The quantification was achieved through monitoring the ion transitions from m/z of 306.083 precursor ion (parent ion) to m/z 275.1 (product ion) for SER, and from m/z of 477.299 precursor ion (parent ion) to m/z 266.3 (product ion) for the internal standard (Loperamide hydrochloride). The data analysis was acquired and quantified using Bio-systems Analyst® software version 1.6 (AB Sciex, Framingham, MA, USA).

LC MS/MS assay validation

The assay was validated in terms of intra-day and inter-day accuracy and precision for low quality control (LQC = 1 ng/ml), middle quality control (MQC = 60 ng/ml) and high quality control (HQC = 90 ng/ml) samples. The accuracy (% recovery) was determined by comparing the calculated SER concentration in the extracted plasma samples with the nominal SER concentration at each QC level. The precision was measured in terms of relative standard deviation % (RSD %) for the recovered concentrations. For determining the intra-day accuracy and precision, three replicate analyses of QC samples of SER were performed on the same day. The inter-day accuracy and precision were assessed by analysis of three batches on three consecutive validation days.