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Method Development and Validation of a Novel UHPLC Coupled with MS/MS System for the Estimation of Brivaracetam in Human (K2EDTA) Plasma Samples and its Application to Pharmacokinetic Study †

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Abstract: Brivaracetam is a novel antiepileptic drug clinically approved to treat partial-onset seizures in adults and adolescents. It has some abuse potential and assigns to the Schedule V category under the Controlled Substance Act by the Drug Enforcement Administration.

It is essential to develop a faster, simple, and highly sensitive method for quantifying Brivaracetam in human plasma by employing simple liquid-liquid extraction. The objective of this study is to develop and validate a novel UHPLC-MS/MS method for the estimation of brivaracetam in human plasma samples and application to pharmacokinetic study. An ultra-high-pressure liquid chromatography-tandem mass spectrometry method was developed and validated according to current regulatory guidelines for bioanalytical methods. Sample processing (50 µL) involved only a simple liquid-liquid extraction by ethyl acetate as an extraction solvent. Brivaracetam-d7 was used as an internal standard. The chromatographic analysis was performed by a Unisol C18 (4.6 X 100 mm, 5µm) column using 0.1% formic acid in water/acetonitrile (20/80 V/V) as an isocratic mobile phase, at a flow rate of 1.0 mL/min with a run time of 2.2 min. Brivaracetam and its internal standard Brivaracetam D7 were detected and quantified in positive ion mode using multiple reaction monitoring transitions at m/z 213.100→168.100 and m/z 220.000→175.100, respectively. The developed method was applied to assess pharmacokinetic parameters like Cmax, Tmax, t1/2, and AUC for Brivaracetam in healthy, male, and adult humans. The method was validated over a concentration range of 20.000 ng/mL to 4000. 000 ng/mL. Both intra- and inter-assay precision and accuracy were <15% for all quality control samples. No matrix effect was observed. Pharmacokinetic results showed that test formulation is bioequivalent with reference formulation.

Conclusion: The present assay is faster, highly sensitive and simpler than previously published analytical reports for brivaracetam in human plasma samples and is suitable for pharmacokinetic evaluation of any marketed formulation.

Keywords: Brivaracetam; liquid-liquid extraction (LLE); UHPLC; MS/MS; bioanalytical method validation; pharmacokinetic.

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Conflicts of Interest

The authors declare no conflict of interest.