Randomized Comparative Bioavailability of a Novel 3D Printed Fast Melt Formulation of Levetiracetam Following the Administration of a Single 1000 mg Dose to Healthy Human Volunteers under Fasting and Fed Conditions

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Purpose
Rapidly-disintegrating or “fast-melt” oral formulations have been developed recently to facilitate drug-intake among patients. Even though these formulations have helped to improve therapy adherence, some of their limitations include: the dissolution time, their facility to be swallowed, and the dosage strengths that may be accommodated. To overcome these limitations, a novel, porous, quickly disintegrating and easier-to-swallow fast-melt formulation, based on powder-liquid 3 dimensional printing (3DP) technology has been developed. The objective of the study was to determine and compare the relative bioavailability of a novel 3DP fast melt containing levetiracetam in healthy male and female subjects.

Methods
This study included 33 subjects in a 3-way crossover design. The 3DP fast-melt formulation was compared against the conventional immediate-release tablet of levetiracetam (Keppra®) after a single 1000 mg dose administration under fasting conditions following the bioequivalence (BE) criteria used by the Food and Drug Administration (FDA). This study also evaluated the food effect on the bioavailability of the levetiracetam 3DP fast-melt. A small sip of liquid was used to administer the fast melt formulation.

Results
The novel 3DP fast-melt showed rapid oral disintegration (mean duration of 11 seconds from sip of water to completion of swallowing) following its administration, and did not affect the pharmacokinetic (PK) profile of levetiracetam. Under fasting conditions, the ranked time to peak concentrations for the 3DP fast melt (test) and the reference tablet were comparable (p-value 0.5444), and both showed a very fast absorption within approximately 30 minutes. Similar values were also evident for the main PK parameters evaluated in this study (Cmax, AUC0-t and AUC0-inf), and the terminal elimination half-life was approximately 7.1 hours for both formulations. The 90% CI for evaluating the bioequivalence and the corresponding point estimates of the relative bioavailability for the ln-transformed PK parameters Cmax, AUC0-t and AUC0-inf were 106.45%, 102.94% and 102.78%, respectively with 90% CI ranging all between 99 and 114%.

A lower absorption peak was observed after administration of the 3DP fast-melt under fed conditions, as expected. In addition, Tmax was delayed by approximately 3.5 hours under fed conditions. The Cmax geometric LSmean of levetiracetam in the fed state was 63.9% of the peak value of the fasting state but the food intake had no effect on the extent of systemic exposure as expressed by AUC (with a mean ratio of about 95%). Finally, no change in the oral mucosa was observed with the 3DP fast-melt while being as safe and well tolerated as the standard levetiracetam tablet.

Conclusion
This study quantified the rapid disintegration of the 3DP levetiracetam fast-melt and confirmed its equivalent rate and extent of absorption to the conventional immediate release tablet in the fasted state, using standard BE criteria. The results presented herein show that the criteria used to assess the relative bioavailability between these two formulations under fasting conditions were all contained entirely within the range of 0.80-1.25. As expected, Cmax and Tmax parameters were influenced by food, but these effects are unlikely to be of clinical significance with chronic administration, and may help reduce the side effects and facilitate compliance.