Development of novel polymethoxyflavonoids formulation for improving bioavailability

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Nobiletin (NOB), a citrus polymethoxylated flavone, attracts attention because of a wide range of pharmacological activities, such as anti-inflammation, anti-cancer, and most notably ameliorative actions on memory impairment and β-amyloid pathology. However, clinical use of NOB could be partly limited due to its poor solubility and oral bioavailability, which might necessitate high doses in order to reach therapeutic plasma concentrations in the central nervous system (CNS) after oral administration. In the present study, amorphous solid dispersion of NOB (NOB/SD) was prepared by wet-milling technique with the aim of improving dissolution behavior and pharmacokinetic properties of NOB.

NOB/SD was prepared with a wet-milling system employing zirconia beads. Physicochemical properties of the NOB/SD were characterized using scanning electron microscopy (SEM) and polarized light microscopy (PLM) with focus on morphology, powder X-ray diffraction (PXRD) for crystallinity, particle size distribution analysis, dissolution testing, and differential scanning calorimetry (DSC) for thermal behavior. Pharmacokinetic (PK) behavior of NOB after the oral administration of crystalline NOB and NOB/SD was also evaluated using ultra-performance liquid chromatography (UPLC)/ESI-MS.

Micronized NOB particles in NOB/SD appeared to be amorphous with a diameter of ca. 270 nm, and there was marked improvement in the dissolution behavior compared with that of crystalline NOB. After oral administration of NOB/SD, higher exposure of NOB was observed with increases of bioavailability and CNS distribution by 13- and 7-fold, respectively, compared with those of crystalline NOB. In the present investigation, a water-soluble SD formulation of NOB was prepared, which showed rapid dissolution/dispersion behavior compared with that of crystalline NOB. These findings suggest that the amorphous solid dispersion strategy could be a viable option for enhancing the bioavailability and CNS delivery of NOB.