Preparation of solid dispersion systems for enhanced dissolution of poorly water soluble diacerein: In-vitro evaluation, optimization and physiologically based pharmacokinetic modeling

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Abstract

Diacerein (DCN), a BCS II compound, suffers from poor aqueous solubility and limited bioavailability. Solid dispersion systems (SD) of DCN were prepared by solvent evaporation, using hydrophilic polymers. In-vitro dissolution studies were performed and dissolution parameters were evaluated. I-Optimal factorial design was employed to study the effect of formulation variables (drug:polymer ratio and polymer type) on the measured responses including; drug content (DC) (%), dissolution efficiency at 15 min (DE (15 min)%) and 60 min (DE (60 min)%) and mean dissolution time (MDT) (min). The optimized SD was selected, prepared and evaluated, allowing 10.83 and 3.42 fold increase in DE (15 min)%, DE (60 min)%, respectively and 6.07 decrease in MDT, compared to plain drug. DSC, XRD analysis and SEM micrographs confirmed complete amorphization of DCN within the optimized SD. Physiologically based pharmacokinetic (PBPK) modeling was employed to predict PK parameters of DCN in middle aged healthy adults and geriatrics. SimcypÈ software established in-vivo plasma concentration time curves of the optimized SD, compared to plain DCN. Relative bioavailability of the optimized SD compared to plain drug was 229.52% and 262.02% in healthy adults and geriatrics, respectively. Our study reports the utility of PBPK modeling for formulation development of BCS II APIs, via predicting their oral bio-performance.

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