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Self-microemulsifying drug delivery system (SMEDDS) of clopidogrel napadisilate monohydrate : assessment of stability and bioavailability

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Purpose. To develop a novel clopidogrel napadisilate monohydrate-loaded solid self-microemulsifying drug delivery system (SMEDDS) with enhanced stability and bioavailability.

Methods. Liquid SMEDDS composed of oil (Peceol), surfactant (Cremophor RH60) and co-surfactant (Transcutol HP) for oral administration was formulated. Pseudo-ternary phase diagram was used to evaluate the emulsification domain and to confirm formulation. Solid SMEDDS formulations were developed by spray drying liquid SMEDDS along with the solid carriers. The physicochemical characterization was accomplished by particle size determination, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Furthermore, their stability, dissolution and pharmacokinetic study were compared to those of napadisilate and bisulfate powder.

Results. The optimized liquid SMEDDS was a system consisting of Peceol, Cremophor RH60 and Transcutol HP at voluminous ratio of 2:3:5. The crystal form of solid SMEDDS was found to be converted to amorphous form, which was confirmed by the analysis of DSC and PXRD. The final dissolution rate of solid SMEDDS containing clopidogrel napadisilate monohydrate was 1.7-fold higher than that of pure powder ($p < 0.05$). Furthermore, time for complete release of SMEDDS was 2-fold less than that of pure powder. These solid SMEDDS improved stability at the accelerated condition of 50 °C/75 % RH for 4 weeks compared to clopidogrel bisulfate. The pharmacokinetic parameters including AUC and C_{max} were significantly increased by solid SMEDDS over that of pure clopidogrel napadisilate monohydrate ($p < 0.05$).

Conclusion. This solid SMEDDS could be an outstanding candidate for improving the stability and bioavailability of clopidogrel napadisilate monohydrate and its low C_{max} value as compared to clopidogrel bisulfate represents that it can reduce the toxicity related with high C_{max} value of clopidogrel bisulfate.