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Bioavailability and stability enhancement of clopidogrel napadisilate monohydrate by solid dispersion system

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Purpose. In order to enhance the bioavailability and stability of clopidogrel napadisilate monohydrate, two solid dispersions containing different surfactant were prepared by spray-drying via surface-attached method.

Methods. Each solid dispersion system was prepared with various ratios of clopidogrel napadisilate monohydrate/HPMC/cremophor RH 60 and clopidogrel napadisilate monohydrate/HPMC/tween 80. The solubility and dissolution of the drug in the solid dispersion were evaluated compared with drug powder in water at pH 1.2, pH 4.0 and pH 6.8. The crystallinity of the solid dispersion was evaluated using SEM, DSC and PXRD. The stability of the solid dispersion was estimated at 50 °C /75 %RH for 6 weeks compared to clopidogrel bisulfate. The bioavailability in rats was evaluated and compared to drug powder.

Results. The aqueous solubility of solid dispersion increased 4.48-fold in a weight ratio of clopidogrel napadisilate monohydrate/HPMC/cremophor RH 60 of 5:1.875:1.875 and 4.65-fold in a weight ratio of clopidogrel napadisilate monohydrate/HPMC/tween 80 of 5:1.25:1.25 each compared to drug powder. The dissolution rate was significantly enhanced in these formulations compared to drug powder. SEM, DSC and PXRD showed that crystallinity of these solid dispersions was not changed to amorphous form. In stability test of these solid dispersions, hydrolyzed degradant and racemized degradant were decreased compared to clopidogrel bisulfate and drug content was not decreased compared to clopidogrel napadisilate monohydrate in spite of increased water content affected from HPMC. Then, the bioavailability of the drug in rat was significantly enhanced in each formulation as AUC and C_{max} became higher.

Conclusion. Thus, the clopidogrel napadisilate monohydrate loaded-solid dispersion could be used to enhance the solubility and bioavailability of poorly aqueous soluble clopidogrel napadisilate monohydrate and be stable in storing of long period of time as compared to clopidogrel bisulfate.