ABSTRACT

FORMATION OF KETOPROFEN COCRYSTAL WITH MALONIC ACID AND NICOTINAMIDE COFORMER FOR IMPROVING THE SOLUBILITY AND DISSOLUTION

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Most of active pharmaceutical ingredient (API) is difficult to dissolve in water, so it requires an effort to increase its solubility. Solubility is a thermodynamic equilibrium of and solvent molecules. Thus, increasing the solubility of API can be done by decreasing the energy interaction of the API molecules in the crystal lattice. Cocrystal is a multicomponent system containing two or more compound molecules in the same crystal lattice. The formation of Cocrystal can be used to increase the solubility of API by decreasing the free energy of crystal lattice. Ketoprofen is a non-steroidal anti-inflammatory drug derived of propionic acid which is used as an analgesic, antipyretic and anti-inflammatory agent. Ketoprofen is a class II drug in the biopharmaceutical classification system so that its solubility needs to be improved. Ketoprofen is thought to form cocrystal with the carboxylic acid or amide compound via synthon acid-acid or acid-amide. Based on this, a study of the formation of ketoprofen cocrystal with malonic acid and nicotinamide coformers was conducted to increase solubility and dissolution of ketoprofen. The detection of the cocrystal formation with the contact Kofler method and the binary phase diagram indicated the mixtures of ketoprofen-malonic acid and ketoprofen-nicotinamide could interact to form a new crystalline phase. Based on this, cocrystal preparation was carried out by the solvent evaporation method using isopropyl alcohol as the solvent. The results of characterization with PXRD, DSC, FTIR, polarized microscope and SEM proved the formation of ketoprofen-malonic acid and ketoprofen-nicotinamide cocrystal. The analysis by MarvinSketch 18.5, Molegro Virtual Docker 5.5 and FTIR spectra showed interaction in ketoprofen-malonic acid cocrystal through the aromatic π system of ketoprofen with C=O group of malonic acid, while the interaction in ketoprofen-nicotinamide cocrystal was through the π---π interaction of the aromatic π system of ketoprofen with the aromatic π system of pyridine ring of nicotinamide. The results of determination of the free energy of crystal lattice of ketoprofen, ketoprofen-malonic acid cocrystal, and ketoprofen-nicotinamide cocrystal were 89.53, 90.87, and 84.62 kJ /mol, respectively. The results of ketoprofen solubility test, ketoprofen-malonic acid cocrystal, and ketoprofen-nicotinamide cocrystal were 0.202±0.003, 0.178±0.004, and 0.252±0.005 mg/mL. These results indicated that the decrease the solubility of the ketoprofen-malonic acid cocrystal is caused by the increase of the free energy of crystal lattice, while the increase the solubility of the ketoprofen-nicotinamide cocrystal is caused by the decrease of the free energy of crystal lattice. The results of the dissolution test showed that the formation of ketoprofen-malonic acid cocrystal reduced the dissolution rate, AUC and DE, while the formation of ketoprofen-nicotinamide cocrystal increased the dissolution rate, AUC and DE of ketoprofen.

Key words: Ketoprofen; cocrystal, solubility, dissolution rate, free energy of crystal lattice