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Characterization and Dissolution Test of Aspirin-Nicotinamide Cocrystal

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Abstract: Cocrystal becoming attractive as solid form to be developed. The formation of intermolecular bonds between active pharmaceutical ingredient (API) and coformer can change the physicochemical properties of an API without altering its pharmacological activity. The aims of this research to determine whether the formation of cocrystal with solvent-drop grinding method performed to increase dissolution rate of cocrystal and characterizationing of cocrystal. Cocrystals formation between aspirin-nicotinamide in equimolar ratio (1:2) have been prepared by solvent-drop grinding method. Cocrystalwas characterized by Infrared spectrophotometry (FTIR), *Differential Scanning Calorimetry and X-Ray Difractometry*(XRD), (SEM) *Scanning Electron Microscope* and dissolution test by basket method in artificial medium-gastric fluid acid. The result of dissolution rate showed that aspirin-nicotinamide cocrystal has increased in significant ($F=28.636 > F_t= 4$ and $\alpha=0.010$). The dissolution rate of cocrystal also showed the linearity of cocrystal dissolution ($R^2=0.9694$), and the rate was 0.5807 mg minute^{-1}t while single aspirin 0.4919 mg minute^{-1}. Based on the DSC and XRD analysis found that the typical peak shift indicates the formation of a mixed cocrystal. This is supported by the SEM microscopic observations, which reveal the shape of cocrystal produced. Hydrogen bond formation of aspirin-nicotinamide ratio (1:2) is heterosynthon between carboxylic and amide groups or between pyridine and carboxylate can be ascertained from the data analysis, infrared spectrophotometry.
Keywords : cocrystal, coformer, aspirin, solvent drop grinding.

Introduction and Experimental

Solubility is rate limiting step or step which controls rate of low solubility drug absorbtion because this step is often the slowest step of all drug releasing step from its form and routes to blood sirculation[1,3-7].

Drug solubility and dissolution rate may be enhanced by various methods, like solid dispertion generating, prodrug, drug inclusion complex with carrier, and drug modification in salt and solvat form, also cocrystal[2,3,7,9]. Cocrystalization is promising method to enhance drug solubility.

Cocrystal can be defined as a crystalline complex consisting of two or more constituents neutral molecules which bind to each other in the crystal lattice through noncovalent interactions, particularly hydrogen bonds. Cocrystal formation involves mixing an active ingredient (host) with the material forming kokristal (guess) in the crystal lattice. Results of this merger will retain the intrinsic properties of the main active substance[4,5,8-12].

Cocrystalization method is drug crystal modifying by adding coformer. In order to enhance drug solubility, cocrystalization agent or coformer (co-crystal former) should have these characteristics: GRAS (Generally Recognized as Safe) status and inert in case of pharmacology, high solubility in water than API, non-covalen bonding ability, compatible in case of chemical and not molding complex bonding with drug. Thus, the active subtances in cocrystalization may crystalized, it should have groups which is able to bind with coformer in non covalent binding [9-15].

Functional groups such as carboxylic acids, amides and alcohol are commonly used for the formation of supramolecular synthon in designing new kokristal. Strong hydrogen bonds include (NH --- O), (OH --- O), (-NH --- N) and (OH --- N). Weak hydrogen bonds that involve-CH and CH --- O --- O = C[5,6,11,12,13].

Aspirin (asetylsalisilic acid), analgetic antipyretic drug, is a BCS (Biopharmaceutical Classification System) class IV drug of low solubility and low permeability[16,17,18]. In this study, aspirin is modified in cocrystal with nicotinamide as coformer to alter physicochemical properties of aspirin especially drug solubility.

Instruments and Materials

Instruments: analytical scale, Differential Scanning Calorimetry (DSC), dissolution test apparatus, Fourier Transform Infrared (FT-IR),glass equipments, micro pipette, mortar and pestle, pH meter, Scanning Electron Microscopy (SEM), UV-Visible Spectrophotometer, quartz cuvette, X-Ray Diffraction (XRD).

Materials: aspirin, concentrated chloride acid, distilled water, ethanol pro analysis, nicotinamide, potassium bromide, sodium chloride.

Cocrystal Preparation by Solvent Drop Grinding Method

Aspirin and nicotinamide were weight with molar ration 1:2 (50 mmol: 100 mmol). Both subtances were ground with a mortar and pestle for 30 minutes in presence of a few drops of EtOH until both were wet. Cocrystal was collected and dried at room temperature.

Cocrystal Characterizations

Cocrystal was characterized by SEM, FT-IR, DSC, and XRD.

Dissolution Test

Dissolution test was performed by basket method according to study of USP 4 type I apparatus [4]. Samples were withdrawn at time interval of 10, 30, 45, and 60 minutes in 5 ml respectively. Then, samples were carried out in Uv-Visible Spectrophotometer to determine aspirin amount.

Result and Discussion

Figure 1.Cocrystal Characterization by using EDS-SEM

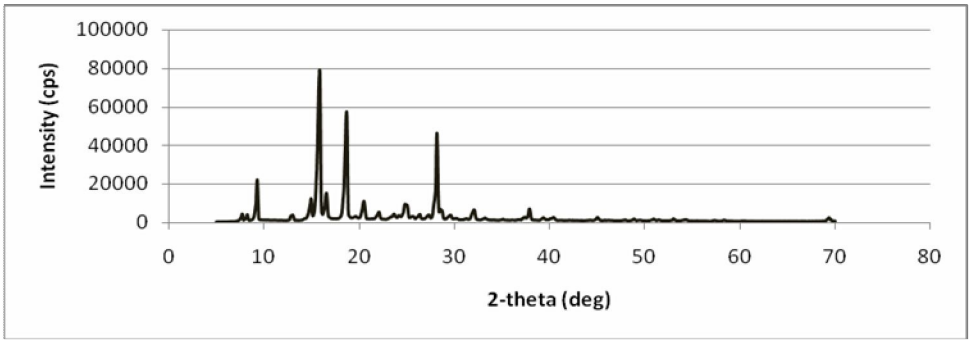

Figure 2. X-Ray Diffractogramof Aspirin-NicotinamideCocrystal

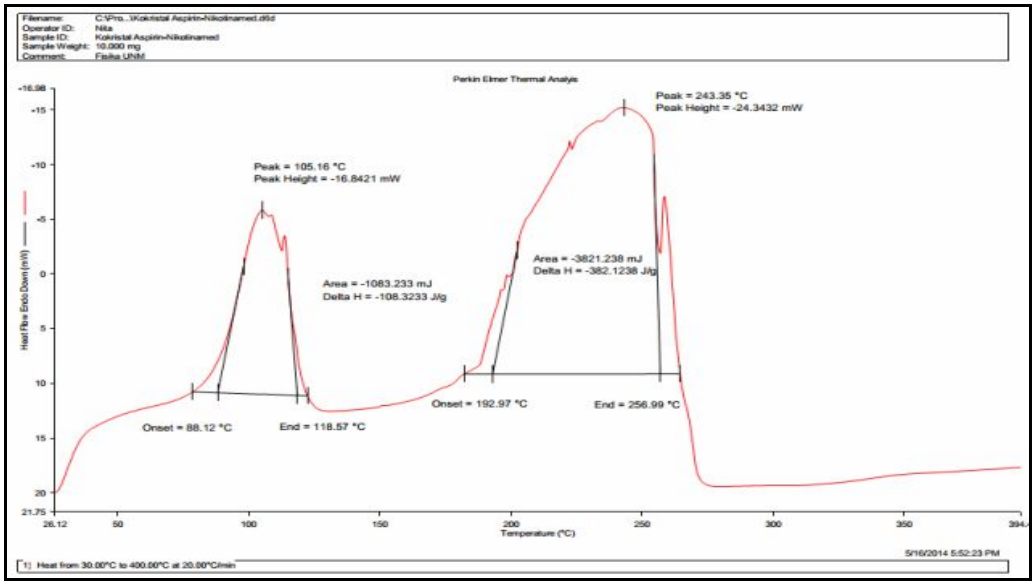

Figure 3. DSC Thermogram of Aspirin-NicotinamideCocrystal

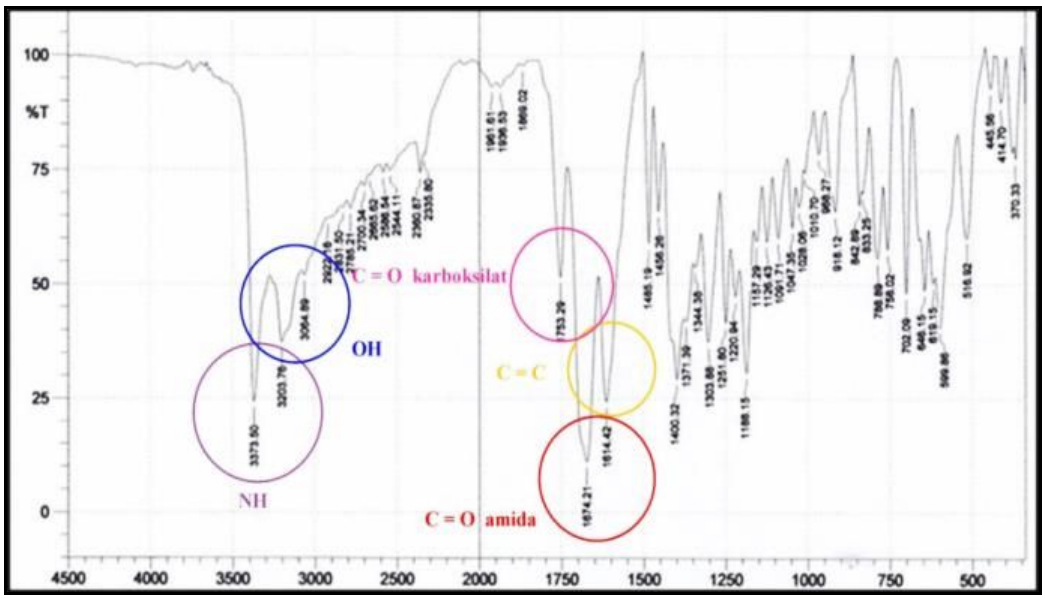

Figure 4.FT-IR Spectra of Aspirin-NicotinamideCocrystal

Table 1.Dissolution Test Result of Aspirin and Cocrystal

t (minute)	Aspirin Release (mg)	
	Aspirin	Cocrystal
10	16.46976744	32.69069767
30	31.9798708	41.84905685
45	35.93609819	49.04565891
60	41.7272739	62.54142119

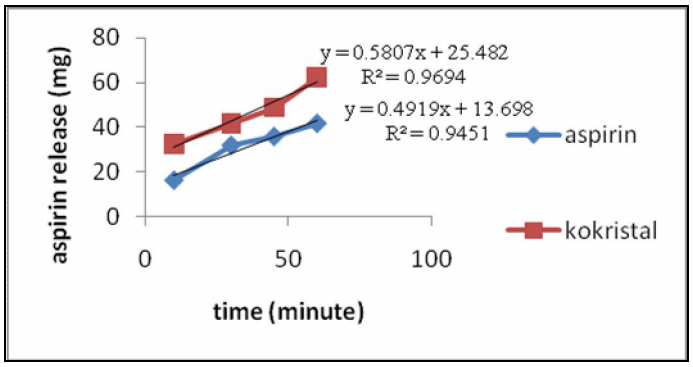

Figure 6. Dissolution Profile of Aspirin and Aspirin-Nicotinamide Cocrystal

Discussion

According to dissolution test result of cocrystal and aspirin (Figure 6), aspirin-nicotinamide cocrystal dissolution rate is more liniear (R^2=0.9694) than aspirin (R^2=0,9451). This result shows that dissolution rate enhances at each unit of time liniearly. Dissolution rate of cocrystal is 0.5807 mg/minute and aspirin is 0.4919 mg/minute. It is assumed that aspirin and nicotinamide are crystallize and able to enhace dissolution rate of single aspirin appropriate to characterization result.

Cocrystal was dried at room temperature and obtained white powder. It was observed by optic microscope, and it was small crystal powder. The powder was investigated and recorded by SEM (Figure 1), it shows that grinding of cocrystal substances cause particle reduction of aspirin and nicotinamide. Particle size reduction is occurred because of crystal lattice damaging and formed amorphous phase as result of giving extrusion. This amorphous phase indicates physic interaction between aspirin and nicotinamide, and also results in new crystallin phase called cocrystal.

X-ray diffraction is a reliable method for the characterization of solids interaction between the two components of the solid (solid state interaction) [9,13], a new crystalline phase is formed or not. If the new crystalline phase formed from the interaction between the two components, it will be observed significantly from the X-ray diffractogram different between components.

Investigation of XRD diffractogram shows aspirin-nicotinamide cocrystal forming by solvent drop grinding method, see Figure 2. It is exhibited by new peak or alteration of diffractogram pattern between standard aspirin, nicotinamide, and aspirin-nicotinamide cocrystal. Diffractogram result of aspirin-nicotinamide interaction has dissimilarity from both single substances. It identifies forming of new crystallin phase [5].

Thermogram result of cocrystal aspirin-nicotinamide exhibits different thermal behaviour from its both single component. There are two endothermic peak: 105°C; H=-108.3 J/g and 243°C; H=-382.1 J/g (see Figure 3). These two peaks appear because of differences melting point of aspirin-nicotinamide mixture.

FT-IR investigation from Figure 4 exhibits peak stretch OH in cocrystal. It indicates hydrogen bonding interaction between aspirin with nicotinamide. Important analysis of cocrystal is infrared spectrum investigation to observe shift of wavenumber and change of peak absorbance. All of them will give information that there is hydrogen bonding interaction between APIs and conformer[14].

Conclusions

It is conclude that cocrystalization shows solubility increasing significantly than standard aspirin. Cocrystalization process is well marked specifically by each characterization methods.

Acknowledgements

This study needs more advanced research concerning various methods or other coformer to enhance aspirin solubility and advanced inspection in computation application to design cocrystal structure.

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