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Abstract

Objective: Acyclovir (ACV) is well-known antiviral agent that has absorption problem, mainly due to its poor solubility in water and oral bioavailability. To improve acyclovir physical properties, especially dissolution properties, acyclovir-nicotinamide(NCT) cocystal was formed. Methods: ACV-NACT cocystal was prepared using slurry method using ethanol as solvent with different concentration. The ACV-NACT cocystal from each sample groups was characterized using powder X-ray diffraction (XRD), and then dissolution properties evaluated. Results: Each ACV-NACT cocystal prepared from slurry method with
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Solvent Concentration Effect on Powder X-Ray Diffraction and Dissolution Profiles of Acyclovir-Nicotinamide Cocrysatls

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Received: 26th Oct, 17; Revised 9th Nov, 17, Accepted: 24th Nov, 17; Available Online: 25th Dec, 2017

ABSTRACT
Objective: Acyclovir (ACV) is well-known antiviral agent that has absorption problem, mainly due to its poor solubility in water and oral bioavailability. To improve acyclovir physical properties, especially dissolution properties, acyclovir-nicotinamide(NCT) cocystal was formed. Methods: ACV-NCT cocystal was prepared using slurry method using ethanol as solvent with different concentration. The ACV-NCT cocystal from each sample groups was characterized using powder X-ray diffraction (PXRD), and then dissolution properties evaluated. Results: Each ACV-NCT cocystal prepared from slurry method with different ethanol concentrations have different PXRD profile. Dissolution analysis (ED50) showed that ACV-NCT cocystalization using slurry methods with 10.0 ml/g as ethanol concentration significantly increase ED50 values compared to acyclovir and acyclovir-nicotinamide physical mixture (n=0.05). Conclusion: ACV-NCT cocystal successfully formed using slurry method with 10.0 ml/g as optimal ethanol concentration.

Keywords: Cocystal, Acyclovir, Nicotinamide, Slurry method.

INTRODUCTION
Acyclovir is synthetic purine nucleoside analogue with inhibitory activity against herpes simplex virus type 1 (HSV-1), 2 (HSV-2) and varicell-zoster virus (VZV)1. Acyclovir is well-known antiviral agent because of its high selectivity and low toxicity, but has absorption problem, mainly due to its poor solubility in water and oral bioavailability2-3. To improve its physical properties, cocystalization method then chosen. Cocystal defined as crystalline material consists of two or more solid component in stoichiometric ratio connected by non-covalent interactions where all the components present are solid under ambient conditions4,5. Pharmaceutical cocystals consist of a drug and a coformer. Nicotinamide is a aqueous soluble vitamin that can be used as coformer and has pyridine and amide functional group that capable to form hydrogen bond with acyclovir in prediction6. Cocystalization with nicotinamide as coformer successfully formed in carbamazepine cocystal7,8,9.

There are several methods that can be used for cocystalization, such as solvent evaporation, melting, grinding and slurry methods. Solvent evaporation method is the most commonly used for cocystalization, but has limitation to used in large scale due to large needs of organic solvent10. Compared to solvent evaporation method, slurry method need smaller amount of solvent added to form drug-coformer suspension. The suspension then stir until cocystalization process complete11.

The aim of this study is to form ACV-NCT cocystal (1:1) using slurry method with variation concentration of ethanol as solvent. Increasing solvent concentration on caffeine-L tartaric acid cocystalization using Sonic Slurry method showed that increasing solvent concentration has an effect on increasing cocystalization rate as long as both cocystal components still saturated enough on solvent12.

MATERIAL AND METHOD
Material
Acyclovir (ACV) hydrate (3:2) was donated by Kimia Farma Tbk (Jakarta, Indonesia) and nicotinamide (NCT) were obtained from Sigma-Aldrich Company (Buchs, Switzerland). Analytical grade ethanol (Merck, Germany) was used for the experiments.

Methods
Preparation of ACV-NCT Physical Mixture
Acyclovir (648,26 mg) and nicotinamide (351,74 mg) equimolar (1:1) were carefully weighed and then mixed homogeneously in mortar.

Preparation of ACV-NCT Cocystal Using Slurry Method
Acyclovir (648,26 mg) and nicotinamide (351,74 mg) equimolar (1:1) were carefully weighed. Nicotinamide was solved in different ethanol concentration (6,8,10,12,15 ml/g) to form saturated and nearly saturated nicotinamide.

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solutions. Acyclovir then added to nicotinamide solutions and drug-coformer suspension stir until an hour, and store at room condition until ethanol fully evaporate.

Characterization by Powder X-Ray Diffraction (PXRD) PXRD (Rigaku MiniFlex 600, Japan) analysis was performed at room temperature. Measurement conditions were set as follows: X-Ray 40kV-15mA, slit DS = 1.25 and 10 mm, SS = 1.25°, RS=0.3 mm, slit condition variable + fixed slit system, scan axis theta/2-theta (fixed), start angle 5°, stop angle 40°, scan speed 5°/min, anode material Cu. Dissolution Profile Evaluation Dissolution profiles studies performed on the samples in powder, all the samples were sieved through a 60 mesh screen and sample corresponding to 100 mg of ACV dose were used. The test were performed using The United States Pharmacopeia (USP) Apparatus 2 (paddle apparatus, Erweka DT-700, Germany) 50 rpm, in 900 ml
Table 1: ED$_{15}$ calculation.

<table>
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<tr>
<th>Samples Groups</th>
<th>ED$_{15}$ (%) ± SD</th>
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<tr>
<td>Acyclovir (ACV)</td>
<td>57.87 ± 3.24</td>
</tr>
<tr>
<td>ACV-NCT physical mixture</td>
<td>71.22 ± 1.99</td>
</tr>
<tr>
<td>ACV-NCT slurry 6 ml/g</td>
<td>68.50 ± 1.47</td>
</tr>
<tr>
<td>ACV-NCT slurry 8 ml/g</td>
<td>70.43 ± 3.37</td>
</tr>
<tr>
<td>ACV-NCT slurry 10 ml/g</td>
<td>82.01 ± 1.97</td>
</tr>
<tr>
<td>ACV-NCT slurry 12 ml/g</td>
<td>67.31 ± 5.17</td>
</tr>
<tr>
<td>ACV-NCT slurry 15 ml/g</td>
<td>60.83 ± 3.96</td>
</tr>
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phosphate buffer pH 6.8 at 37°C. ED$_{15}$ values from each samples then calculated.

Statistic Analysis

ED$_{15}$ from each samples analyzed using ANOVA One Way and LSD analysis as post hoc test (α=0.05).

ACV-NCT Cocrystallization Using Slurry Method

Cocrystallization of ACV and NCT performed using slurry method with different ethanol concentration as solvent. ACV and NCT were incongruently soluble at ethanol, therefore, ACV (less soluble component) added to saturated or near saturated NCT (more soluble component) solution then stir together to form ACV-NCT cocystal. Minimal ethanol concentration to dissolve and form NCT saturated solution was 6 ml/g. Increase ethanol concentration until 15 ml/g then form a near saturated NCT solution.

PXRD Analysis

PXRD patterns from acyclovir (ACV), nicotinamide (NCT), and ACV-NCT cocystal obtained from slurry method with different ethanol concentrations showed at Figure 2.

Diffraction peaks differences between each slurry condition compared to ACV, NCT and ACV-NCT physical mixture are: (1) 6 ml/g : new peak at 6,408°, acv peak at 16,08° disappear, (2) 8 ml/g : new peak at 8,1°, acv peak 16,08° at disappear, (3) 10 ml/g : new peaks at 11,9° 17,63°, acv peak 16,08° at disappear, (4) 12 ml/g : new peak at 17,63° 17,01° acv peak 16,08° at disappear, (5) 15 ml/g : new peak at 16,88°. The formation of cocrystals is primally characterized by powder X-ray diffractometer (PXRD). Cocystal successfully formed when PXRD patterns of the products were different from its component. The differences of PXRD patterns showed with new characteristic peaks belong to cocystal appears and/or characteristic peaks from its components disappear. Results from PXRD analysis showed that all of cocrystals from slurry method have different PXRD patterns compared to its component. There are several changes that can be seen. New diffractogram peaks found (cocrystals with different ethanol condition have new peaks at different position) and a characteristic peak of ACV at 20 16,08° disappear on cocystal samples (except on 15 ml/g, ACV peak still found). New PXRD patterns of ACV-NCT cocystal from slurry method showed that new solid forms with new crystal lattice are successfully formed, with 10 ml/g has the most PXRD pattern changes.

Dissolution Profiles Evaluation

Dissolution profile from ACV, ACV-NCT physical mixture, and ACV-NCT cocystal from slurry method with different ethanol concentration showed at Figure 3. Dissolution evaluations from each samples performed at phosphate buffer pH 6.8; 37°C. Dissolution profiles comparison at Fig.3 showed that cocystal ACV-NCT slurry 10 ml/g has the highest % ACV solved at 5 minutes. Compared to other time points, 5 until 15 minutes has larger differences on % ACV solved, so calculation of ED$_{15}$ (%) then conducted. ED$_{15}$ calculations for each samples can be seen on Table 1. Results from ED15 calculation at Table 1 showed that ACV-NCT slurry 10 ml/g has the highest value, and significantly increase % ACV solved compared to ACV, physical mixture and the other slurry samples. ED$_{15}$ value of ACV-NCT cocrystals slurry then decrease at 12 ml/g and 15 ml/g of ethanol concentration, because at that concentration, nicotinamide not saturated enough to form cocystal with acyclovir. Statistical analysis of ED$_{15}$ value using ANOVA One way showed that there was significant differences (*p<0.05) between each sample groups, and slurry 10 ml/g significantly different from acyclovir, physical mixture and other slurry samples (LSD post hoc test, α=0.05).

CONCLUSION

ACV-NCT cocystal successfully formed using slurry method. Results from PXRD analysis and dissolution evaluation showed that 10 ml/g was an optimal ethanol concentration for ACV-NCT cocrystallization using slurry method in this experiment. This study confirm that solvent concentration used during cocrystallization process with slurry method has an effect on cocystal formation.

CONFLICT OF INTEREST

Declared None

REFERENCES


