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Research Article

Solvent Concentration Effect on Powder X-Ray Diffraction and Dissolution Profiles of Acyclovir-Nicotinamide Cocrystals

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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) cocrystal was formed. Methods : ACV-NCT cocrystal was prepared using slurry method using ethanol as solvent with different concentration. The ACV-NCT cocrystal from each sample groups was characterized using powder X-ray diffraction (PXRD), and then dissolution properties evaluated. Results : Each ACV-NCT cocrystals prepared from slurry method with different ethanol concentrations have different PXRD profile. Dissolution analysis (ED_{15}) showed that ACV-NCT cocrystallization using slurry methods with 10,0 ml/g as ethanol concentration significantly increase ED_{15} values compared to acyclovir and acyclovir-nicotinamide physical mixture (α=0,05). Conclusion : ACV-NCT cocrystal successfully formed using slurry method with 10,0 ml/g as optimal ethanol concentration.

Keywords: Cocrystal, 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 varicellar-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 bioavailability[2,3]. To improve its physical properties, cocrystallization method then chosen.

Cocrystal 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 conditions[4,5]. Pharmaceutical cocrystals consist of a drug and a coformer. Nicotinamide is a aqueous soluble vitamin that can be used as conformer and has pyridine and amide functional group that capable to form hydrogen bond with acyclovir in prediction[6]. Cocrystallization with nicotinamide as coformer successfully formed in carbamazepine cocrystal[7,8,9].

There are several methods that can be used for cocrystallization, such as solvent evaporation, melting, grinding and slurry methods. Solvent evaporation method is the most commonly used for cocrystallization, but has limitation to used in large scale due to large needs of organic solvent[10]. Compared to solvent evaporation method, slurry method need smaller amount of solvent added to form drug-coformer suspension. The suspension then stir until cocrystallization process complete[11].

The aim of this study is to form ACV-NCT cocrystal (1:1) using slurry method with variation concentration of ethanol as solvent. Increasing solvent concentration on caffeine-L tartaric acid cocrystallization using SonicSlurry method showed that increasing solvent concentration has an effect on increasing cocrystallization rate as long as both cocrystal components still saturated enough on solvent[12].

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) equimolar (1:1) were carefully weighed and then mixed homogeneously in mortar.

Preparation of ACV-NCT Cocrystal Using Slurry Method

Acyclovir (648,26 mg) and nicotinamide (351,74) 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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A B

Figure 1: Molecular structures of ACV (A) and NCT (B).

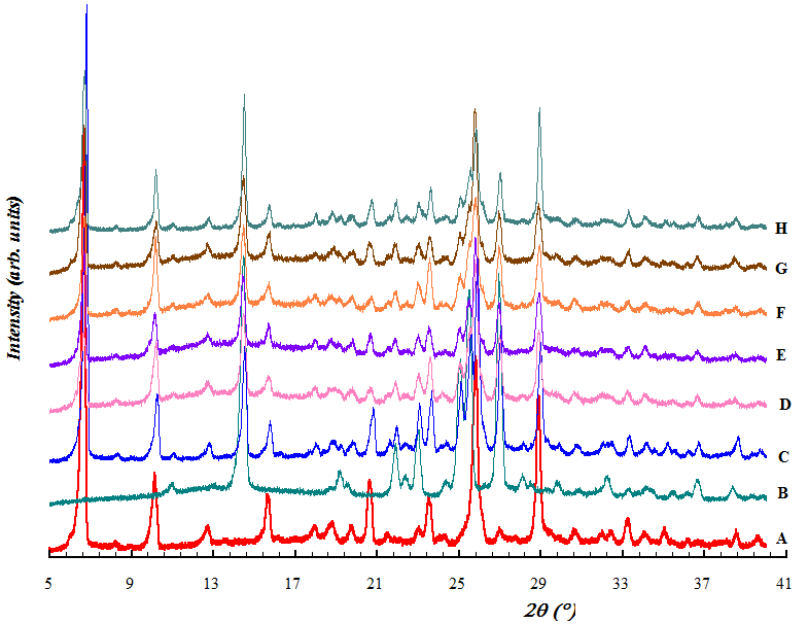

Figure 2: PXRD patterns of acyclovir (A), nicotinamide (B), ACV-NCT physical mixture (C), ACV-NCT cocrystals slurry 6 ml/g (D), 8 ml/g (E), 10 ml/g (F), 12 ml/g (G), 15 ml/g (H).

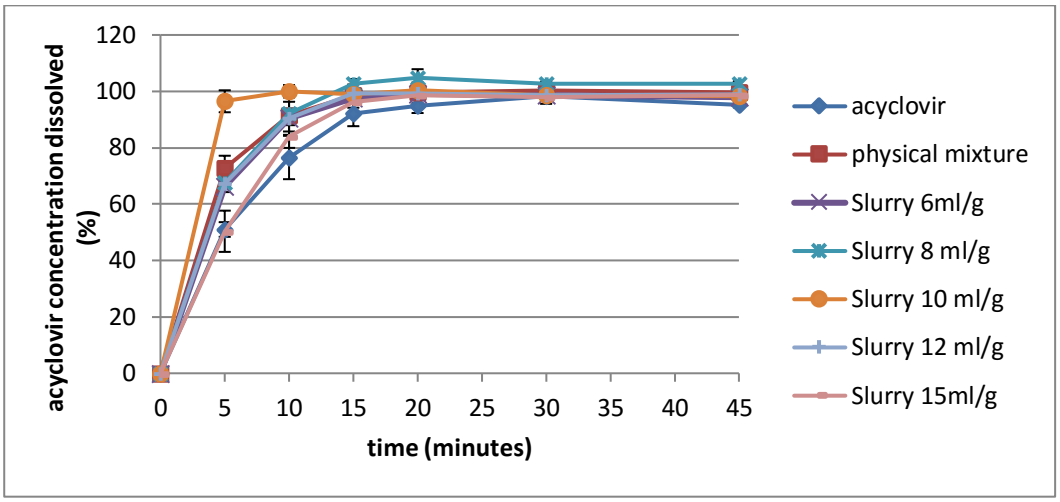

Figure 3: Dissolution profiles of ACV, ACV-NCT physical mixture, ACV-NCT cocrystals slurry method (6,8,10, 12, 15 ml/g).

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.

Samples Groups	ED_{15} (%) ± SD
Acyclovir (ACV)	57,87 ± 3,24
ACV-NCT physical mixture	71,22 ± 1,99
ACV-NCT slurry 6 ml/g	68,50 ±1,47
ACV-NCT slurry 8 ml/g	70,43 ± 3,37
ACV-NCT slurry 10 ml/g	82,01 ± 1,97
ACV-NCT slurry 12 ml/g	67,31 ± 5,17
ACV-NCT slurry 15 ml/g	60,83 ±3,96

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 cocrystal[14]. 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 cocrystal 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) . Cocrystal successfully formed when PXRD patterns of the products were different from its component[1-3]. The differences of PXRD patterns showed with new characteristic peaks belong to cocrystal appears and/or characteristic peaks from its components disappear[15]. 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 2θ 16,08° disappear on cocrystal samples (except on 15 ml/g, ACV peak still found). New PXRD patterns of ACV-NCT cocrystal 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 cocrystal 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 cocrystal 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 cocrystal 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 cocrystal formation.

CONFLICT OF INTEREST

Declared None

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