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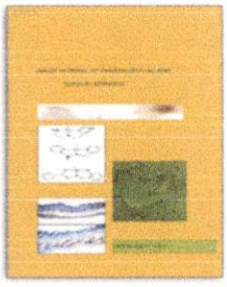

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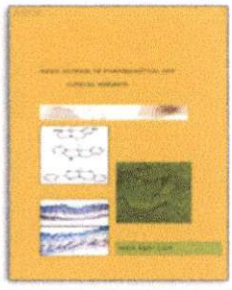

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COCRYSTALLIZATION ACYCLOVIR-SUCCINIC ACID USING SOLVENT EVAPORATION METHODS

Agnes Nuniek Winantari, Dwi Setyawan, Siswandono Siswodihardjo, Sundono Nurono Soewandhi

Abstract

Objective : The aim of this research is to prepare and characterize cocrystals of acyclovir through cocrystallization of acyclovir – succinic acid (AS) to improve the physical properties of the drug.

Methods : AS cocrystals was prepared using solvent evaporation method. The cocrystals were characterized by Polarization Microscope, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), and Fourier Transform Infrared Spectroscopy (FTIR).

Results : Physical characterization using polarization microscope and SEM showed the AS cocrystals have unique crystal habit and morphology. Phase diagram at molar ratio of 50% : 50% (acyclovir : succinic acid) showed a decrease in the melting temperature i.e 176.23 ^{o}C in comparison with the melting point of the constituent materials (acyclovir 253.53 ^{o}C and succinic acid 187.29 ^{o}C). The PXRD pattern of AS cocrystals (ethanol) exhibited new diffraction peaks at 2θ = 5.91; 9.16; and 13.40. Besides, cocrystals of AS (glacial acetic acid) indicated new peaks at 2θ = 5.98; 9.19; and 13.43. Furthermore, there was a shift in the N-H, O-H and C=O.

Conclusion : Cocrystallization of acyclovir-succinic acid (AS) in ethanol and glacial acetic acid were succesfully formed using solvent evaporation methods.

Keywords

acyclovir, succinic acid, cocrystal, characterization, solvent evaporation method

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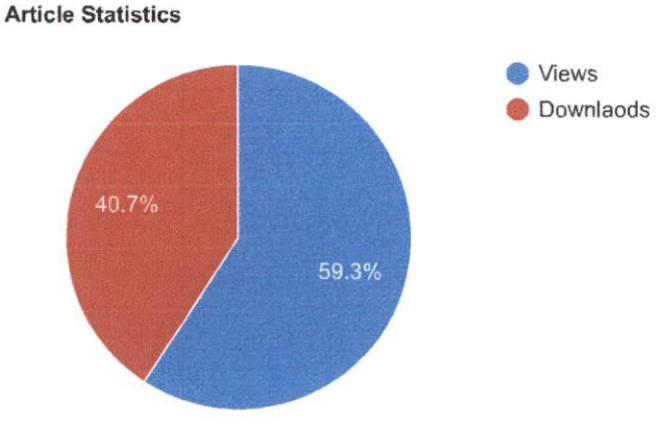

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Research Article

COCRYSTALLIZATION ACYCLOVIR-SUCCINIC ACID USING SOLVENT EVAPORATION METHODS

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ABSTRACT

Objective: The aim of this research is to prepare and characterize cocrystals of acyclovir through cocrystallization of acyclovir-succinic acid (AS) to improve the physical properties of the drug.

Methods: AS cocrystals were prepared using solvent evaporation method. The cocrystals were characterized by polarization microscope, scanning electron microscopy (SEM), differential scanning calorimetry, powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy.

Results: Physical characterization using polarization microscope and SEM showed the AS cocrystals have unique crystal habit and morphology. Phase diagram at a molar ratio of 50:50% (acyclovir:succinic acid) showed a decrease in the melting temperature, i.e., 176.23°C in comparison with the melting point of the constituent materials (acyclovir 253.53°C and succinic acid 187.29°C). The PXRD pattern of AS cocrystals (ethanol) exhibited new diffraction peaks at 2θ=5.91°; 9.16°; and 13.40°. Besides, cocrystals of AS (glacial acetic acid) indicated new peaks at 2θ=5.98°; 9.19°; and 13.43°. Furthermore, there was a shift in the N-H, O-H, and C=O.

Conclusion: Cocrystallization of AS acid in ethanol and glacial acetic acid were successfully formed using solvent evaporation methods.

Keywords: Acyclovir-succinic acid, Cocrystal, Characterization, Solvent evaporation method.

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INTRODUCTION

The properties of the pharmaceutical solid such as solubility and dissolution rate are important as the ability to manufacture the solid dosage form at scale. Attempting to find a solid with the desired properties and manufacturability, companies spend significant effort looking for polymorphs, salts, and cocrystal of their active pharmaceutical ingredients (API's) [1-5].

Cocrystal is a homogenous crystalline material composed of a neutral target and a neutral coformer held together through noncovalent bonds. For pharmaceutical applications, it is essential that the coformers have generally recognized as safe status. The physicochemical properties of API's can be modified while the intrinsic activities of these drug molecules remain the same. From the thermodynamic point of view, pharmaceutical cocrystals are stable and high energy forms. Therefore, they can have impact on solubility and dissolution rate of the drug. The strategy involves drug-coformer combinations that have the potential of forming energetically and structurally robust interactions [3-8]. Pharmaceutical cocrystals often rely on hydrogen-bonded assemblies between an API and coformer with well-defined stoichiometries. For a target API, we are interested in coformers with functional groups that can interact (i.e., form H-bonds) with the functional groups on the API. Common functional groups - such as carboxylic acids, amides, and alcohols - are typically found to interact with one another in cocrystals [3,9,10].

Acyclovir, a guanosine analog antiviral drug with a solubility of 1.62 mg/mL. Due to its poor solubility and permeability, the bioavailability of acyclovir attains just 15-30% [11-14]. Carboxylic acids are considered as coformers to form cocrystals with acyclovir. A group of carboxylic acids including succinic acid, glutaric acid, and adipic acid [13].

Solvent evaporation is the most conventional technique of cocrystallization which includes super saturation of solution by evaporation, cooling and addition of solubility changing solvent or substance [15].

The aim of this research was to prepare and characterize cocrystals of acyclovir through cocrystallization of acyclovir-succinic (AS) acid to improve the physical properties of the drug. The obtained of cocrystals were characterized by microscope polarization, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy (FTIR).

MATERIALS AND METHODS

Materials

Acyclovir commercial material was obtained from Sigma (USA). Succinic acid, ethanol, and glacial acetic acid were purchased from Merck Chemicals (Germany) without any purification.

Methods

Phase diagram preparation of AS acid

AS acid was sifted and weighed to obtain a similar range of particle size. Both of samples were mixing at different molar ratios, i.e., (10/90), (20/80), (30/70), (40/60), (50/50), (60/40), (70/30), (80/20), and (90/10) to obtain the AS physical mixture. The mixture was gently mixed in a mortar for 5 minutes. Examination of melting point of AS physical mixture was determined by DSC. Phase diagram of AS describes the molar fraction of the mixture against the endothermic peak [16].

Preparation of AS cocrystals by solvent evaporation

AS acid carefully weighed equimolar. Each compound was dissolved in ethanol separately. The both of solutions were mixed and stirred for a few minutes. Equimolar solution of both components was evaporated

at room temperature for 48 hrs. The obtained cocrystal solids were stored in a desiccator under vacuum [17].

Characterization by polarized microscope

About 1-2 mg of physical mixture between AS acid was placed on object glass. A drop of ethanol was added to each physical mixture until dissolved and allowed to recrystallize. Recrystallization process was observed under a polarizing microscope. The microscopic images were recorded with an Olympus SC-30 digital color camera attached to the Olympus BX-50 polarized microscope [18].

Characterization using SEM

Sample was placed on the sample holder and coated with gold aluminum with a thickness of 10 nm. The sample was then observed at various magnification using SEM instrument (FEI Inspect S50, USA) with voltage was set at 20 kV and 12 mA [16].

Thermal analysis by DSC

DSC was performed using Mettler Toledo. About 4 mg of each sample was placed in crimped sample pan. The sample was heated from 30 to 300°C at a heating rate of 10°C/minutes under nitrogen purged [18].

Characterization by PXRD

PXRD (Phillips X'Pert diffractometer) analysis was performed at room temperature. Condition of measurement was set as follows: Cu metal target, Kα filter, voltage of 40 kV, and 40 mA. The analysis was performed on the range of 2θ of 5-40°C. Sample was placed on the sample holder and flatted to prevent particle orientation during preparation [16].

Characterization by FTIR

IR spectra were recorded using Jasco 4200-type A. The dried pure AS acid, physical mixture, and binary system were previously ground and mixed thoroughly with potassium bromide. The IR spectrum was obtained using IR spectrophotometer in wave length range of 400-4000/cm [17].

RESULTS AND DISCUSSION

The cocrystallization process of AS cocrystal was observed under polarized microscope. Polarizing light microscopy is particularly useful for studying the optical properties of crystals. When crossed polarized light (the vibration directions of the two polarizers are oriented 90°C from one another) passes through an anisotropic crystal, the crystal will show bright interference colors, as long as it is not in an extinction position or aligned on an optic axis [19]. As shown in Fig. 1, AS cocrystal has unique crystal habit.

The phase diagram of AS binary system consists of different molar ratio of AS acid. The result indicated that the molar ratio of 50:50% show a decreased melting temperature of each component. Acyclovir melted at 253.53°C and succinic acid melted at 187.29°C, whereas the binary system of AS melted at 176.23°C. Decreasing of melting temperature exhibited that it formed a cocrystal as shown in Fig. 2 and Table 1.

DSC is thermal analysis method to evaluate changes in thermodynamic properties that occur when the material supplied heat energy. Changes can be observed in the process of melting, recrystallization or solid phase transformations indicated by endothermic or exothermic peaks. Fig. 3 showed new endothermic peak appears at 176.23°C (ΔH=1.07 Jg^{-1}) for AS physical mixture; 177.45°C (ΔH=0.87 Jg^{-1}) for AS cocrystal (ethanol) and 178.41°C (ΔH=0.78 Jg^{-1}) for AS cocrystal (glacial acetic acid). The thermal behavior of the cocrystals was distinct with a different melting transition from that seen with either of the individual components; this suggests the formation of a new phase [11]. The changes in peak position may be attributed to change in powder geometry of samples during preparation [20].

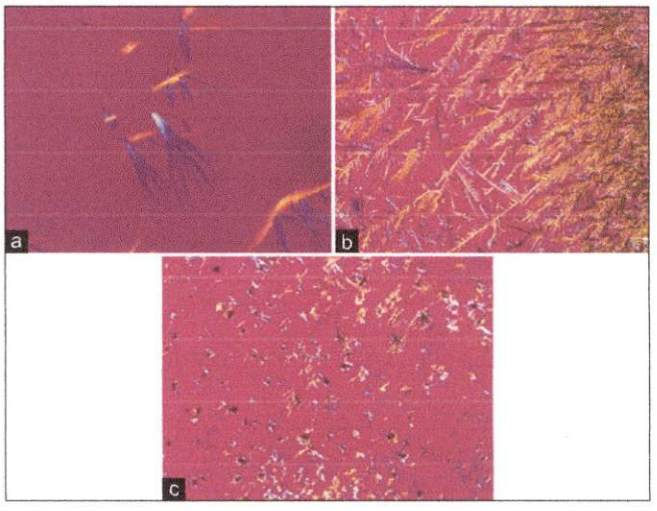

Fig. 1: Photomicroscope (a) acyclovir, (b) succinic acid, (c) acyclovir-succinic cocrystal

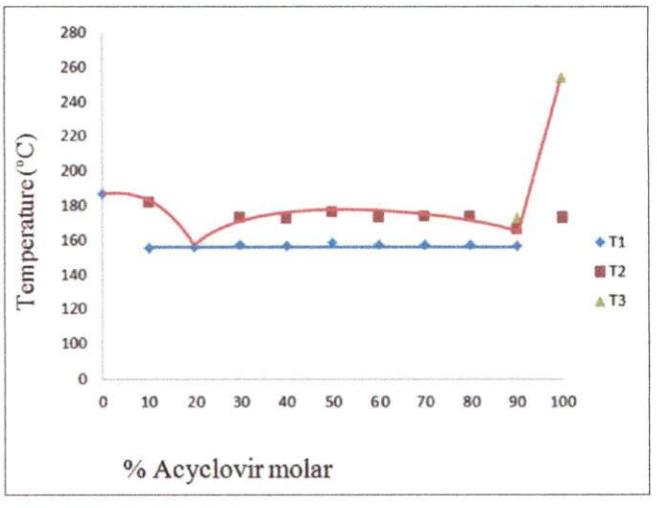

Fig. 2: Phase diagram of acyclovir-succinic binary systems with various composition

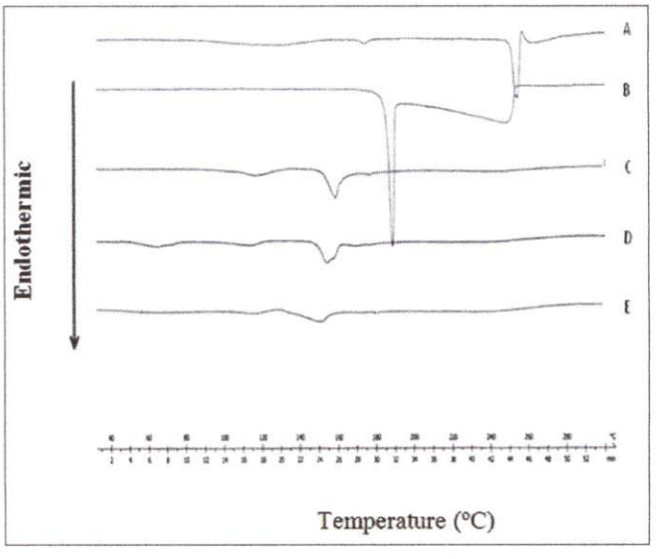

Fig. 3: Differential scanning calorimetry thermogram. (A) Acyclovir, (B) succinic acid, (C) physical mixture acyclovir-succinic (AS) (1:1), (D) cocrystal of AS in ethanol, (E) cocrystal of AS in glacial acetic acids. Arrow sign (↓) show specific diffraction peak in cocrystal of AS

Since every compound produces its own characteristic powder pattern owing to the unique crystallography of its structure, PXRD is clearly the most powerful and fundamental tool for a specification of the polymorphic identity of an analyte [21].

Table 1: Endothermic of AS acid and binary systems of AS in various composition

Sample	Endothermic peak (°C)		
	T1	T2	T3
Succinic acid	187.29	-	-
AS physical mixture (1:9)	155.64	181.68	-
AS physical mixture (2:8)	156.08	-	-
AS physical mixture (3:7)	157.15	173.42	-
AS physical mixture (4:6)	156.65	172.27	-
AS physical mixture (5:5)	158.42	176.23	-
AS physical mixture (6:4)	157.45	172.99	-
AS physical mixture (7:3)	157.35	173.62	-
AS physical mixture (8:2)	157.40	173.75	-
AS physical mixture (9:1)	156.91	166.37	173.14
Acyclovir	-	174.01	253.53

AS: Acyclovir-succinic

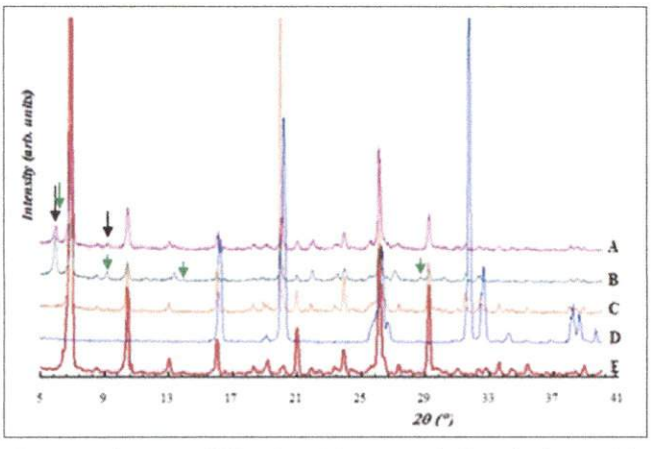

Fig. 4: Powder X-ray diffraction. (A) Cocrystal of acyclovir-succinic (AS) (acetic acid), (B) cocrystal of AS (ethanol), (C) physical mixture of AS (1:1), (D) succinic acid, (E) acyclovir

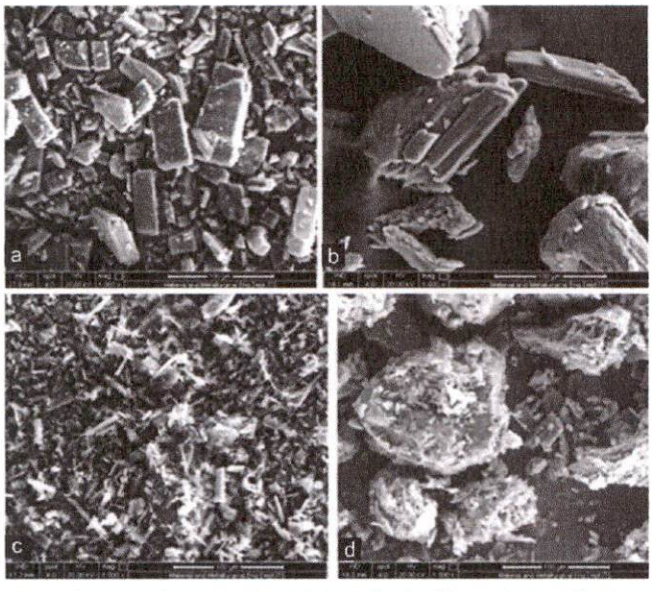

Fig. 5: Microphotographs of (a) acyclovir, (b) succinic acid, (c) acyclovir-succinic (AS) cocrystal (ethanol), (d) AS cocrystal (glacial acetic acid)

New crystalline phase is formed from the interaction between the two components will be observed clearly from the XRD. Fig. 4 showed the PXRD of AS cocrystals compared to the single component and physical mixture of both components without treatment. The PXRD pattern of AS cocrystals different from the pattern of a physical mixture of AS and pure component. The PXRD pattern of AS cocrystals showed some new interference peaks typical at 2θ=5.91°; 9.16°; and 13.40° (ethanol) and 2θ=5.98°; 9.19°; and 13.43° (glacial acetic acid), which were not found in the diffractogram of AS acid and their physical mixture. These unique PXRD patterns of AS cocrystals indicate the formation of new crystalline phases [14].

Fig. 5 shows the microscopic analysis with a SEM. The powder of acyclovir appears in the form of particles with irregular shape and size (Fig. 5a). Succinic acid look like rod shape (Fig. 5b). The AS cocrystal (ethanol) in Fig. 5c appears like a needle shape in which the original morphology of both components has disappeared. Fig. 5d performed the AS cocrystal (glacial acetic acid) with a more homogeneous aggregate mixture of AS.

The IR spectrum of acyclovir two-thirds hydrate had two peaks in the region of 3500-3300/cm, corresponding to NH and OH, respectively, and the 1600/cm region was represented by a band corresponding to the amide group [22]. The spectrum of succinic acid had one peak at 3439/cm due to O-H, and the region of 1694/cm showed a band corresponding to C=O stretch [23]. The peaks due to N-H stretching acyclovir at 3440 cm^{-1} are now shifted to 3442/cm, similar both in ethanol and glacial acetic acid. The increase in the N-H stretching frequency in the AS cocrystals implies that amine group is participating in a weak hydrogen bond. In addition, the peak due to C=O stretching of acyclovir at 1611, 1661, and 1694/cm is shifted to 1612, 1664 and 1693/cm both in ethanol and glacial acetic acid. The peak due to C=O stretching of succinic acid at 1694/cm is now present as a triple peak at 1612, 1664, and 1693/cm. It is probably due to the stretching of the C=O employed in hydrogen bonds.

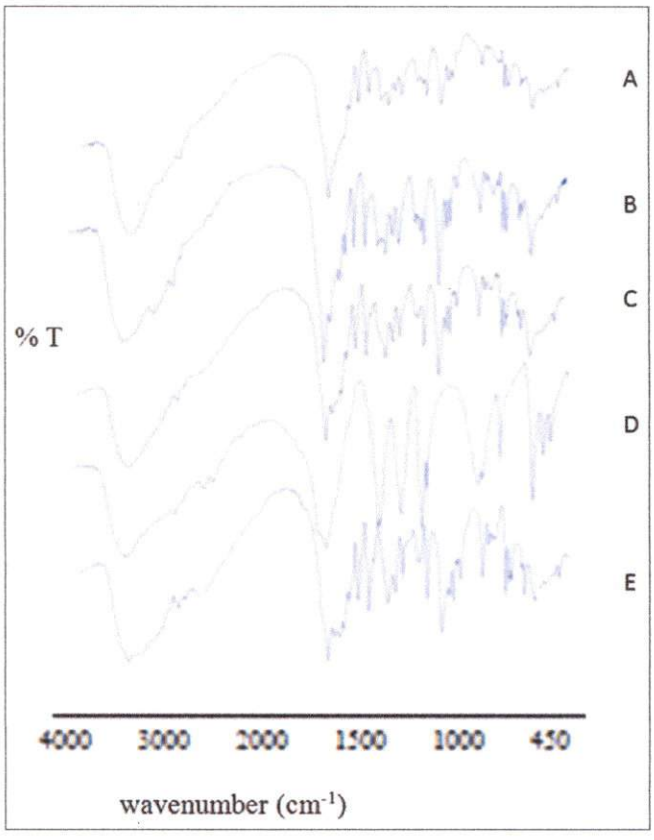

Fig. 6: Fourier transform infrared spectroscopy spectrum. (A) Acyclovir-succinic (AS) cocrystal (glacial acetic acid), (B) AS cocrystal (ethanol), (C) physical mixture of AS (1:1), (D) succinic acid, (E) acyclovir

A bathochromic shift in the C=O stretching frequency in succinic acid from 1694 to 1693/cm both in ethanol and glacial acetic acid further explains the formation of the AS cocrystals. Subsequently, the decrease in the OH stretching frequency from 3439/cm in succinic acid to 3442/cm both in ethanol and glacial acetic acid in AS cocrystals suggests that the carboxyl group is participating in a weak hydrogen bond (Fig. 6).

CONCLUSION

New crystalline phase is formed from the interaction between AS acid using solvent evaporation method. It has been characterized by polarized microscope, SEM, DSC, PXRD, and FTIR.

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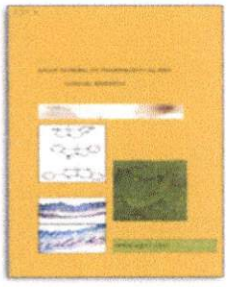

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