



Preparation and Solid State Characterization of Binary Mixtures of Acyclovir – Succinic Acid

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Abstract : Physical interaction of acyclovir – succinic acid (AS) was studied. The aim of this study is to prepare and characterize binary mixture of AS. Methods of cocrystallization was solvent evaporation in equimolar ratio between acyclovir and succinic acid using ethanol and methanol. The cocrystals were characterized by Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), and Fourier Transform Infra Red (FTIR) spectroscopy. Physical characterization showed a new endothermic peak at 175.36°C according to DSC analysis. The PXRD patterns of AS binary mixture after cocrystallization are different from pure components. Furthermore, specific peaks was found at $2\theta = 24,77^\circ$, $35,88^\circ$ and $37,99^\circ$ (AS in ethanol); $19,99^\circ$ and $21,01^\circ$ (AS in methanol). In addition, there are a shift in the O-H, N-H and C=O spectrum of FTIR.

Keywords : acyclovir, succinic acid, solvent evaporation, characterization, binary mixture.

Introduction

Initial R& D efforts were focused on finding new chemical entity with desired molecular structure and physical properties. Most of the active pharmaceutical ingredients (API) exists in solid state, solid does not crystallize on its own. It crystallizes several forms showing unpredictable crystal properties. There are number of approaches can be used to modify solids such as solvation, hydration, salting and polymorphism. Apart from available approaches of API modification, cocrystallization is an emerging alternative approach enhancement of physical properties¹.

Cocrystals, which refer to solid form with two or more different molecules within the same crystal lattice in a certain stoichiometric ratio, have been of great interest to the pharmaceutical industry because they have potential to enhance physicochemical properties of the API. Many cocrystals have been reported to modulate solubility, intrinsic dissolution rate, mechanical properties, compaction, purification, stability or even bioavailability compared with the API². 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^{3,5,6,7}. 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. Thus, carboxylic acids are considered as coformers to form cocrystals with acyclovir, including succinic acid.^{3,8,9,12}

Acyclovir is a guanosine analogue antiviral drug. It is one of the most commonly used antiviral drugs because of its selectivity and low cytotoxicity. It has absorption problems mainly due to its poor solubility in water (1,62 mg/mL). This factor negatively influences its oral bioavailability which is approximately 15-30%^{10,11,12,13}.

Different methods have been used to produce cocrystals : solution crystallization, solid state and solvent drop grinding, and crystallization from melt. For scale up purposes, solution crystallization is the most popular^{3,14,15}.

Materials and Method

Materials

Acyclovir was obtained from Sigma-Aldrich (USA). Succinic acid, ethanol and methanol were purchased from Merck Chemicals (Germany) without any purification.

Preparation of binary mixture of AS by solvent evaporation

Acyclovir and succinic acid carefully weighed equimolar. Each compound was dissolved in solvent separately. The two solutions were mixed and stirred for a few minutes. Equimolar solution of both components was evaporated at room temperature for 48 hours. The obtained of solid binary system stored in a dessicator under vacuum.

Thermal Analysis by DSC

Differential Scanning Calorimetry (DSC) was performed using Mettler Toledo. About four 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/min under nitrogen purged.

Characterization by PXRD

Powder X-ray diffraction (Phillips X'Pert diffractometer) analysis was performed at room temperature. Condition of measurement was set as follows : Cu metal target, K α filter, voltage of 40kV, 40 mA. The analysis was performed on the range of 2 theta of 5-40°. Sample was placed on the sample holder and flatted to prevent particle orientation during preparation.

Characterization by FTIR

Infrared spectra were recorded by using Jasco 4200-type A. The dried pure acyclovir, succinic acid, physical mixture and binary system were previously ground and mixed thoroughly with potassium bromide. The infrared spectrum was obtained using infrared spectrophotometer in wave length range of 400-4000cm⁻¹.

Results and Discussion

As shown in figure 1, an endothermic peak at 251.08°C was presented in the DSC thermogram of acyclovir. Succinic acid demonstrated an endothermic peak at 186.90 °C. In the thermogram of the AS physical mixture, it was observed an endothermic peak at 175.36 °C. The thermal behaviour of AS binary mixture showed an endothermic peak at 173.41°C (ethanol) and 172.15°C (methanol), that was distinct and unique from the individual components and physical mixture, demonstrating the formation of a new phase¹⁶.

Differential Scanning Calorimeter (DSC) was used to evaluate the results by observing the thermal profile and arranging phase diagrams. Melting is a first order process that can be observed in the form of an

endothermic peak in DSC curves. Recall that unlike the peak temperature, the onset temperature of melting will be independent of the DSC heating rate¹⁷.

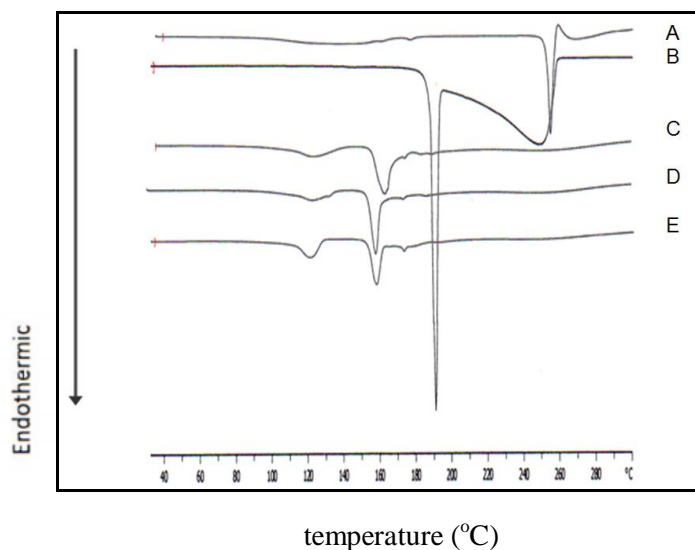


Figure 1 : DSC thermogram of A) asiklovir, B) succinic acid, C) physical mixture of AS (1:1), D) binary mixture of AS (1:1) in ethanol, E) binary mixture of AS (1:1) in methanol

PXRD is one the most powerful techniques used for the study of crystalline and partially crystalline solid-state materials. It is mainly used to characterize the crystallographic structure of polycrystalline or powdered solid samples; different crystalline phases show distinctly different PXRD patterns. This method provides an irreplaceable technique for identifying and characterizing different solid forms of APIs (polymorphs, hydrates, solvates and cocrystals). PXRD provides fundamental structural information on the material¹⁸.

The crystalline states for the starting materials, AS binary mixtures, and physical mixture have been presented in figure 2. In which AS binary mixtures exhibited new characteristic interference peaks at 2θ : 24.77°, 35.88°, 37.99° (in ethanol) and 19.99°, 21.01° (in methanol). The obtained binary mixtures had a unique powder pattern, different from that of the two components or their physical mixtures¹⁶.

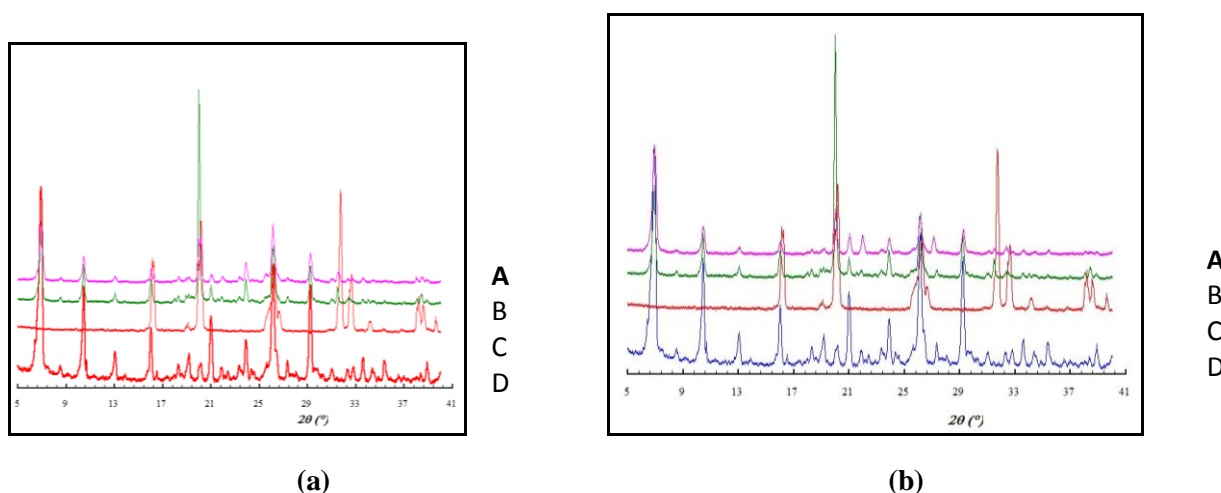


Figure 2 : PXRD diffractogram (a) in ethanol and (b) in methanol. A) AS binary mixture AS (1:1), B) physical mixture AS (1:1), C) succinic acid , D) acyclovir

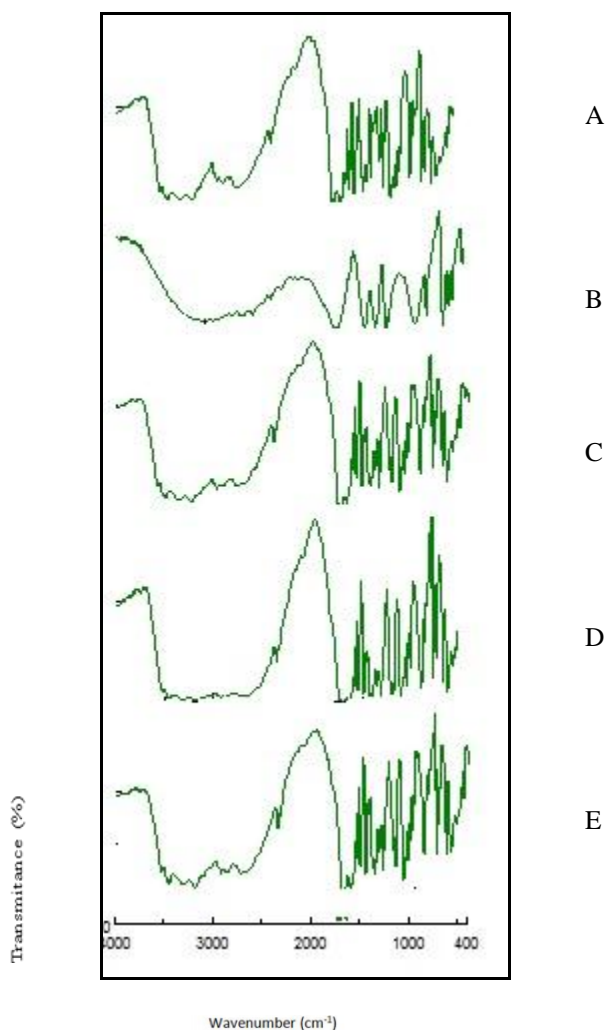


Fig. 3 : FTIR spectra of a) acyclovir, b) Succinic acid, c) AS physical mixture, d) AS cocrystals (ethanol), e) AS cocrystals (methanol)

The infra red spectrum of acyclovir had peaks in the region of $3500\text{-}3300\text{ cm}^{-1}$, corresponding to primary and secondary amines, respectively, and the 1600 cm^{-1} region was represented by a band corresponding to the amide group¹⁰. The main absorption bands of acyclovir are a broad band 3500 cm^{-1} due to (NH,OH), C=O stretching at 1600 cm^{-1} , CH-aliphatic stretching at 2950 cm^{-1} and CH-aromatic stretching at 3050 cm^{-1} ²⁰. The spectrum of succinic acid had one peak at 3439 cm^{-1} corresponding to a O-H group, and the region of 1694 cm^{-1} showed a band corresponding to C=O stretch¹⁹. The loss of the transmission peaks at 3500 cm^{-1} referred to NH bending bands. Loss of C=O stretch at 1600 cm^{-1} , C-H aromatic at 3050 cm^{-1} , and O-H bending region at 3439 cm^{-1} showed the presence of hydrogen bonding between acyclovir and succinic acid due to the formation of new crystalline phase, both in ethanol either in methanol by solvent evaporation technique. This indicate the formation of cocrystal of AS.

Conclusion

Binary mixtures of acyclovir-succinic acid were formed using solvent evaporation methods in ethanol and methanol. They have been characterized by DSC, PXRD, and FTIR.

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