Cocrystals of Acyclovir with Promising Physicochemical Properties

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Received 1 September 2014; revised 30 September 2014; accepted 13 October 2014

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24248

ABSTRACT: Cocrystal forming ability of antiviral drug acyclovir (ACV) with different coformers was studied. Three cocrystals containing ACV with fumaric acid, malonic acid, and DL-tartaric acid were isolated. Methods of cocrystallization included grinding with dropwise solvent addition and solvent evaporation. The cocrystals were characterized by powder X-ray diffraction, differential scanning calorimetry, and thermogravimetric analysis. The crystal structure of the cocrystal with fumaric acid as conformer was determined by single crystal X-ray diffraction. Formation of supramolecular synthon was observed in the cocrystal. Stability with respect to relative humidity for the three cocrystals was evaluated. The aqueous solubility of the ACV-cocrystal materials was significantly improved with a maximum of malonic acid cocrystal, which was about six times more soluble at 35°C compared with that of parent ACV. The dissolution profile indicates that at any particular dissolution time, the concentration of cocrystals in the solution was higher than that of the parent ACV, and malonic acid cocrystals had a maximum release of about twice than the hydrated ACV. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: co-crystal; synthon; crystal engineering; single crystal; stability; dissolution rate; solubility

INTRODUCTION

Acyclovir (2-amino-1,9-dihydro-9-((2-hydroxyethoxy)methyl)-6*H*-purin-6-one, hereinafter abbreviated as ACV, Fig. 1) is an antiviral agent administered for the treatment of infections such as herpes simplex (HSV-1 and HSV-2), shingles, and varicella (chickenpox). ACV has been marketed under several brand names such as Cyclovir, Herpex, Acivir, Acivirax, Zovirax, Zoral, Xovir, and Imavir, and it is available as 200, 400, and 800 mg tablets as well as flavored liquid.

The 1988 Nobel Prize in Medicine was awarded to G.B. Elion, partly for the invention and development of ACV. The commercial ACV exists as a hydrated form and the crystal structure revealed a 3:2 ACV:water hydrate with a monoclinic space group.[1] The dihydrated form with a triclinic unit cell[2] is obtained by dissolving commercial ACV in water at 60°C. A metastable anhydrous form was obtained by heating commercial ACV at a temperature between 130°C and 150°C.[3] Two stable anhydrous forms were obtained by heating commercial ACV at a temperature above 150°C and 180°C, respectively.[3] Sohn and Kim[4] showed existence of one more anhydrous form of ACV when commercial ACV was dissolved in methanol at 60°C followed by cooling crystallization to room temperature. An acetic acid solvate form has been reported after dissolving ACV in acetic acid followed by slow evaporation at room temperature.[4] However, the hydrated and anhydrous forms are poorly soluble in water.

Acyclovir belongs to the Class IV drugs, according to the Biopharmaceutics Classification System, which have low solubility and low permeability. Hence, to explore various solid forms of ACV that can enhance its solubility, dissolution profile, and bioavailability is of significance. Various methods have been used to increase the solubility of ACV. For example, solubility and dissolution rate of ACV could be improved by forming complex with cytosine,[5] self-microemusifying of drug delivery system,[6] and inclusion compound with β-cyclodextrin.[7] Pharmaceutical cocrystals are obtained by combining one or more solid components (conformers) together with an active pharmaceutical ingredient (API).[8–12] There are only three cocrystals of ACV reported, but the stability of the cocrystals with respect to atmospheric humidity was not described.[13,14] Moreover, ACV–fumaric acid cocrystal that was reported earlier differs from the fumaric acid cocrystal reported herein. Although there is no definite structure reported by the previous authors, but by observing the PXRD pattern it is clear that the cocrystal reported earlier is different from ours. Probably the synthon formation via H-bonding is completely different from what we reported.

The aim of this study, therefore, was to rationally design and prepare a series of pharmaceutically acceptable ACV cocrystals, evaluate the stability of the cocrystals with respect to atmospheric humidity, and also to improve the physicochemical properties of ACV. Three dicarboxylic acids, viz. fumaric acid, malonic acid, and DL-tartaric acid, were selected as cocrystal formers. The dicarboxylic acids were selected as conformers from the view of crystal engineering. In the context of current crystal engineering experiment, the desired supramolecular interaction involved two hydrogen bonding viz. O–H···N and C–O···H forming ACV base–dicarboxylic acid heterodimer synthon (Scheme 1). Moreover, there was also possibility of formation of homo synthon between two ACV molecules via N–H···N hydrogen bonding interaction (Scheme 1). The following ACV cocrystals were prepared in this study: ACV/fumaric acid (cocrystal I), ACV/malonic acid (cocrystal II), and ACV/tartaric acid (cocrystal III). Although the formation of ACV/tartaric acid and ACV/fumaric acid was already reported,[13,14] but there is a lack of stability tests with respect to the atmospheric relative humidity (RH) and a systematic crystal engineering study.

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This article contains supplementary material available from the authors upon request or via the Internet at http://wileylibrary.com.

Journal of Pharmaceutical Sciences
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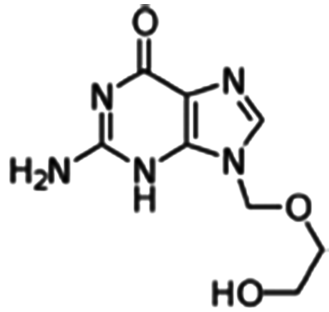
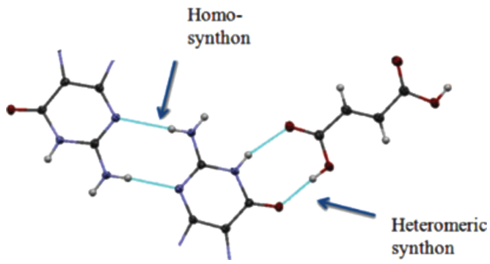


Figure 1. Chemical structure of acyclovir.



Scheme 1. Heteromeric synthon showing N–H···O and O–H···O hydrogen bonding interactions and homo-synthon showing N-H···O hydrogen bonding.

Two different approaches were employed to prepare cocrystals of ACV viz. solution evaporation and solvent drop grinding. Physical states of ACV cocrystals were characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). Formation of heterodimer and homo synthon was confirmed by the crystal structure of ACV–fumaric acid, determined by single crystal X-ray diffraction. For the three ACV cocrystals, the stability with respect to atmospheric RH was evaluated. Solubility and dissolution rates of the cocrystals were also evaluated and compared with those of parent ACV.

EXPERIMENTAL PROCEDURE

Materials

Apotex PharmaChem Inc. (Brantford, Ontario, Canada) donated 3:2 ACV: water hydrated form. Other chemicals were purchased from Sigma–Aldrich (London, Ontario) and were used as received. The anhydrous ACV was prepared by heating 3:2 ACV:water hydrated form at 180°C for an hour.[2,4,13]

Cocrystal I (1:1 ACV/Fumaric Acid)

This material was prepared by solution evaporation and grinding technique. Anhydrous ACV (225 mg, 1 mmol) and fumaric acid (116 mg, 1 mmol) after carefully weighing were dissolved in 10 mL of acetic acid in a sealed tube and heated at 100°C by a hot plate with constant stirring with a magnetic stirrer for 2 h. The solution was then filtered through 5 μm filter paper (VWR brand; VWR International Ltd., London, Ontario) to remove insolubles, and allowed to evaporate slowly at room temperature under a fume hood. The cocrystals were also obtained by grinding 1:1 stoichiometric amount of anhydrous ACV/fumaric acid with a mortar and pestle for 20 min with the addition of 5 drops from a pipette (ca. 0.1 mL) of methanol. The ground material was dissolved in water (10 mL) and kept for crystallization at room temperature. Single crystals of hydrated form of ACV–fumaric acid were obtained after 7 days and were analyzed by single crystal X-ray diffraction.

Cocrystal II (1:1 ACV/Malonic Acid)

The cocrystal of ACV/malonic acid was obtained only by solvent evaporation technique. Anhydrous ACV (225 mg, 1 mmol) and malonic acid (104 mg, 1 mmol) were dissolved in 10 mL of acetic acid and heated at 100°C on a hot plate with constant stirring using a magnetic stirrer for 2 h in a sealed tube. The filtered solution was then evaporated slowly at room temperature under a fume hood.

Cocrystal III (1:1 ACV/Tartaric)

This material was prepared both by solution evaporation and grinding technique. Anhydrous ACV (225 mg, 1 mmol) and DL-tartaric acid (116 mg, 1 mmol) after carefully weighing were dissolved in 10 mL of acetic acid in a sealed tube and heated at 100°C by a hot plate with constant stirring with a magnetic stirrer for 2 h. The solution was then filtered through 5 μm filter paper (VWR brand; VWR International Ltd.) to remove insolubles, and allowed to evaporate slowly at room temperature under a fume hood. The cocrystals were also obtained by grinding 1:1 stoichiometric amount of anhydrous ACV/DL-tartaric acid with a mortar and pestle for 20 min with the addition of 5 drops from a pipette (ca. 0.1 mL) of methanol.

Powder X-Ray Diffraction

The PXRD spectra were collected on a Rigaku-Miniflex benchtop X-ray powder diffractometer (Carlsbad, California) using CuKα ($\lambda = 1.54059$ Å) radiation obtained at 30 kV and 15 mA. The scans were run from 5.0° to 40.0° 2θ, increasing at a step size of 0.05° 2θ with a counting time of 2 s for each step. The diffractograms were processed using JADE 7.0 software. Calibration was performed using a silicon standard.

Single Crystal X-Ray Diffraction

Single crystals of ACV–fumaric acid were grown from a water solution at room temperature. The single crystal sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of 5682 reflections with $4.9° < 2\theta < 58.56°$. The frame integration was performed using SAINT.[15] The resulting raw data were scaled and absorption corrected, using a multiscan averaging of symmetry equivalent data using SADABS.[16]

The structure was solved by direct methods using the SIR2011 program.[17] Most of the non-hydrogen atoms were obtained from the initial solution. The remaining atomic positions were obtained from a subsequent difference Fourier map. The hydrogen atoms were introduced at idealized positions and were allowed to ride on the parent atom. The structural model was fit to the data using full matrix least-squares based on F^2. The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL-2013 program from the SHELX suite of crystallographic software.[18]

 DOI 10.1002/jps.24248

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