Preparation and Physicochemical Characterization of Acyclovir Cocrystals with Improved Dissolution Properties

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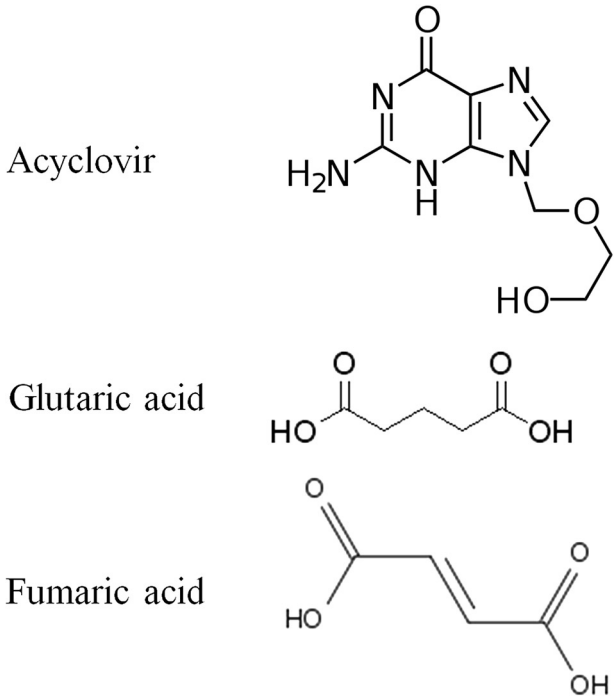
ABSTRACT: Acyclovir is a well-known antiviral agent. It can be administered in very high doses (from 200 to 1000 mg even three–four times daily). It has absorption problems mainly due to its poor solubility in water (about 0.2 g/100 mL at 25°C) and its oral bioavailability is approximately 15%–20% with a half-life of about 3 h. To improve acyclovir solubility and/or its dissolution properties, two cocrystals of this drug were successfully produced with glutaric acid (AGA1:1) and fumaric acid (AFA1:1) as conformers, using a cogrinding method. Their effective formation was investigated by a broad range of techniques: thermal analysis, Fourier transform infrared spectroscopy, X-ray powder diffraction, solid state nuclear magnetic resonance, and scanning electron microscopy coupled with energy dispersive X-ray spectrometry. The water solubility of the AGA1:1 cocrystal was not improved in comparison to acyclovir, while AFA1:1 showed a slight increased solubility at equilibrium. The main difference was detected in terms of intrinsic dissolution rates (IDR). The IDR of the new phases were much faster compared with acyclovir, particularly at neutral pH. AFA1:1 showed the most rapid dissolution behavior in water; within 10 min, the drug was released completely, while just 60% of acyclovir was dissolved in 1 h. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: Acyclovir; cocrystal; grinding; dissolution rate; solubility; glutaric acid; fumaric acid; calorimetry (DSC); solid state NMR; SEM-EDS

INTRODUCTION

Acyclovir {2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one}(Scheme 1) is a guanosine–analogue antiviral drug. It is one of the most commonly used antiviral drugs because of its selectivity and low cytotoxicity. It is primarily used for the treatment of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and varicella–zoster virus (VZV).[1,2] Acyclovir can be considered a prodrug: It is administered in an inactive form and is converted into two phosphorylated forms thanks to its affinity for the enzyme thymidine kinase, which is encoded by HSV and VZV.[3] The active triphosphate form is incorporated into viral DNA and stops its replication. This drug is commonly marketed as tablets (200, 400, and 800 mg and 1 g) and topical cream (5%) that is used primarily for labial herpes simplex. Furthermore, it is also administered intravenously as a bolus infusion of 5 mg kg^{-1} every 8 h, when high concentrations of drug are required, and as ophthalmic ointment (3%). Although acyclovir is one of the most important antiviral drugs, it has absorption problems due to its poor solubility in water (about 0.2% at 25°C). This factor negatively influences its oral bioavailability, which is approximately 15%–20%, with a short half-life of 2–3 h.[4–7]

Therefore, the aim of this study was to improve the physicochemical properties of acyclovir by cocrystal formation, a successful method to improve pharmaceutical properties of poorly soluble compounds.[8–15] Whereas the definition of the term cocrystal is still debated,[8,16,17] for the purpose of this work, we mean a cocrystal as a multicomponent crystalline solid containing stoichiometric amounts of discrete neutral molecular



Scheme 1. Chemical structures of acyclovir, GA, and FA.

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species that are solids under ambient conditions and interact by hydrogen bonds or other noncovalent and nonionic interactions. Cocrystals are similar to salts (ionic cocrystals), because both are solid forms that can be patented and are known to modulate important physicochemical properties such as solubility, stability, or biovailability. We must remember that more than half of all medicines are administered as salts, but this approach has some limitations compared with cocrystals. In fact, salt formation is confined to acid-base reaction, governed by an appropriate ΔpK_a value, while cocrystals offer a different pathway, where any pharmaceutical substance could potentially be cocrystallized without having ionizable groups. Furthermore, there is a greater number of potential nontoxic cocrystal formers (coformers) that can be used in cocrystallization.[9] The most important advantage of multicomponent systems, such as cocrystals, is that changes occurring in the crystal packing of the drug can lead to a variation of the physicochemical properties, such as melting point, stability, solubility, and dissolution rate, whereas the pharmacologic activity of the drug is generally not influenced. Because the hydrogen bond is the most common interaction, crystal formation can be rationalized considering the presence of hydrogen bonds donors and acceptors in the starting molecules. There are some basic functional groups able to generate strong and directional hydrogen bonds, such as carboxylic acids, amides, alcohols, and heterocyclic basis. Therefore, the presence of these functional groups in the structure of the cocrystallized substances may lead to the formation of supramolecular synthons.

Most cocrystals are prepared using "green methods" as solvent drop grinding or dry grinding, in which the solvent is either used in small quantities or not used at all.[8] Solid-state reactions activated by grinding are known as mechanochemical reactions. These processes appeared in the scientific literature more than 160 years ago, and today they represent an attractive alternative to solution processes for solvent-free preparation of supramolecular aggregates, cocrystals, and coordination networks.[18–20] The possibility of using a solvent-free method is very important because it offers a fast, easy, and no-waste methodology for the processing of existing compounds. Indeed, using the method of crystallization from solution, a suitable solvent in which each component is soluble must be identified so that a large number of screening experiments must be carried out. On the contrary, in the solid-state grinding, the experimental burden may be strongly reduced.[18,21]

The improvement of the physicochemical properties of acyclovir by means of solvent-free cocrystallization is the aim of this article. A cocrystal screening process was performed with several coformers [succinic acid, sorbic acid, glutaric acid (GA), fumaric acid (FA), salicylic acid, and L-tartaric acid] possessing functional groups able to generate H-bond motifs (supramolecular heterosynthons) with the drug. The carbonyl and aminic groups, nitrogen atoms of the purine ring, and the alcoholic function of the acyclovir molecule are particularly suitable for supramolecular heterosynthon formation with carboxylic groups of these coformers.

Cocrystals were found using only GA and FA (Scheme 1) as the coformers. The resulting binary systems were characterized using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), Fourier infrared spectroscopy (FT-IR), solid-state NMR (SSNMR), and scanning electron microscopy coupled with the energy dispersive X-ray spectrometry (SEM-EDS).[10,22] In particular, FT-IR and NMR were used to elucidate the hydrogen-bonding motifs.

The new phases obtained were further characterized in terms of solubility and dissolution rate in comparison to the starting active principle. Acyclovir solubility is pH dependent (more soluble at lower pH), while an improvement of the dissolution rate, particularly at neutral pH, may enhance drug disposition even when the gastric fluid pH is increased by the presence of food.

EXPERIMENTAL

Materials

Acyclovir (A) was donated by Solchem Italiana S.p.A. (Lodi, Italy) and the coformers were obtained from the Sigma–Aldrich Company (Milan, Italy). Among the selected coformers (succinic acid, sorbic acid, glutarico acid, fumaric acid, salicylic acid, and L-tartaric acid), only glutaric acid and fumaric acid gave interesting results that will be presented in the following.

The binary systems were prepared through dry grinding: Drug and coformer in a molar ratio 1:1 were ground in a planetary mill (Pulverisette 7, Fritsch, Germany) at a rate of 20 g with 50 agate balls (5 mm diameter). DSC measurements put into evidence that the grinding time required for the complete reaction between the components and the formation of pure cocrystals with glutaric acid (AGA1:1) and fumaric acid (AFA1:1) was 12 h.

Instruments

Thermal Analysis

Thermal characterization was carried out using a TGA Q2000 IR apparatus and a DSC Q2000 apparatus both interfaced with a TA 5000 data station (TA Instruments, New Castle, Delaware). The DSC instrument was calibrated using ultrapure (99.999%) indium (melting point = 156.6°C; $\Delta H = 28.54$ J g^{-1}) as standard. The calorimetric measurements were carried out in open standard aluminium pans under nitrogen flow (45 mL·min^{-1}) at 10 K·min^{-1}. All data from thermal measurements are the average of three or more experiments.

Spectroscopic Techniques

Fourier transform infrared spectra were obtained using a Nicolet FT-IR iS10 spectrometer (Nicolet, Madison, Wisconsin) equipped with attenuated total reflectance sampling accessory (Smart iTR with ZnSe plate) by coadding 256 scans in the 4000–650 cm^{-1} range at 4 cm^{-1} resolution.

X-Ray Powder Diffraction

X-Ray Powder Diffraction measurements were performed using a D5005 Bruker diffractometer (Karlsruhe, Germany) (CuKα radiation, $\lambda(K\alpha_1) = 1.54056$ Å; voltage of 40 kV and current of 40 mA) equipped with a θ–θ vertical goniometer, Ni filter, monochromator, and scintillator counter. The patterns were recorded at room temperature in step-scan mode (step size: 0.020°, counting time: 3 s per step) in the $5 < 2\theta^\circ < 35$ angular range.

Solid-State NMR

The SSNMR spectra were acquired on a 400-MHz spectrometer (Avance III, Bruker) based on a wide-bore 9.4 T magnet

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