Polymorphism in Sulfadimidine/4-Aminosalicylic Acid Cocrystals: Solid-State Characterization and Physicochemical Properties

CHRISTINE GROSSJOHANN,[1] DOLORES R. SERRANO,[1] KRZYSZTOF J. PALUCH,[1] PETER O'CONNELL,[1] LIANA VELLA-ZARB,[2] PANAGIOTIS MANESIOTIS,[3] THOMAS MCCABE,[4] LIDIA TAJBER,[1] OWEN I. CORRIGAN,[1] ANNE MARIE HEALY[1]

[1]School of Pharmacy and Pharmaceutical Sciences, Panoz Institute, Trinity College Dublin, Dublin, Ireland
[2]Department of Chemistry, University of Malta, Msida, Malta
[3]Pharmaceutical and Molecular Biotechnology Research Centre, Waterford Institute of Technology, Waterford, Ireland
[4]School of Chemistry, Trinity College Dublin, Dublin, Ireland

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ABSTRACT: Polymorphism of crystalline drugs is a common phenomenon. However, the number of reported polymorphic cocrystals is very limited. In this work, the synthesis and solid-state characterization of a polymorphic cocrystal composed of sulfadimidine (SD) and 4-aminosalicylic acid (4-ASA) is reported for the first time. By liquid-assisted milling, the SD:4-ASA 1:1 form I cocrystal, the structure of which has been previously reported, was formed. By spray drying, a new polymorphic form (form II) of the SD:4-ASA 1:1 cocrystal was discovered which could also be obtained by solvent evaporation from ethanol and acetone. Structure determination of the form II cocrystal was calculated using high-resolution X-ray powder diffraction. The solubility of the SD:4-ASA 1:1 cocrystal was dependent on the pH and predicted by a model established for a two amphoteric component cocrystal. The form I cocrystal was found to be thermodynamically more stable in aqueous solution than form II, which showed transformation to form I. Dissolution studies revealed that the dissolution rate of SD from both cocrystals was enhanced when compared with a physical equimolar mixture and pure SD. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: polymorphism; sulfadimidine; 4-aminosalicylic acid; cocrystals; spray drying; milling; solid state; dissolution; solubility

INTRODUCTION

New pharmaceutical approaches are demanded to enhance the productivity of the pharmaceutical industry, which is witnessing an oncoming crisis because of the combined effects of increasing costs for R&D, several blockbuster drugs falling off the patent cliff, decreasing numbers of drugs being approved by the regulatory agencies, and numerous drug candidates in the pipeline with poor aqueous solubility.[1,2] The use of salt formation as an approach to improve drug solubility is not always a successful alternative, especially when molecules have no ionizable functional groups or when they are prone to degradation. Engineering of pharmaceutical cocrystals can be an attractive approach for the pharmaceutical industry, as they offer multiple possibilities to modify the physicochemical properties of an active pharmaceutical ingredient (API) without creating or breaking covalent bonds while still maintaining the intrinsic activity of the drug molecule.[3,4] A major advantage of cocrystal formation is the possibility of transforming a crystalline API into a solid form that exhibits a higher dissolution rate, comparable to that obtained with the amorphous form, while at the same time maintaining the long-term physical and chemical stability of the crystalline API.[5]

Pharmaceutical cocrystals are generally formed from an API and one or more pharmaceutical compounds (generally regarded as safe—GRAS) known as cocrystal formers or coformers. Molecules that contain multiple hydrogen bond donor and acceptor functions allow for the formation of a diverse range of stable supramolecular motifs in solution, and thereafter the opportunity of cocrystal engineering.[6] Reaction crystallization techniques and grinding are common strategies to produce cocrystals in pharmaceutical companies. Nevertheless, spray drying, a well-established scale-up technique, can be considered as a novel approach in which pure cocrystals can be formed.[7]

In spite of the fact that newer antimicrobial drugs have displaced many sulfonamides, their low cost and relatively high efficiency against common bacterial diseases means that they still enjoy relatively widespread use, especially in developing countries.[6] Based on the multiple hydrogen bond donor and acceptor groups of sulfadimidine (SD), cocrystal engineering can be used as an approach, not only to improve its physicochemical properties, but also to exploit a synergistic effect when combined with coformers such as 4-aminosalicylic acid (4-ASA), which possesses anti-inflammatory properties[8] and antibacterial activity, like SD.[9] The formation of the cocrystal composed of one molecule of SD and one molecule of 4-ASA by the solvent evaporation method has been reported by Caira in 1992.[9] The hypothesis supporting this work is that spray drying may be used as an alternative production method to prepare the SD:4-ASA cocrystal. The main objective in this study was to investigate cocrystal formation between SD and 4-ASA by grinding, in the form of dry and liquid-assisted milling and by spray drying, followed by comparative solid-state characterization and analysis of the physicochemical properties and dissolution profiles of the cocrystal forms prepared.

Correspondence to: Anne Marie Healy (Telephone: +353-1-896-1444; Fax: +353-1-896-2810; E-mail: healyam@tcd.ie)

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MATERIALS

Sulfadimidine and 4-ASA were purchased from Sigma–Aldrich (Wicklow, Ireland) with a purity ≥ 99%. Ethanol and acetone were supplied from Corcoran Chemicals (Dublin, Ireland). Methanol, HPLC grade, was purchased from Fisher Scientific (Dublin, Ireland), potassium hydrogen phosphate was obtained from Sigma–Aldrich (Wicklow, Ireland) and phosphoric acid from Merck (Darmstadt, Germany). Water, analytical and HPLC grade, was prepared from an Elix 3 connected to a Synergy UV system (Millipore, Feltham, UK). All other chemicals purchased from commercial suppliers were of analytical grade.

METHODS

Preparation of Cocrystals and Physical Mixture of SD:4-ASA

Grinding (Dry and Liquid-Assisted Milling)

Dry and liquid-assisted comilling was carried out for different molar ratios of SD:4-ASA (1:2, 1:1, 2:1) in a Retsch PM100 planetary ball mill (Haan, Germany) using three stainless steel balls in each milling jar (50 mL). A maximum of 2.5 g of sample mass was used. In the case of liquid-assisted milling, five drops of ethanol were added to the solid mix prior to milling using a 3.5 ml disposable transfer pipette (Fisher Scientific, Dublin, Ireland). The milling was carried out at room temperature for 15, 30, and 45 min at a rotation speed of 400 rpm. For the milling time of 45 min, the milling process was stopped after 30 min for 10 min in order to avoid a high temperature in the jar and thus the risk of melting/decomposition of the compounds.

Spray Drying

Spray drying was performed using a Büchi B-290 Mini Spray Dryer connected to a compressor (HaughTM SO 45E2 ASY) operating in the open-mode. Solution concentrations of 1% (w/v) of SD:4-ASA in 1:2, 1:1, and 2:1 molar ratio were prepared using ethanol. The solutions were delivered to a 2-fluid atomization nozzle using a peristaltic pump at a speed of 30% (9–10 mL/min) and the aspirator was operated at 100%. The flowmeter for the standard 2-fluid nozzle was set at 4 cm which is equivalent to 473 NL/h (Büchi Labortechnik, Flawil, Switzerland). The inlet temperature was fixed at 78°C and the appropriate outlet temperature varied between 50°C and 57°C.

Crystallization from Solution

Sulfadimidine and 4-ASA in 1:1 molar ratio were dissolved in 20 mL of hot ethanol and acetone. The solution was covered with an aluminum foil in which a syringe needle (0.3×12 mm^2; Sterican®) was inserted and left for slow evaporation of the solvent, while maintaining the elevated temperature of the solution using an oil bath (70°C).

Physical Mixture

4-ASA and SD in 1:1 molar ratio were manually mixed using a mortar and pestle.

Solid-State Characterization

Powder X-ray Diffraction

Powder X-ray analysis was performed using a Miniflex II Rigaku diffractometer with Ni-filtered Cu Kα radiation (λ = 1.54 Å). The tube voltage and tube current used were 30 kV and 15 mA, respectively. Each sample was scanned over a 2θ range of 5°–40° with a step size of 0.05°/s. The program Mercury 2.3[10] was used for calculation of X-ray powder patterns on the basis of the single crystal structure.

Thermal Analysis

Differential Scanning Calorimetry. Differential scanning calorimetry (DSC) was performed using a Mettler Toledo DSC 821e instrument under nitrogen purge. Sample powders (3–5 mg) were placed in aluminum pans, sealed, pierced to provide three vent holes, and heated at a rate of 10°C/min in the temperature range of 25°C–225°C.[11]

Thermogravimetric Analysis. Thermogravimetric analysis (TGA) was performed using a Mettler TG 50 module. Samples were placed into open aluminum pans (5–7 mg) and analyzed at a constant heating rate of 10°C/min under nitrogen purge.[11]

Attenuated Total Reflection–FTIR Spectroscopy

IR spectra were recorded on a PerkinElmer Spectrum 1 FT-IR Spectrometer equipped with a UATR and a diamond/ZnSe crystal accessory. Each spectrum was scanned in the range of 650–4000 cm^{-1} with a resolution of 4 cm^{-1} and a minimum of six scans were collected and averaged in order to gain good quality spectra. Data were evaluated using Spectrum v 5.0.1. software.

Solid-State Nuclear Magnetic Resonance Spectroscopy

All measurements were performed using a broadband 3.2 mm solid-state nuclear magnetic resonance (ssNMR) probe and a 400 MHz JEOL ECX400 spectrometer. Samples were prepared by packing an adequate amount of each sample, as received, into 3.2 mm Silicon nitride (Si3N4) ssNMR rotors. The sample spinning rate was set to 10 kHz. ^{13}C NMR spectra (100 scans) were recorded using the CPMAS (Cross Polarization – Magic Angle Spinning) pulse sequence. Prior to each spectrum, the corresponding T_1 constant (spin–lattice relaxation) was measured using the saturation recovery pulse sequence.

Elemental Analysis

Elemental analysis was carried out using an Exeter Analytical CE440 CHN analyzer. The molar amount of carbon as carbon dioxide, nitrogen, as nitrogen oxide and hydrogen as water, was determined by oxidation of the sample (n = 3, around 10 mg) and the thermal conductivity analysis of obtained gases and water vapor.

Cocrystal Structural Determination

Powder X-ray Diffraction for Structure Determination

Powder X-ray diffraction (PXRD) patterns were recorded at room temperature on a Bruker D8 ADVANCE high-resolution laboratory X-ray powder diffractometer using Cu-Kα1 radiation from a primary Ge(111)-Johansson-type monochromator and a Våntec position-sensitive detector (PSD) in Debye–Scherrer geometry. Data collection spanned over 20 h, covering a range of 2° to 65° along 2θ in steps of 0.008° with a 6° opening of the PSD. The sample (crystals obtained by crystallization from solution, see section *Crystallization from Solution*) was spun during measurement to ensure better particle statistics. Structure determination and refinement of powder data were carried out using

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