PHARMACEUTICS, PREFORMULATION AND DRUG DELIVERY

Physicochemical, Crystallographic, Thermal, and Spectroscopic Behavior of Crystalline and X-ray Amorphous Ciclesonide

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ABSTRACT: Single crystal structure experiments revealed that the orthorhombic needles of Ciclesonide crystallized in $P2_12_12_1$ space group with four independent molecules in the unit cell. Amorphous Ciclesonide was prepared by lyophilization and characterized in comparison with crystalline material by differential scanning calorimetry (DSC), Fourier transformed (FT)-Raman spectroscopy, powder X-ray diffraction, dissolution, and saturation solubility experiments. Significant differences in the dissolution, thermal, and spectrometric behavior were observed for both solid-state phases. DSC- and FT-Raman methods for the determination of amorphous content in crystalline Ciclesonide samples were established. Isothermal and dynamical recrystallization studies on amorphous Ciclesonide were conducted using dispersive hot-stage Raman microscopy. The recrystallization was observed to be a two-step process with an induction period (most likely nuclei formation) followed by the actual recrystallization (crystal growth). The recrystallization rate constants and Avrami exponents ($n = 2$) were determined from the isothermal experiments at various temperatures using Johnson–Mehl–Avrami theory. Isothermal activation energies were obtained from Arrhenius plots using the temperature dependence of (a) the rate constants (160.4 kJ/mol) and (b) the induction time (140.9 kJ/mol) of the isothermal hot-stage experiments. J Pharm Sci 97:3765–3780, 2008

Keywords: Ciclesonide; crystal structure; amorphous; recrystallization; Avrami kinetics; dissolution behavior; differential scanning calorimetry (DSC); FT-Raman spectroscopy; dispersive Raman hot-stage microscopy

INTRODUCTION

A major issue in pharmaceutical sciences today is to increase the dissolution rate and bioavailability of poorly soluble drugs. A possible approach is the use of dosage forms containing amorphous material of the active ingredient,[1–4] which possesses a higher dissolution rate and apparent solubility than its crystalline counterpart.[5] The amorphous state, however, is thermodynamically metastable,

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thus amorphous systems tend to spontaneous transformations into the crystalline state.[6–8] This can be very critical for the pharmaceutical product, as the bioavailability and therefore also the product efficacy may be affected in case that the recrystallization process occurs during the shelf-life of the product. It also has to be taken into consideration that the use of amorphous material might have a crucial impact on other physico-chemical parameters of the compound such as the hygroscopicity, mechanical, and flow parameters as well as chemical stability in the solid state.[9] For these reasons it is necessary to establish suitable analytical and spectroscopic methods for the detection, characterization, and quantification of amorphous materials. Up to now many techniques have been described in the literature for the detection and quantification of amorphous content as well as for the characterization of the isothermal and non-isothermal recrystallization behavior of compounds in the amorphous state. Powder X-ray diffraction,[10] near IR-[11] or Fourier transformed (FT)-Raman spectroscopy,[9] microcalorimetry,[12,13] solution calorimetry,[14] differential scanning calorimetry (DSC),[15–17] and gravimetry[18] were successfully applied to study such systems.

In this study, we investigated crystalline and amorphous Ciclesonide (refer to Fig. 1) by means of single crystal and powder X-ray diffraction, DSC, FT-Raman spectroscopy, and dispersive hot-stage Raman microscopy. The dissolution behavior in water at 37°C of both crystalline and X-ray amorphous Ciclesonide was studied in order to demonstrate the impact of amorphicity on physicochemical properties.

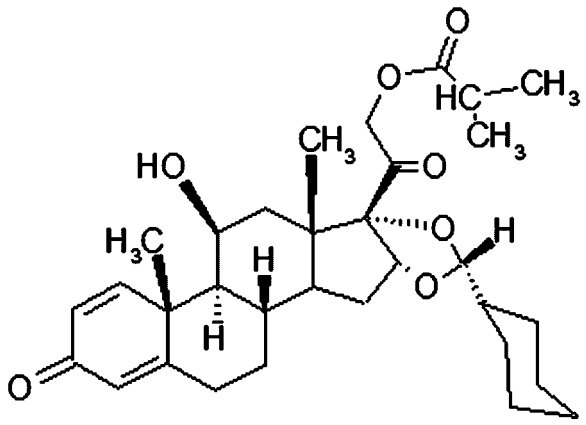

Figure 1. Chemical structure of 16,17-[(cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-pregna-1,4-diene-3,20-dione[11β,16α(R)] (Ciclesonide).

FT-Raman and DSC methods for the quantification of amorphous content in "crystalline" Ciclesonide batches were established and tested in a comparative manner.

Finally the isothermal recrystallization kinetics of amorphous Ciclesonide was studied in detail using dispersive hot-stage Raman microscopy, a method rarely used for the investigation of such phenomena. Johnson–Avrami–Mehl theory has been applied to determine the crystallization rate constants. Activation energies were obtained from Arrhenius analysis of the data.

EXPERIMENTAL PART

Single Crystal X-ray Diffraction

A crystal ($0.8 \times 0.015 \times 0.01$ mm^3) was measured at $T = 298(2)$ K on a Stoe IPDS diffractometer using the Mo-Kα radiation ($\lambda = 0.71073$ Å). The measured theta range was 1.90°–24.39°. All crystallographic calculations were carried out using the SHELXLT program package, refinement was carried out using the full-matrix least squares method.[19] The positions of the hydrogen atoms were refined isotropically. This gave a goodness-of-fit of 0.764 and the following R-values ($I > 2\sigma(I)$): R1 = 0.0494, wR2: 0.0896.

Crystallographic data for the structure analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 656903. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB21EZ UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk www://www.ccdc.cam.ac.uk).

FT-Raman Spectroscopy

FT-Raman spectra were recorded on a Bruker Optics RAM II module, which was coupled to a Bruker Optics Vertex 70 FT-IR spectrometer. The RAM II module was equipped with a liquid nitrogen cooled high sensitivity germanium detector (D-418 TF) and a diode pumped 500 mW Nd:YAG laser (wavelength: 1064 nm). Data acquisition and analysis were performed using the software package OPUS 5.4 from Bruker Optics. For each spectrum 512 scans were collected in 180° reflection mode using a spectral resolution of 2 cm^{-1} in order to provide Raman spectra with a low S/N ratio in combination with well-resolved Raman signals. To avoid heating of the colorless samples the laser power was set to a