Journal of Pharmaceutical Analysis 6 (2016) 179–183

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Journal of Pharmaceutical Analysis

journal homepage: www.elsevier.com/locate/jpa
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Original Article

Monitoring real time polymorphic transformation of sulfanilamide by diffuse reflectance visible spectroscopy ☆

Tracy O. Ehiwe [a], Bruce D. Alexander [a], John C. Mitchell [a,*], Martin J. Snowden [a], Laura J. Waters [b]

[a] Medway Centre for Formulation Science, Faculty of Engineering and Science, University of Greenwich at Medway, Chatham Maritime, Kent ME4 4TB, UK
[b] School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK

ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form
17 December 2015
Accepted 18 December 2015
Available online 8 January 2016

Keywords:
Polymorphic transformation
Sulfanilamide
Diffuse reflectance visible spectroscopy
Powder X-ray diffraction
Differential scanning calorimetry

ABSTRACT

This study investigated the development of a novel approach to surface characterization of drug polymorphism and the extension of the capabilities of this method to perform 'real time' in situ measurements. This was achieved using diffuse reflectance visible (DRV) spectroscopy and dye deposition, using the pH sensitive dye, thymol blue (TB). Two polymorphs, SFN-β and SFN-γ, of the drug substance sulfanilamide (SFN) were examined. The interaction of adsorbed dye with polymorphs showed different behavior, and thus reported different DRV spectra. Consideration of the acid/base properties of the morphological forms of the drug molecule provided a rationalization of the mechanism of differential coloration by indicator dyes. The kinetics of the polymorphic transformation of SFN polymorphs was monitored using treatment with TB dye and DRV spectroscopy. The thermally-induced transformation fitted a first-order solid-state kinetic model (R^2=0.992), giving a rate constant of 2.43×10^{-2} s^{-1}.

1. Introduction

Polymorphic transformations can have a significant influence on the processing and storage of crystalline powders. Change in crystalline structure affects the therapeutic effectiveness and stability of drug products; therefore, the ability to monitor the effect of process stages on drug polymorphic transformation is crucial in drug manufacture [1]. The transformation from one polymorphic form to another can be thermally, mechanically or moisture-induced.

Solid-state phase (polymorphic) transformations are generally based on overlapping mechanisms of nucleation, growth and impingement [2,3]. Solid-state kinetic evaluation typically involves modeling the fraction transformed as a function of time.

Eq. 1 represents a generic integral rate equation for solid-state kinetics:

$$g(a) = kt \quad (1)$$

where g is a function of the extent of reaction, a is the fraction of phase transformed or extent of growth of new phase, k is the rate constant, and t is time. The kinetics of the phase transformation is heterogeneous in nature, which suggests that several factors affect the kinetics of transformation including activation energy of nucleation and growth, difference in the crystal imperfections, particle size and particle morphology, and variation in growth rate along crystallographic axes. These factors contribute to the development of different models used in the characterization of the kinetics of solid-state phase transformation resulting in acceleratory, deceleratory, linear or sigmoidal shapes for their respective isothermal α-time curves [3,4].

A variety of techniques have been employed to characterize the kinetics of polymorphic transformation in situ. Examples include near infrared spectroscopy (NIR) [5,6], vibrational spectroscopy [7,8], powder X-ray diffraction (PXRD) [9] and temperature-controlled simultaneous small/wide angle X-ray scattering [10]. Previous reports also include the study of the thermodynamics of the conversion of sulfanilamide (SFN) polymorphs by energy dispersive X-ray diffraction [11]. Monitoring processes, especially by in situ methods including diffuse reflectance visible (DRV) spectroscopy, offer a better understanding of the intrinsic properties of systems, thus improving process control [12].

This study reports on a novel 'real time' method for monitoring thermally induced conversion of polymorphs using DRV spectroscopy and kinetic evaluation of the generated data. Polymorphs of SFN were examined. The two polymorphs (SFN-β and SFN-γ) studied are enantiotropically related and the conversion of SFN-β to SFN-γ can be induced at elevated temperatures. Although other reports on the analysis of polymorphs include the use of NIR [5,6]

☆Peer review under responsibility of Xi'an Jiaotong University.
* Corresponding author.
E-mail address: J.Mitchell@Greenwich.ac.uk (J.C. Mitchell).

http://dx.doi.org/10.1016/j.jpha.2015.12.002

and vibrational spectroscopy [7,8], we have used DVR spectroscopy as the technique of choice for this study. We have experience in using DRV spectroscopy for the differentiation of crystalline and amorphous forms of carbohydrate pharmaceutical excipients, and in this study, we explored the extension of the sensitivity, simplicity of operation and ease of data analysis of this technique to more complex active pharmaceutical ingredients. Furthermore, initial attempts to monitor polymorphic interconversion using Raman spectroscopy was proved ineffectively.

2. Experimental

2.1 Chemicals and preparation

SFN-β was prepared by recrystallization in water. Commercial sulfanilamide (> 99.0%) from Sigma Aldrich (Dorset, England) was dissolved in hot water (at 100 °C) and left to cool to ambient temperature (23.5 °C). SFN-β was filtered under suction and dried over calcium chloride in a desiccator. SFN-γ was obtained from recrystallized SFN-β that was heated at 140 °C for 2 h. All polymorphs were stored in a desiccator over calcium chloride (0% RH) prior to analysis to eliminate moisture-induced transformations.

2.2 Instrumentation

Philips PW1729 Powder X-ray diffractometer experiments were carried out with a PW1050 goniometer (Lelyweg, Netherlands). Differential scanning calorimetry (DSC) was performed on a Mettler Toledo FP85 DSC system (Greifense, Sweden). Raman spectroscopy was carried out on a Thermo-Nicolet NXR FT-Raman 9610 spectrometer (Wisconsin, USA). DRV spectroscopy was performed on a Hewlett-Packard 8453 photodiode Array UV–vis Spectrophotometer (California, USA) equipped with a Labsphere RSA-HP-8453 diffuse reflectance accessory (Illinois, USA). Hot-stage microscopy was preformed using a Leica optical microscope (Wetzlar, Germany) fitted with a Mettler FP52 hot stage apparatus (Greifense, Switzerland).

Single crystal data for all polymorphs obtained from the Cambridge Crystal Structural Database (CCSD Codes, SFN β SULAMD03 [13] and SFN γ SULAMD02 [14]) were imputed into the Reflex module of Materials Studio 5.0 software program from Accelrys (San Diego, USA) to obtain simulated powder X-ray data and Miller indices for all reflections.

A full description of the DRV spectroscopy methodology can be found in a previous report by Major, et al. [15].

3. Results and discussion

3.1 Preparation and characterization of SFN-β and SFN- γ polymorphs and SFN-β-TB and SFN-γ-TB

In this study two polymorphs of SFN were examined. The two polymorphs, SFN-β and SFN-γ studied, are enantiotropically related and the conversion of SFN-β to SFN-γ can be induced at elevated temperatures, making them good candidates for 'real time' polymorphic interconversion.

The two polymorphs of SFN (β and γ forms) were prepared and analyzed using X-ray diffraction and scanning calorimetry. Four polymorphs of SFN have been recorded, but β and γ are more accessible. The β form is the most stable form under ambient conditions.

The experimental and simulated PXRD patterns for SFN-β and SFN- γ polymorphs are shown in Fig. 1. The PXRD patterns are different and show defined and sharp peaks which are indicative

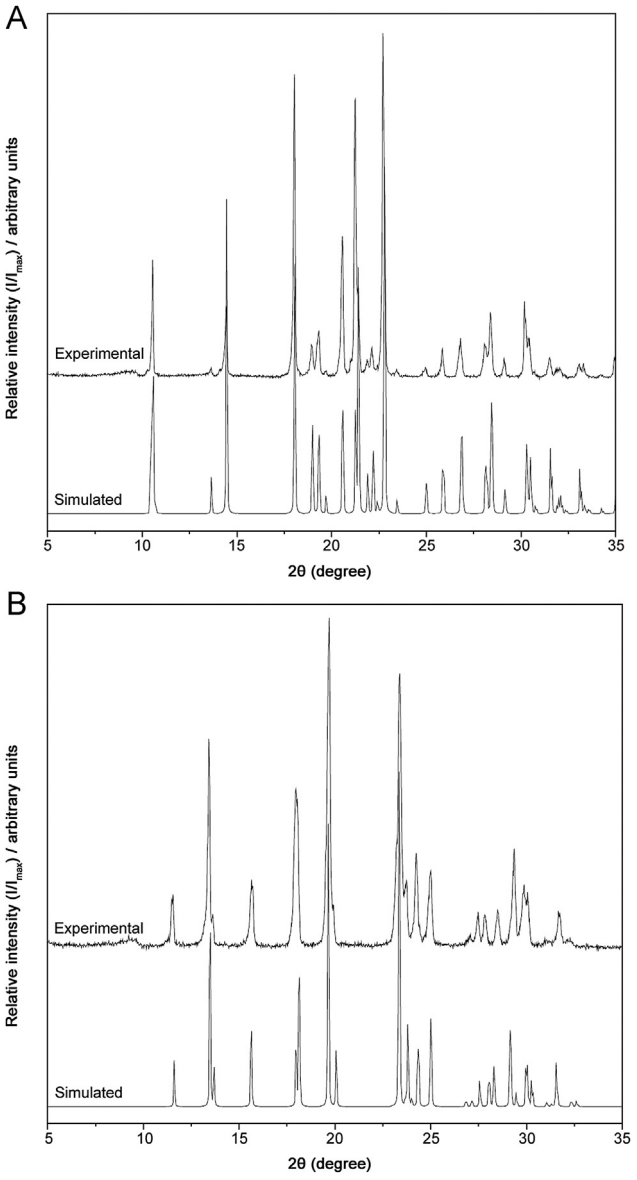

Fig. 1. PXRD patterns for (A) SFN-β and (B) SFN-γ.

of their crystalline nature. Experimental 2theta angles agree within ±0.20° of simulated data confirming polymorphic purity; however, peak intensities vary significantly as a result of preferred orientation of several atomic planes to incident X-ray beam.

The thermal behaviors of SFN polymorphs were also analyzed. DSC-thermograms show a single endothermic event for SFN-γ (T_f = 162.3 ± 0.3 °C and ΔH_f = 146.0 ± 1.0 J/g) attributed to melting. However, three endothermic transitions T_f = 128.3 ± 1.3 °C, ΔH_f = 6.9 ± 3.0 J/g; T_f = 156.0 ± 1.3 °C, ΔH_f = 1.33 ± 0.5 J/g; and T_f = 162.3 ± 0.3 °C, ΔH_f = 121.0 ± 3.5 J/g , were observed for SFN-β attributable to incomplete β→γ transformation, melting of residual SFN-β and melting of SFN-γ, respectively.

Dye deposition was achieved using drop-wise addition of 1 mL of methanolic dye solution (200 mg/L) of thymol blue (TB) directly onto 2 g of solid carefully homogenized using a spatula and dried. The typical amount of dye adsorbed per gram of solid was 0.1 mg, which corresponds to the limit of detection of adsorbed dye by the DRV instrument for most of the investigated polymorphic systems. Three separate sample preparations and DRV spectroscopic measurements were conducted for each polymorph. SFN-β was always air-dried as oven-drying sometimes introduced SFN-γ impurity.