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Identification and quantitative determination of eletriptan hydrobromide polymorphs: Thermal, diffractometric and spectrometric studies

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Abstract

The quantitative characterisation of the solid form of drug substances and drug products is gaining importance due to product quality and performance that is based on stringent regulatory guidelines. Therefore, in this study, thermal, X-ray diffraction and spectroscopic methods were evaluated to obtain a simple, quick and precise method for the quantitative analysis of binary mixtures of eletriptan hydrobromide polymorphs in powder form. The two polymorphs are discernible using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). Quantitative methods using each technique were developed and validated using spiked standards prepared by geometrical mixing of the pure polymorphs. The estimated limit of detection values of the methods using DSC, PXRD and DRIFTS were determined to be 0.24%, 2.01% and 2.06%, respectively. A careful evaluation of the validation results from the three methods indicated that DSC performed better than PXRD and DRIFTS. The DSC method was determined to be the best alternative to PXRD and DRIFTS due to its measurement capability, simplicity, cost effectiveness and quickness. The real-time sample batch analysis was performed, and the advantages and applications of the study are discussed.

Keywords: Polymorphs; Quantification; Powder X-ray diffraction; Differential scanning calorimetric; Diffuse reflectance infrared Fourier transform spectroscopy

1. Introduction

Polymorphism occurs when a pure chemical compound exists in two or more structural orientation with different physical properties. Because different polymorphs exhibit different physical properties, such as density, melting point and solubility, polymorph characterisation is important in the manufacture of chemicals, especially pharmaceuticals. The production of redundant or impure polymorphs yields a product that is not useful for the desired purpose. Identification and quantification of polymorphic forms is required in the production of pharmaceuticals [1,2]. Various problems may arise due

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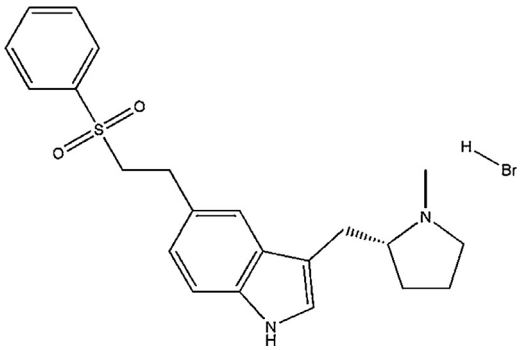

Fig. 1. Molecular structure of eletriptan hydrobromide.

to the differences in the flow properties, compatibility, crystal morphology, water uptake properties and processability of the different forms [3,4]. The appearance or disappearance of a redundant crystalline form during process development can lead to detrimental results during manufacturing or storage of the dosage form [5–7]. Therefore, the polymorphs need to be characterised during the beginning stage of drug development [8].

Many techniques are available for the analysis and quantification of polymorphic mixtures. Powder X-ray diffraction [9,10], diffuse reflectance infrared spectroscopy [11,12], Raman spectroscopy [13–15] and differential scanning calorimetric [16,9] have been extensively used to quantify polymorphic mixtures with methods ranging from univariate correlations to multivariate chemometric approaches.

A migraine is a neurovascular headache, and migraines are characterised by recurrent headaches that typically last from 4 to 72 h. Simple analgesics and non-steroidal anti-inflammatory drugs are useful if taken at the earliest signs of the attack. Eletriptan hydrobromide, which is intended for the treatment of migraine headaches, is known to exist as α and β-polymorphs. Attacks not responding to simple analgesics or non-steroidal anti-inflammatory drugs may be treated with selective serotonin (5HT1) agonists, such as eletriptan [17,18] (Fig. 1).

The crystal structures of eletriptan α and β polymorphs have been reported, and the polymorphs exhibit conformational polymorphism where the β form is less stable than the α form [19]. To the best of our knowledge, no efforts have been made to quantify the α and β mixtures of eletriptan. In this study, a quantification model for binary mixtures was developed using DSC, PXRD and DRIFTS, and the advantage of DSC over PXRD and DRIFTS are discussed based on the results from a real sample.

2. Materials and methods

Eletriptan α- and β-polymorphs were obtained from PharmaTrain (Hyderabad, India) and confirmed using DSC, PXRD and DRIFTS. The eletriptan α and β-polymorphs and their required concentrations for quantification using DSC, PXRD and DRIFT were prepared by accurately weighing the material on highly sensitive microbalances (i.e., Mettler Toledo XP2U, Max 2.1 g-Min 1 μg and Mettler Toledo MX5, Max 5.1 g-Min 1 μg). Potassium bromide (KBr) was obtained from Merck (Darmstadt, Germany).

2.1. Differential scanning calorimetry (DSC)

A Mettler Toledo DSC 831^e with the STARe software was used for recording and processing the DSC thermograms of the eletriptan α and β-polymorphs. To identify and quantify the two forms, approximately 5 mg of the individual polymorphs and their mixtures were accurately weighed and heated in a closed aluminium pan at a programmed heating rate of 25 °C/min in a temperature range from 100 °C to 210 °C under a nitrogen flow at 40 ml/min. An empty aluminium pan was used as a reference.

2.2. X-ray powder diffraction (XRD) analysis

The X-ray powder diffraction patterns were collected at room temperature on a Bruker D8 advance X-ray diffractometer with a Cu anode and Lynx eye detector. The instrument was calibrated for the peak position and relative intensity using the Corundum standard (i.e., NIST traceable, standard reference material number 1976a). To identify the polymorphs, the eletriptan α and β polymorphs were scanned from 3° 2θ to 45° 2θ with step size of 0.01° 2θ and a time per step of 0.1 s. After selecting the non-interfering peak for quantification, the patterns were collected from 5° 2θ to 10° 2θ with step size of 0.01° 2θ and a time per step of 0.9 s. The instrument was operated at a generator voltage of 40 kV and a generator current of 40 mA. A variable divergent slit and an anti-scattering slit were used for V_{20} mm, and a nickel filter was used in the secondary beam path. The spiked concentrations were scanned in the selected range using the instrumental parameters mentioned in the PXRD analysis. The Eva software was used for data processing and evaluation.