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Quantitative analysis of less soluble form IV in commercial carbamazepine (form III) by diffuse reflectance fourier transform spectroscopy (DRIFTS) and lazy learning algorithm

K. Kipouros, K. Kachrimanis *, I. Nikolakakis, S. Malamataris

Department of Pharmaceutical Technology, School of Pharmacy, University of Thessaloniki, Thessaloniki 54124, Greece

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Abstract

Carbamazepine is a poorly soluble drug, with known bioavailability problems related to its polymorphism, and a form (C-monoclinic or form IV) less soluble than the pharmaceutically acceptable (P-monoclinic or form III) can be formed under various conditions, possible to occur during drug formulation. Therefore, quantitative analysis of form IV in form III is important to the drug formulators. In the present study, a fast and simple non-destructive method was developed for quantification of form IV in form III, by using DRIFTS spectral data subjected to the standard normal variate transformation (row centering and scaling) and to the lazy learning algorithm. Fast principal component (fast PCR) and partial least squares (PLS) regression methods of multivariate calibration were also used, which were compared with lazy learning. The lazy learning algorithm was performing better than the fast PCR and PLS methods (root mean squared error of cross-validation 1.318% versus 3.337 and 3.058%, respectively). Even with a small number of calibration samples it gave satisfactory predictive performance (root mean squared error of prediction <2.0% versus >3.3% of fast PCR and >2.6% of PLS), in the concentration range below 30% (w/w) of form IV. This is attributed to the capability of handling non-linearity in the relation of reflectance and concentration as well as to local modeling using a pre-selected number of nearest neighbor concentrations.

Keywords: Diffuse reflectance; DRIFTS; Carbamazepine; Crystal polymorphism; Lazy learning; Fast PCR; PLS

1. Introduction

Carbamazepine exists in four well-characterized anhydrous crystal forms, a P-monoclinic (form III) [1,2], a triclinic (form I) [3], a trigonal (form II) [4] and a C-monoclinic polymorph (form IV) [5]. Moreover it can form a dihydrate [6,7] and several co-crystals or molecular adducts [8]. Carbamazepine presents an exceptional case of packing polymorphism, with very small conformational differences of the molecules between different crystal forms and particularly between the two different monoclinic polymorphs (P or form III and C or form IV). The main difference between the P- and C-monoclinic forms lies in the packing arrangement of the carboxamide dimers, Fig. 1, and particularly in the distance of the C–H···O bonds formed between a vinylic hydrogen of the azepine ring and carbonyl oxygen. It is less than 0.2 Å according to Grzesiak et al. [9] or 0.26 Å based on comparison of the structures deposited in the CSD [9,10].

P-monoclinic polymorph designated as form III is marketed in commercial preparations because it is relatively stable at ambient temperature and has higher solubility and bioavailability, while C-monoclinic polymorph can be formed under various conditions, possible to occur during drug formulation. Its preparation has been reported by dehydration of the dihydrate [6], by salting out from ethanolic solution designated as form II [11], by slow evaporation and by spray drying of methanol solutions [5,9,12]. Form IV exhibits lower solubility than form III. Consequently, the presence of form IV in the raw material and final pharmaceutical product may be responsible for bioavailability problems [13]. Although the pharmacopoeias (USP, Ph. Eur. and BP)

* Corresponding author. Tel.: +30 2310 997666; fax: +30 2310 997652.
E-mail address: kgk@pharm.auth.gr (K. Kachrimanis).

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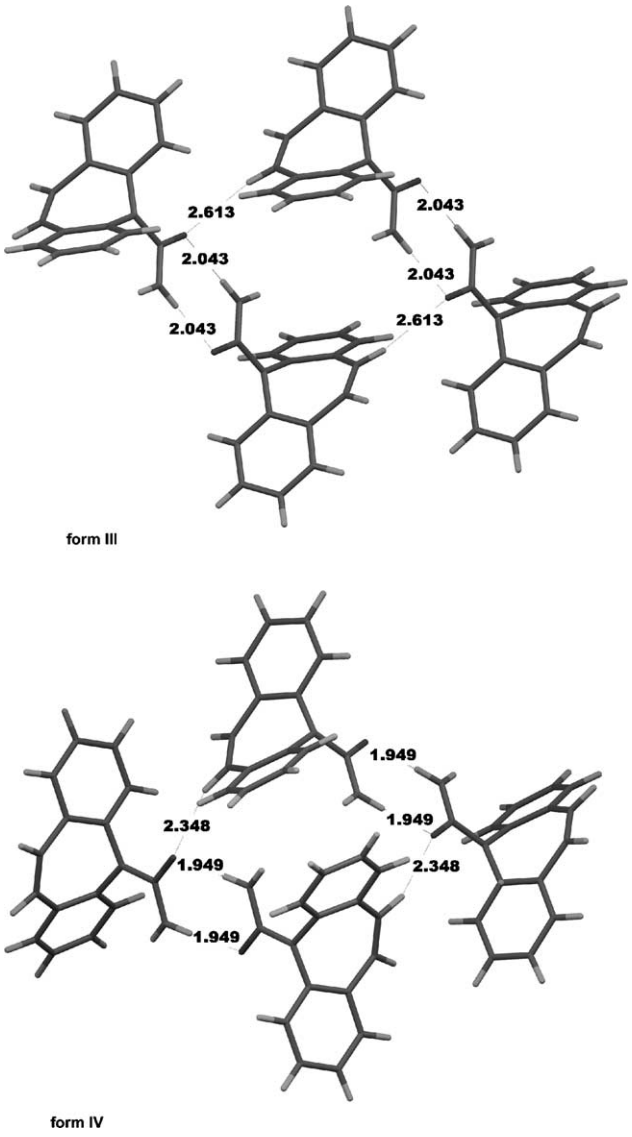

Fig. 1. Molecular models of carbamazepine crystal forms III and IV, showing the subtle packing differences of dimers.

stipulate the use of polymorph III, they do not set limits for the other polymorphs of carbamazepine. Until now mainly quantification of form I in form III has been extensively studied although there are reports of possible existence of several polymorphs in various formulations [14–16]. Particularly form IV until its recent characterization by Lang et al. [5] was regarded either as mixture of the trigonal and other forms [6], as form observed only under the microscope [17], as trigonal [4], and even after the characterization, as α-carbamazepine or form I [18]. Therefore, it is of primary importance for the drug manufacturer to be able to identify and quantify crystal form IV of carbamazepine in form III by means of a fast and simple method.

Vibrational spectroscopy methods, such as FTIR and Raman, are in general well-suited for the identification and quantification of polymorphic materials besides X-ray powder diffractometry (X-RPD), which is the most powerful technique, because it combines absolute specificity with high degree of accuracy [14,15,19]. Diffuse reflectance FTIR spectroscopy (DRIFTS) in particular, is a non-destructive method that does not require expensive instrumentation and involves very little sample preparation minimizing the risk of inducing a polymorphic transition, like X-RPD and Raman spectroscopy. But, for the case of the monoclinic carbamazepine polymorphs (IV and III), quantitative analysis by DRIFTS is difficult because of similar molecular conformations and hydrogen bonding networks in forms IV and III that lead to very subtle differences of the FTIR spectra, while significant particle size and packing effects result in non-linearity between the content and spectral features (peak height or area) [20]. Therefore, the use of multivariate calibration models is a prerequisite for a successful quantification [21,22]. In the present study, the quantitative analysis of the less soluble crystal form IV in the pharmaceutically acceptable raw material (form III) is attempted by employing DRIFTS spectroscopy combined with multivariate calibration based on the lazy learning algorithm. Fast principal component (fast PCR) and partial least squares (PLS) regression, which are conventional linear multivariate calibration methods known for their good predictive ability, are also applied for comparison purposes.

2. Materials and methods

2.1. Materials

Commercial carbamazepine (form III) was donated by Pharmathen, Greece (Lot F010001, Farchemia Srl., Treviglio, Italy) and was used as received. Carbamazepine form IV was prepared by spray drying methanol solutions of carbamazepine (4.7%, w/w) on a Büchi Mini Spray Dryer B 191 (Büchi Labortechnik AG, Switzerland). Inlet temperature was 80 °C, outlet temperature 55 °C and feeding pump rate at 25% (or 445 ml/h). The airflow rate was 600 N l/h and the aspirator rate at 100%. The crystal form and purity of both carbamazepine polymorphs (III and IV) used as starting materials was verified by X-RPD before testing by scanning electron microscopy and intrinsic dissolution test assessment.

2.2. Methods

2.2.1. Powder X-ray diffraction

X-RPD patterns were recorded on a powder diffractometer (Bruker AXS D8, Germany). The experiments were performed in symmetrical reflection mode with Cu Kα radiation (1.5418 Å) using Göbel mirror bent-gradient multilayer optics. Powder samples were scanned in the angular range of 3–40°, with a step of 0.05° and count time 1 s per step. The scattered intensities were measured with a scintillation counter.