Journal of Crystal Growth 375 (2013) 119–124

Contents lists available at SciVerse ScienceDirect

Journal of Crystal Growth

journal homepage: www.elsevier.com/locate/jcrysgro

Pholcodine monohydrate: Crystal structure and polymorphism

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ARTICLE INFO

Article history:
Received 20 February 2013
Received in revised form
8 April 2013
Accepted 11 April 2013
Communicated By: S.R. Qiu
Available online 19 April 2013

Keywords:
A1. Crystal structure
A1. Polymorphism
A1. Recrystallization
A1. X-ray diffraction
B2. Pharmaceuticals

ABSTRACT

The first crystal structure elucidation of pholcodine monohydrate, an important antitussive active pharmaceutical ingredient is reported herein. The studied compound crystallizes in the orthorhombic system in the space group $P2_12_12_1$. Each H_2O molecule is shared by two pholcodine molecules *via* three strong hydrogen bonds. The detailed crystallization screening from several different organic solvents afforded single crystals with various quality, all exhibiting prism-to-needlelike micro morphology. The investigation of the obtained single crystals by means of several physico-chemical, solid-state instrumental techniques (FT-IR, DSC, TG/DTG and XRPD) proved that pholcodine monohydrate exists in a single crystalline modification, identical to the commercial form of the compound.

1. Introduction

Pholcodine monohydrate (7,8-didehydro-4,5α-epoxy-17-methyl-3-[2 (morpholin-4-yl)ethoxy]morphinan-6α-ol monohydrate) (Fig. 1) is a semisynthetic morphine derivative extensively used worldwide as antitussive active pharmaceutical ingredient (API) [1–3]. The substance is considered generally safer for medical application compared to similar morphine antitussive analogs (e.g. codeine) because it neither causes depression of respiration, nor central nervous system excitation, thus avoiding the risk of euphorizing properties or addiction [3]. Although it has been in active pharmaceutical use since the late 1950s, recently it gained new scientific attention, as the pharmacokinetics and metabolism are not known in detail [2,4,5]. In addition, during the past decade considerable emphasis has been placed on the need to develop and validate suitable high performance liquid chromatography (HPLC) methods for identification and quantification of the bulk API and the corresponding process and degradation impurities [6,7].

Pholcodine monohydrate has seen several decades of intense pharmaceutical/medical application history, but it is peculiar that negligible scientific information were reported concerning its solid-state properties. Moreover, to the best of our knowledge, no results are published related either to pholcodine crystal structure or its polymorphism being unusual, having in mind the well established scientific facts about the possible influences of different polymorphs of a single API toward the physico-chemical properties such as solubility, stability and occasionally even the bioavailability of the corresponding drug product [8–11]. Detailed search in the Cambridge Structural Database (June 2012 version) confirmed that the crystal structure of pholcodine monohydrate (or any other pholcodine derivative) has not been elucidated.

The main scientific goal of the present study is to determine, for the first time, the crystal structure of pholcodine monohydrate and to describe its structural features in detail. The commercial sample of pholcodine monohydrate was crystallized from a series of organic solvents in order to isolate the suitable single crystals for X-ray structure analysis. As the polymorphism and/or solvatomorphism of this compound was not reported in the literature, all crystallized samples were analyzed by means of a combination of several solid-state instrumental techniques, such as: optical microscopy, Fourier transform infrared (FT-IR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TG/DTG) and X-ray powder diffraction (XRPD). The application of such powerful methodology is already proven to be a very fast, precise and reliable research approach for adequate study of polymorphism and/or solvatomorphism in morphine related antitussive API like codeine phosphates analogs [10,11]. Presentation of the obtained data from the solid-state properties screening of pholcodine monohydrate will

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0022-0248/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jcrysgro.2013.04.031

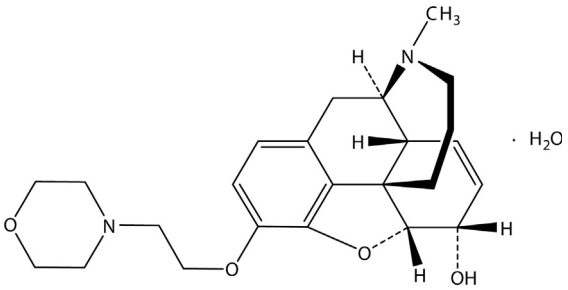

Fig. 1. Structural formula of pholcodine monohydrate.

be also beneficial in the pharmaceutical research and quality control laboratories worldwide.

2. Materials and methods

2.1. Materials

Pholcodine monohydrate, assay: 99.59% by potentiometric titration on dried substance and loss on drying: 4.4% [1], used in this study is a commercial sample of the compound as produced by ALKALOID AD (Macedonia). Methanol, absolute ethanol, acetone, ethyl acetate, tetrahydrofuran (THF) and *N,N*–dimethylformamide (DMF) with *pro analysis* quality were acquired from Merck and used without further purification.

2.2. Crystallization of pholcodine monohydrate

In order to obtain the suitable single crystals of pholcodine monohydrate for X-ray structure analysis, commercial sample of the staring material was crystallized by slow evaporation of hot solutions of the drug in several solvents. Absolute ethanol (water content≤0.1%) and methanol (water content≤0.03%) were selected from the protic class of solvents, acetone (water content≤0.05%) and ethyl acetate (water content≤0.05%) from the Lewis bases class of solvents and tetrahydrofuran (water content≤0.02%) and *N,N*–dimethylformamide (water content≤0.3%) from the dipolar aprotic class of solvents. Saturated solutions of pholcodine monohydrate were obtained by adding the substances in preheated (35 °C) solvent (10 mL) until the undissolved portion was still observable after 10 min of constant mixing using a magnetic stirrer. The saturated solution was quickly filtered into 25 mL crystallization vessels, and the filtrate was left to evaporate at controlled ambient temperature of 23 ± 2 °C under constant laminar air stream. After complete solvent evaporation, the crystallizing vessels were placed under dried silica atmosphere to stabilize 48 h before further analysis.

2.3. Fourier transform infrared (FT-IR) spectroscopy

The FT-IR spectra were recorded on a Varian 660 FT-IR spectrometer using three different sampling protocols. Standard KBr pellets method was applied, collecting the spectra in the 4000–400 cm^{-1} region. FT-IR spectra obtained as Fluorolube (4000–2000 cm^{-1}) and Nujol (2000–550 cm^{-1}) dispersions were recorded using 10–20 mg of samples dispersed manually in two drops of the agent. The prepared dispersion was applied on KBr pellets in a form of thin film and FT-IR transmission spectra were recorded. Attenuated total reflectance (ATR) spectra (4000–550 cm^{-1} region) were obtained by MIRAcle ZnSe ATR module (PIKE technologies) with low pressure micrometer clamp. Corrections of the ATR spectra for the wavenumber-dependent variations in the depth of penetration were undertaken using the in-built ATR correct Algorithm 2 in the Varian Resolutions Pro software [12]. The following settings were introduced in the algorithm menu: crystal angle of incidence (45°), crystal (ZnSe), crystal refractive index (2.403), and sample refractive index (1.5). All spectra were averaged from 32 scans per spectrum and the resolution was set to 4 cm^{-1}.

2.4. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)

DSC measurements were carried out in cyclic mode of operation. The procedure started by heating from 25 °C to 120 °C, cooling to 0 °C and reheating to 120 °C, applying a heating/cooling rate of 5 °C/min. The measurements were carried out under dynamic nitrogen atmosphere (30 mL/min) in pierced aluminum pans with Netzsch DSC 204 F1 *Phoenix* instrument. The TG and DTG curves were recorded in the 30–400 °C range, on a Netzsch TG 209 F1 *Iris* analyzer using ceramic/aluminum sample pans.

2.5. Optical microscopy

Microscopic images were obtained using Malvern-Morphologi G3S particle size and morphology analyzer microscope, coupled with a 5 megapixel CCD camera. The micro-images were obtained using bright field mode at 5, 10 and 20-fold optical magnifications.

2.6. X-ray powder diffraction

The X-ray powder diffraction (XRPD) measurements were conducted on a Rigaku Ultima IV powder X-ray diffractometer. Each studied sample was manually dispersed over a silicon sample plate and the data were collected at room temperature on a D/tex detector in the 2θ range from 3 to 45° (scan rate 2 °/min). CuKα radiation was obtained from a generator set at 40 kV and a current of a 40 mA.

2.7. Single crystal X-ray structure analysis

The molecular and crystal structures of the title compound were determined by single crystal X-ray diffraction. The diffraction data were collected at 120 K (liquid nitrogen). The diffraction measurement was performed on an Oxford Diffraction Xcalibur Kappa CCD X-ray diffractometer using graphite-monochromated MoKα radiation ($\lambda=0.71073$ Å). The data sets were collected using the ω scan mode over the 2θ range to 54°. Programs CrysAlis CCD and CrysAlis RED [13] were used for data collection, cell refinement and data reduction. The structure was solved by direct methods and refined using SHELXS and SHELXL programs, respectively [14]. The structural refinement was performed on F^2 using all data. The hydrogen atoms bound to non-chiral carbon atoms were placed in calculated positions and treated as riding on their parent atoms [C–H=0.93 Å and $U_{iso}(H)=1.2\ U_{eq}(C)$]. The riding mode was dependent on the type of hybridization of the C atom. The hydrogen atoms bound to chiral carbon atoms were located in the difference Fourier map and refined in subsequent refinement cycles. All calculations were performed using the WINGX crystallographic suite of programs [15]. The molecular structure of the compound is presented by ORTEP-3 [16] and POV-RAY [17] programs. The hydrogen bonding projection was prepared using Mercury 2.3 [18]. Hirshfeld surfaces [19] and corresponding fingerprint plots [20] were prepared using CrystalExplorer 2.1. Table. S1 lists the general, single crystal X-ray diffraction and refinement data for the title compound at 120 K.

3. Results and discussion

Crystallization experiments using different solvents afforded crystals of varying quality (Fig. S1). The first crystals appeared in the filtrates of acetone and ethyl acetate solution, 2 h after filtration.