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Structural and Physicochemical Studies of Olopatadine Hydrochloride Conformational Polymorphs

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ABSTRACT

Crystal and molecular structures of 2 conformational polymorphs (forms I and II) of olopatadine hydrochloride, an antiallergic agent, are presented. Both crystal modifications crystallize in the monoclinic crystal system with 1 olopatadine hydrochloride molecule in the *Z* configuration in the asymmetric unit. Molecules are arranged into the centrosymmetric association through the interactions of the intermolecular strong and weak hydrogen bonds of N-H…Cl, O-H…Cl and C-H…Cl, C-H…O types. Conformational change between polymorphs is proved by calculations of a maximum torsion angle deviation (max [Δθ]) and a root-mean-square deviation between the atomic positions (rmsd[r]). The physicochemical characterization of polymorphs is performed by X-ray powder diffraction, infrared and Raman spectroscopy, differential scanning calorimetry. The comparison of the melting points and heats of fusions shows that the forms are monotropically related.

Introduction

Polymorphism is the ability of the compound in a solid state to exist in different crystalline forms. Molecules, having the same chemical composition, exhibit different spatial arrangements and exist in different configurations and conformations.[1-5]

Different polymorphs of a solid compound exhibit distinct physical properties, such as, hygroscopicity, solubility, dissolution rate, melting point, and stability,[4,6] all of which play a very important role in the pharmaceutical industry. If an active pharmaceutical ingredient exhibits polymorphism, there is a risk that during a manufacturing process (such as drying, milling or tableting) or during storage, an undesirable form can arise. Such a form, possessing lower solubility and permeability limited absorption, can result in decreased drug plasma concentration. For this reason, the Biopharmaceutics Classification System classifies drugs taking into account their solubility and permeability. Because a change in the polymorphic form may influence the effectiveness of the drug product and its toxic properties, regulations required by the International Conference on Harmonisation Q6A guideline according to the decision tree #4 call for the control of the solid-state behavior.[7]

The olopatadine hydrochloride (11-[(Z)-3-(dimethylamino) propylidene]-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid monohydrochloride) molecule (Scheme 1) includes a 7-membered oxacycloheptane ring, also called oxepane, which is present in many natural products displaying interesting biological profiles.[8,9]

Olopatadine is an antiallergic/antihistaminic H1-receptor antagonistic drug and a selective H1−receptor antagonist, inhibiting the release of histamine and other proinflammatory mediators from mast cells.[10] The ophthalmic solution was approved for the treatment of seasonal allergic conjunctivitis.[11] According to the scientific discussion concerning the approval of Opatanol eye drops, olopatadine hydrochloride has not revealed any polymorphism.[12] This phenomenon is of no importance when the active substance

Single X-ray crystal data of olopatadine hydrochloride forms I and II were deposited at the Cambridge Crystallographic Data Centre. The deposition numbers CCDC 1048618 (form I) and CCDC 801834 (form II) contain supplementary crystallographic data. These data can be obtained free of charge via https://summary.ccdc.cam.ac.uk/structure-summary-form?access=referee (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom; fax: +44-1223-336033; e-mail: data_request@ccdc.cam.ac.uk).

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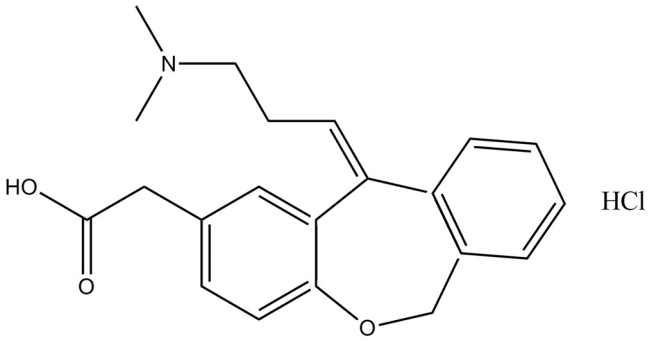

Scheme 1. Molecular structure of olopatadine hydrochloride.

is in the form of a solution. But, olopatadine hydrochloride is also recommended for oral administration (e.g., Allelock® tablets marketed by Kyowa Hakko Kirin Company Ltd.) in the treatment of allergic rhinitis, chronic urticaria, eczema dermatitis, prurigo, pruritus cutaneous, psoriasis vulgaris, and erythema exsudativum multiforme.[13,14]

According to patent publications, olopatadine hydrochloride exhibits polymorphism. In the International Patent Application (Patent Cooperation Treaty) published as WO 2007/105234, 2 polymorphic forms I and II as well as an amorphous form in the *Z* configuration and another polymorph in the *E* configuration were described.[15] Forms A and B were disclosed in the Patent Cooperation Treaty publication WO 2007/110761.[16] In addition, WO 2007/119120 revealed forms named A and B.[17] A diffractogram comparison of forms I and A proved that they are identical (Supplementary Fig. A1). The diffractograms of forms II and B are matching each other as well (Supplementary Fig. A2). Single crystal X-ray diffraction studies of olopatadine trihydrate (in the *Z* configuration) were described by Ohshima et al.[18] The compound crystallized in the monoclinic space group $P2_1$ with the following unit cell parameters: a = 12.416(0), b = 19.209(2), c = 8.708(0) Å, $\alpha = \gamma = 90°$, $\beta = 92.92(0)°$. The single X-ray crystal data were deposited in The Cambridge Crystallographic Data Centre (refcode KUFBIW).

Syntheses of olopatadine hydrochloride monohydrate and its *E* isomer were also described by Bosch et al.[19]

Two different conformational processes in the solution of olopatadine hydrochloride on the basis of NMR variable temperature studies were proposed by Lei et al.[20] The reason for this phenomenon was attributed to the 7-membered ring interconversions.

In this article, crystal and molecular structures of the conformational polymorphic forms of olopatadine hydrochloride in the *Z* configuration are studied. The effect of the solvent on the polymorphs formation is also described. The polymorphic purity of olopatadine hydrochloride samples is carefully investigated by means of powder X-ray diffraction (PXRD), infrared (IR), Raman spectroscopy, and differential scanning calorimetry (DSC).

Experimental

Materials

All analytical grade solvents were purchased from Avantor Performance Materials Poland S.A. (Gliwice, Poland).

Olopatadine hydrochloride forms I and II were produced by Pharmaceutical Research Institute in Warsaw from a commercial sample (batch number: 090902, Chemiron International Ltd.).

The crystals of form I were obtained by the vapor diffusion technique. About 15 mg of olopatadine hydrochloride sample was dissolved in 1 mL of dimethylformamide in a small vial and then placed in a larger tube containing 3 mL of ethyl acetate. This tube was then sealed and kept under ambient conditions.

The crystals of form II were obtained by dissolving about 2.5 g of olopatadine hydrochloride in 50 mL of methanol in reflux. The solution was evaporated under vacuum at 55°C to get a solid. The solid obtained by this method was maintained in the same temperature and pressure to remove any traces of the solvent.

Infrared Spectroscopy

IR spectra were recorded on the Nicolet iS10 instrument (Thermo Scientific, Waltham, MA) in the range from 4000 to 400 cm^{-1} with the spectral resolution of 4 cm^{-1}. For 1 spectrum, 16 scans were recorded. Samples were measured in KBr pellets. The sample concentration in the pellet was 0.74%.

Raman Spectroscopy

The Fourier transform Raman spectra were recorded on the Nicolet NXR 9650 instrument (Thermo Scientific, Waltham, MA) using 1064-nm excitation from the neodymium-doped yttrium vanadate laser in the range from 3700 to 150 cm^{-1} with the spectral resolution of 4 cm^{-1}.

Differential Scanning Calorimetry

DSC measurements were performed by means of the DSC822e cell with IntraCooler (Mettler-Toledo GmbH, Schwerzenbach, Switzerland). About 7 mg (weighing accuracy: 0.01 mg) of the studied samples were weighed into standard aluminum crucibles (40 μL). The crucibles were hermetically sealed and perforated before measurements. The samples were heated from 25°C to 280°C at 10°C/min. The measurements were performed in the nitrogen atmosphere at the flow rate of 60 mL/min.

Powder X-Ray Diffraction

The diffractograms were recorded on the MiniFlex diffractometer (Rigaku Corporation, Tokyo, Japan) using CuKα1 radiation. The samples were pressed on a glass plate. The instrument was operated in the range from 3° to 40° with the scan rate of 0.02°/min.

Mercury software[21] was used to generate theoretical powder diffraction patterns of olopatadine hydrochloride polymorphs on the basis of single crystal X-ray diffraction data generated in the article.

Single Crystal X-Ray Diffraction

The X-ray diffraction data for olopatadine hydrochloride forms I and II were collected using the BRUKER KAPPA APEX II ULTRA diffractometer (Bruker AXS, Madison, WI) controlled by the APEX II software,[22] equipped with the MoKα rotating anode X-ray source (λ = 0.71073 Å, 50.0 kV, 22.0 mA) with the radiation monochromatized by multilayer optics and with the APEX-II CCD detector. The data collections for both compounds were carried out at 100 K using the Oxford Cryostream Cooling Device. The crystals were mounted on Mounted CryoLoop with a droplet of Pantone-N oil and immediately cooled down. The crystals were positioned at 50 mm from the charged coupled device camera. A total of 3700 frames were measured at 0.5° intervals with the counting time of 10-20 s. Indexing, integration and initial scaling were performed with the SAINT[23] and SADABS[24] software. The multiscan absorption was applied in the scaling procedure. The structures were solved by direct methods using the SHELXS-97[25] program and refined with the SHELXL-97.[26] The refinement was based on F^2 for all reflections