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Solid state investigation and characterization of the polymorphic and pseudopolymorphic forms of indapamide

Pradeep Ghugare[a,b,c,*], Vaijanath Dongre[c], Pravin Karmuse[b,c], Ragnesh Rana[b], Dharmendra Singh[b], Ashok Kumar[b], Zoeb Filmwala[a]

[a] Nadkarni Sacasa Research Laboratory, Department of Chemistry, St. Xavier's College, Mumbai 400001, India
[b] Ipca Laboratories Ltd., Chemical Research Division, Kandivli Industrial Estate, Kandivli (W), Mumbai 400 067, India
[c] Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Santacruz (E), Mumbai 400 098, India

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ABSTRACT

Solid state investigation and polymorphic screening of indapamide, a diuretic drug generally used for the treatment of hypertension was carried out. Substantial differences were obtained in the solid state properties of crystals confirming the existence of a polymorphic and three pseudopolymorphic forms of indapamide. Detailed methods of preparation of the polymorphs and pseudopolymorphs are described. X-ray powder diffraction (XRPD), diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were employed for the characterization of different crystalline forms of indapamide. The stoichiometric ratio of solvents associated with the drug molecules in the pseudopolymorphic forms were calculated using TGA, nuclear magnetic resonance (NMR) spectroscopy and headspace gas chromatographic (HS-GC) analysis.

1. Introduction

Indapamide (Fig. 1), a non-thiazide sulfonamide diuretic drug is primarily used in the treatment of hypertension as well as edema caused by congestive heart failure. It works by preventing the kidney from reabsorbing salt and water that is destined to be eliminated in the urine. The loss of salt from the muscle causes the muscle to relax and the relaxation of the vessels result in reduced blood pressure [1–3].

Polymorphism is defined as the ability of a substance to exist as two or more crystalline phases or forms that have different arrangements and/or conformations of the molecule in crystal lattice [4]. Crystalline polymorphs have same chemical composition but different crystal structures. Solvates, also known as pseudopolymorphs are crystalline solid adducts containing solvent molecules in the crystal structure, in stoichiometric or non-stoichiometric proportions, giving rise to unique difference in the physical and chemical properties of drug. The pharmaceutical solids having different chemical and physical properties can affect the bioavailability and stability of the drug [5–7]. The various effects of pharmaceutical processing on the drug polymorphs, solvates and phase transitions are described in detail by Brittain and Fiese [8]. Identification and characterization of polymorphic behavior in a pharmaceutical substance is therefore, an essential aspect of drug development.

The possibility of polymorphism or pseudopolymorphism may exist for any particular compound, but the conditions required for unknown polymorphs or pseudopolymorphs are not easily determined [9]. It has been estimated that large number of pharmaceuticals exhibit polymorphism. For example, 70% of barbiturates, 60% of sulfonamides and 23% of steroids are believed to exist in different polymorphic and pseudopolymorphic forms [10]. Number of reports describing the polymorphic behavior of sulfonamides is available in the literature [11–15].

Crystal structure of commercial form of indapamide using powder diffraction data has been reported, [16] wherein the authors demonstrated the presence of 3% water in commercial indapamide, [17] due to its existence as a non-stoichiometric hydrate form. To date, however, no reports are available on the polymorphic and pseudopolymorphic forms of indapamide in the literature. Present work describes the investigation and characterization of a new polymorphic and three pseudopolymorphic forms (solvates) using DSC, TGA, XRPD and DRIFT techniques.

* Corresponding author at: Nadkarni Sacasa Research Laboratory, Department of Chemistry, St. Xavier's College, Mumbai 400001, India. Tel.: +91 22 66474756.
E-mail addresses: p_d_ghugare@yahoo.com (P. Ghugare), dr_zoab@yahoo.com (Z. Filmwala).

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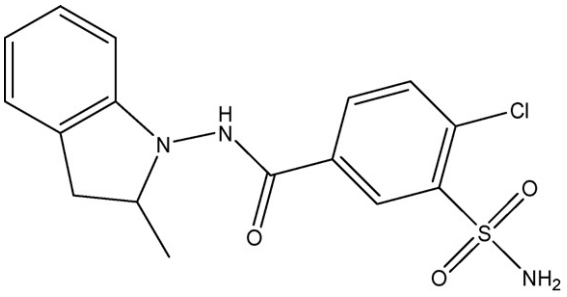

Fig. 1. Chemical structure of indapamide.

2. Experimental

2.1. Materials and reagents

The indapamide bulk drug sample was obtained from Chemical Research Division, Ipca laboratories Ltd., Mumbai, India. Laboratory grade solvents used for crystallization, analytical grade solvents used for HS-GC and KBr used for DRIFT analysis were purchased from Merck KGaA, Darmstadt, Germany. Analytical grade *N*,*O*-bis-(trimethylsilyl) trifluro acetamide (BSTFA) was purchased from Spectrochem, Mumbai, India. Dimethyl sulfoxide-d_6 and tetramethylsilane for NMR were from Aldrich Chemical Co. Milwaukee, WI, USA. Hydranal Composite5 used for Karl fisher titrimetry was purchased from Riedel de Haen, Seelze, Germany.

2.2. Methods

Indapamide is soluble in acetonitrile, ethyl acetate, glacial acetic acid, methanol, ethanol and other alcoholic solvents. It is very slightly soluble in ether and chloroform, while practically insoluble in water. Various crystallization experiments were carried out using individual as well as combinations of solvents at normal and elevated temperature. Polymorphic screening of samples using XRPD and TGA was carried out to check formation of polymorphic and pseudopolymorphic forms.

2.2.1. Preparation of anhydrous form (form-I)

A saturated suspension of indapamide prepared by adding excess of indapamide in glacial acetic acid was maintained at 65–70 °C with constant stirring for 2 h. Small portion of the mixture was removed after regular time interval of 30 min and dried. The melting point of the dried compound was measured. Initially, melting point of the compound was in the range of 168–175 °C. After 2 h, the melting temperature shifted to the range of 185–193 °C, heating was then stopped and the suspension was allowed to cool to room temperature. The solid obtained was separated from the solution by vacuum filtration and dried at 50–55 °C for 2–3 h under vacuum.

2.2.2. Preparation of solvates

The saturated solutions of indapamide in acetone were prepared in three different 250 ml flasks and maintained at 35 °C with constant stirring. In order to prepare different solvates equal volume of carbon tetrachloride, cyclohexane and diethyl ether were slowly added to the respective flask. After complete addition, the solutions were kept at 35 °C for about half an hour and then cooled to room temperature. The precipitates formed were filtered by vacuum filtration followed by washing with excess amount of respective precipitating solvent. The solids obtained were dried at 50–55 °C under vacuum. Formation of solvates was checked by TGA analysis. The samples precipitated using carbon tetrachloride, cyclohexane and diethyl ether were labeled as solvate-I, solvate-II and solvate-III, respectively.

2.3. Stability studies

In order to test ability to uptake water, samples of form-I, solvate-I, II and III were stored at room temperature in open air (about 55% RH) and in a desiccator for 1 year. Samples including the commercial form were also subjected for manual grinding using mortar and pestle to study physical stability and solid–solid transition. The resulting samples were analyzed for solid state transition by DRIFT, water content by TGA and Karl Fischer titrimetry (KFT).

2.4. Instrumentation

2.4.1. Scanning electron microscopy (SEM)

The SEM images were obtained on a JSM-6360A system (JEOL, Tokyo, Japan), using an acceleration potential of 10 kV. The samples were sputter coated with platinum to eliminate charging effects.

2.4.2. Diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy

The DRIFT spectra were recorded in the solid state as KBr powder dispersion using a Spectrum One FT-IR spectrometer (PerkinElmer, Beaconsfield, UK) equipped with diffuse reflectance sampling accessory. The spectrum for each sample was recorded with an average of 16 co-added scans in transmission mode over a spectral region of 450–4000 cm^{-1} with a resolution of 4 cm^{-1}.

2.4.3. X-ray powder diffraction (XRPD)

XRPD patterns of samples were recorded at room temperature on an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands) with Cu Kα radiation, (λ = 1.5406 Å) passing through nickel filter, divergence slit (10 mm), antiscattering slit (10 mm) and soller slit (0.02 rad). The X-ray generator was set at a voltage of 45 kV and current of 40 mA. The diffractometer was calibrated for accuracy of peak positions with silicon powder (ASTM-692). Samples were subjected to XRPD analysis in continuous mode with a step size of 0.008° 2θ and step time of 15 s over an angular range of 3–40° 2θ. To minimize the preferred orientations, the samples were prepared by back loading technique using the PW1770/10 sample preparation kit. The sample holder was rotated in a plane parallel to its surface at the speed of 30 rpm during the measurements. Obtained diffractograms were analyzed with X'Pert HighScore Plus diffraction software (version 2.1b).

2.4.4. Thermal analysis (DSC and TGA)

DSC thermograms were recorded on a Q-100 instrument (TA Instruments, New Castle, DE, USA). Samples weighing 2–3 mg were heated in crimped aluminum pans with pierced lead from 30 to 210 °C at the rate of 10 °C/min. Nitrogen was used as a purging gas under ambient flow rate.

The mass loss of the sample as a function of temperature was determined using a TGA Q-500 instrument (TA Instruments, New Castle, DE, USA). The samples were placed in open platinum crucibles and heated at the rate of 25 °C/min in the range of 30–400 °C under a nitrogen purge (20 ml/min). The DSC and TGA data was processed using Universal Analysis 2000 software (version 4.3A).

2.4.5. Nuclear magnetic resonance (solution-state)

NMR spectra were obtained on a 400 MHz instrument (Bruker, Faellanden, Switzerland). The spectra were processed with XWIN NMR software (version 3.1). The samples were prepared by dissolving 5 mg of each form in 600 μl of DMSO-d_6 spiked with 0.03% of tetramethylsilane as reference (δH = 0 ppm).

2.4.6. Headspace gas chromatography (HS-GC)

A 6890 series gas chromatographic system (Agilent, Wilmington, DE, USA) equipped with flame ionization detector and Gerstel