

Polymorph Investigation of Lysergic Acid Diethylamide (LSD) D-Tartrate

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Abstract

The polymorphic landscape of lysergic acid diethylamide (LSD) D-tartrate was evaluated. It was found that LSD D-tartrate exists in one crystalline form and an amorphous form (non-crystalline form).

Introduction

The goal of this study was to evaluate the polymorphic landscape of LSD D-tartrate (Figure 1).



Figure 1. The structure of LSD D-tartrate.

Materials

A total of two different lots of LSD D-tartrate were purchased from Cayman Chemical Company (Ann Arbor, MI) and used as-received.

Results and Discussion

Characterization of Commercial LSD D-Tartrate

Two samples of commercial LSD D-tartrate were characterized by X-ray powder diffraction (XRPD). XRPD patterns of both samples exhibited the same crystalline pattern. The crystalline form corresponding to the XRPD pattern was designated as Form A (Figure 2).



Figure 2. XRPD patterns of LSD D-tartrate as-received

One of the lots was further characterized by differential scanning calorimetry (DSC), thermogravimetry (TG), dynamic vapor sorption (DVS) with XRPD of the post-DVS sample, optical microscopy (OM), infrared (IR) spectroscopy, Raman spectroscopy, and ¹H nuclear magnetic resonance (NMR) spectroscopy (Figure 3 to Figure 8). It was determined that the material is crystalline, unsolvated, and melts around 201 °C, based on DSC. DVS data indicated it is slightly hygroscopic. The material remained unchanged (based on XRPD) after DVS analysis (Figure 9).



Figure 3. 1H NMR spectrum of LSD D-tartrate as-received



Figure 4. DSC and TGA thermograms of LSD D-tartrate as-received



Figure 5. DVS sorption/desorption data of LSD D-tartrate as-received



Figure 6. OM and Polarized light microscopy images of LSD D-tartrate as-received

Figure 7. IR spectroscopy of LSD D-tartrate as-received

Figure 8. Raman spectroscopy of LSD D-tartrate as-received

Figure 9. XRPD pattern of LSD D-tartrate post-DVS analysis

Polymorph Evaluation of LSD D-Tartrate

Approximate solubilities of LSD D-tartrate in a few solvents were estimated prior to performing polymorph screening studies (Table 1).

Solvent	Solubility (mg/mL)
Acetone	< 15
Acetonitrile (ACN)	< 15
Ethanol (EtOH)	< 15
Ethyl Acetate (EtOAc)	< 15
<i>N,N</i> -Dimethylformamide (DMF)	52
Methanol (MeOH)	10
Water	36

Table 1. Estimated Solubilities of LSD D-Tartrate (Form A).

Polymorph screening experiments were designed to target potential polymorphs of LSD D-tartrate and incorporated both thermodynamic and kinetic conditions of growth. Experiments were conducted with crystalline starting material and the majority of the experiments produced solids whose XRPD patterns matched that of Form A (Table 2). A total of 8 experiments resulted in solids whose XRPD patterns exhibited noncrystalline or disordered forms of LSD D-tartrate. Non-crystalline LSD D-tartrate was used to perform additional polymorph screen experiments. From such experiments, most experiments produced solids whose XRPD patterns matched Form A (Table 3).

Method	Solvent	Filename	XRPD Result
	Acetone/water (10:3 v/v)	—	no solids obtained
	Acetone/DMF (5:2 v/v)	RX4-6549	А
	ACN/water (10:3 v/v)	_	no solids obtained
	CHCl ₃ /DMF	RX4-7135	Α
	CHCl ₃ /MeOH	RX4-6980	А
	Dioxane/water	_	no solids obtained
Cooling	EtOAc/DMF	RX4-7134	А
	EtOH	RX4-6545	Α
	EtOH/water (10:1 v/v)	RX4-6501	Α
	Hexanes/EtOH	RX4-7133	А
	IPA	RX4-6504	А
	iPrOAc/DMF		no solids obtained
	iPrOAc/MeOH	RX4-6840	А
	MEK/DMF		no solids obtained
	MEK/MeOH	RX4-6843	А
	МеОН	RX4-6503	А
	MTBE/DMF		no solids obtained
Cooling	MTBE/MeOH	RX4-6842	А
C C	THF/DMF	_	no solids obtained
	THF/water	_	no solids obtained
	Water	RX4-7139	NC
	Water/acetone	RX4-7138	NC + peaks
	DMF/DEE	RX4-6684	Â
	DMF/MTBE	RX4-6681	А
	EtOH/DEE	RX4-6910	Α
	EtOH/Hexanes	RX4-6911	А
Desistation	EtOH/MTBE	RX4-6909	А
Precipitation	IPA/MTBE	RX4-6881	Α
	MeOH/MTBE	RX4-6682	NC
	Water/ACN	RX4-7137	NC + peaks
	heat stress of above sample	RX4-7158	NC + peaks
	Water/IPA	RX4-7136	A
	Acetone	RX4-6844	А
	DCM/water	RX4-6841	А
Slurry	EtOAc/water (20:1 v/v)	RX4-6502	А
	EtOAc	RX4-6846	А
	EtOH	RX4-6547	А
	IPA	RX4-6548	А
	МеОН	RX4-6546	A
Slurry	Toluene/water	RX4-6845	A
	Water	RX4-7143	A
–	ACN/water	RX4-6847	A
Evaporation	CHCl ₃	RX4-6989	A

 Table 2. Samples Generated and Analyzed (starting with Form A)

	DCM/water	RX4-6983	А
	DMF	RX4-6577	А
	IPA/water	RX4-6683	NC
	iPrOAc/MeOH	RX4-6981	NC
	MeOH	RX3-12178	А
	Toluene/water	RX4-6982	А
	Water	RX3-12179	А
Lyophilization	Dioxane	RX1-29670	NC

DMF=dimethyl formamide, ACN=acetonitrile, CHCl₃=chloroform, EtOH=ethanol, IPA=isopropanol, MeOH=methanol, MTBE=methyl tert-butyl ether, iPrOAc=isopropyl acetate, DCM=dichloromethane, NC=non-crystalline

Table 3. Samples	s Generated an	d Analyzed	(starting with	non-cr	ystalline	material).
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Method	Solvent	Filename	XRPD Result
	EtOH/DEE	RX4-6987	А
Liquid Vapor Dillusion	EtOH/Hexanes	RX4-6913	А
Slurry	ACN	RX4-6916	А
	CHCl₃	RX4-6918	А
	EtOH	RX4-6914	А
	MEK	RX4-6915	А
	2-Me THF	RX4-6917	А
	Acetone	RX4-6984	А
Vapor stress	DCM	RX4-6985	А
	THF	RX4-6986	А
Heat/humidity stress	—	RX4-6988	NC
	_	RX4-6912	NC + A

ACN=acetonitrile, CHCl₃=chloroform, EtOH=ethanol, DEE=diethyl ether, MEK=methyl ethyl ketone, THF=tetrahydrofuran, 2-Me THF=2-methyl tetrahydrofuran, DCM=dichloromethane, NC=non-crystalline

The sample of non-crystalline LSD D-tartrate (XRPD pattern in Figure 10) was further characterized by modulated DSC. Based on the data, the material appears to have a glass transition temperature of approximately 68 °C (Figure 11).

Some experiments from water/acetonitrile and water/acetone produced solids that contained unique peaks by XRPD that were not attributable to Form A or D-tartaric acid (Figure 12). At this time, it is not clear what these peaks are. They could be a new meta-stable polymorph that, if allowed to further crystallize, would convert to Form A. They could also be due to degradation or a new polymorph of D-tartaric acid. Further study would be needed to determine the nature of these peaks.

Figure 12. Overlay plot of LSD D-tartrate Form A (top), D-tartaric acid (middle), and XRPD pattern containing unique peaks (bottom)

Experimental

X-ray Powder Diffraction (XRPD)

The Rigaku Smart-Lab X-ray diffraction system was configured for reflection Bragg-Brentano geometry using a line source X-ray beam. The x-ray source is a Cu Long Fine Focus tube that was operated at 40 kV and 44 ma. That source provides an incident beam profile at the sample that changes from a narrow line at high angles to a broad rectangle at low angles. Beam conditioning slits are used on the line X-ray source to ensure that the maximum beam size is less than 10mm both along the line and normal to the line. The Bragg-Brentano geometry is a para-focusing geometry controlled by passive divergence and receiving slits with the sample itself acting as the focusing component for the optics. The inherent resolution of Bragg-Brentano geometry is governed in part by the diffractometer radius and the width of the receiving slit used. Typically, the Rigaku Smart-Lab is operated to give peak widths of 0.1 °2 θ or less. The axial divergence of the X-ray beam is controlled by 5.0-degree Soller slits in both the incident and diffracted beam paths.

Powder samples were prepared in a low background Si holder using light manual pressure to keep the sample surfaces flat and level with the reference surface of the sample holder. Each sample was analyzed from 2 to 40 °2 θ using a continuous scan of 6 °2 θ per minute with an effective step size of 0.02 °2 θ .

Differential Scanning Calorimetry (DSC)

The DSC analysis was carried out using a TA Instruments Q2500 Discovery Series instrument. The modulated DSC analysis was carried out using a TA Instruments Q2000 instrument. The instrument temperature calibrations were performed using indium. The DSC cell was kept under a nitrogen purge of ~50 mL per minute during each analysis. Samples were placed in a standard, crimped aluminum pan and analyzed as outlined below:

	Parameters
DSC	The sample was heated from approximately 25 °C to 350 °C at a rate of 10 °C per minute.
modulated	The sample was cooled to -50 °C and held at temperature for 2 minutes. It was then modulated
DSC	+0.32 C every 30 seconds while being heated to 250 C at a fate of 4 C per minute.

Thermogravimetric (TG) Analysis

The TG analysis was carried out using a TA Instruments Q50 instrument. The instrument balance was calibrated using class M weights and the temperature calibration was performed using alumel. The nitrogen purge was ~40 mL per minute at the balance and ~60 mL per minute at the furnace. Each sample was placed into a pre-tared platinum pan and heated from approximately 25 °C to 350 °C at a rate of 10 °C per minute.

Dynamic Vapor Sorption (DVS) Analysis

The DVS analysis was carried out using a TA Instruments Q5000 Dynamic Vapor Sorption analyzer. The instrument was calibrated with standard weights and a sodium bromide standard for humidity. Approximately 10-25 mg of sample was loaded into a metal-coated quartz pan for analysis. The sample was analyzed at 25 °C with a maximum equilibration time of one hour in 10% relative humidity (RH) steps from 5 to 95% RH (adsorption cycle) and from 95 to 5% RH (desorption cycle). The movement from one step to the next occurred either after satisfying the equilibrium criterion of 0.01% weight change or, if the equilibrium criterion was not met, after one hour. The percent weight change values were calculated using Microsoft Excel®.

Infrared (IR) Spectroscopy

The IR spectrum was obtained on a Nicolet 6700 FT-IR system. The sample was analyzed using a Nicolet SMART iTR attenuated total reflectance device.

Raman Spectroscopy

The Fourier transform (FT) Raman spectrum was acquired on a Nicolet model 6700 spectrometer interfaced to a Nexus Raman accessory module. This instrument is configured with a Nd:YAG laser operating at 1024 nm, a CaF₂ beamsplitter, and a indium gallium arsenide detector. OMNIC 8.1 software was used for control of data acquisition and processing of the spectra. The sample was packed into a 3-inch glass NMR tube for analysis.

Optical Microscopy

The optical microscopy experiment was carried out on a Leica DM 2500 P compound microscope. Images were captured using a QImaging MicroPublisher 3.3 RTV camera. Images were collected at 10× magnification.

Nuclear Magnetic Resonance (NMR) Spectroscopy

The ¹H NMR spectrum was acquired on a Bruker Avance II 400 spectrometer. The sample was prepared by dissolving material in DMSO-d₆. The solution was filtered and placed into a 5-mm NMR tube for subsequent spectral acquisition. The temperature controlled (295K) ¹H NMR spectrum acquired on the Avance II 400 utilized a 5-mm cryoprobe operating at an observing frequency of 400.18 MHz.

XRPD Data

Polymorph investigation of LSD D-tartrate Triclinic Labs

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