Two new polymorphs and one dihydrate of lenalidomide: solid-state characterisation study

Lina Jia a, Zhonghua Li a\* and Junbo Gong ab\*

a State Key Laboratory of Chemical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, P. R. China

b Key Laboratory Modern Drug Delivery and High Efficiency in Tianjin University, Tianjin 300072, P. R. China

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1. ***Instrument***

*Powder X-ray Diffraction.*

Powder X-ray diffraction was measured on a Rigaku D/MAX 2500 X-ray diffractometer using Cu-Kα radiation (λ = 1.54178 Å). The voltage and current were 40 kV and 100 mA, respectively. Samples were measured in reflection mode in the 2θ range of 2-40 ° with a scan speed of 8°/min. Data was acquired at ambient temperature (20 °C).

*Thermogravimetric Analysis (TGA).*

Thermogravimetric analysis was conducted in a Mettler TGA/DSC 1 STARe System, using a nitrogen gas purge flow of 20 mL/min and a scan rate of 10 °C/min.

*Differential Scanning Calorimetry (DSC).*

Differential scanning calorimetry was performed with a Mettler DSC 1 STARe System. Two-point calibration using indium and tin was performed to check the temperature axis and heat flow of the equipment. Samples weighting 3-5 mg were heated in standard aluminium pans at a scan rate of 10 °C/min under a nitrogen gas flow of 50 mL/min.

*Fourier-Transform Infrared (FTIR) Spectroscopy.*

Fourier transform infrared (FTIR) spectra was collected by a BRUKER ALPHA ATR platinum in the range of 4000 to 400 cm−1, with a resolution of 4 cm−1 at ambient conditions.

*Powder Dissolution Experiment*

*UV Standard Curve.* The standard curve was established using U-3010 Spectrophotometer. The detection wavelength was set at 304 nm (n = 3). **LDM** solutions in water of specific concentrations were prepared, 0.0208, 0.0416, 0.0624, 0.0832 mg/mL. Then the standard curve was obtained, y = 10.605x, R2 = 0.9997, **Figure S8**.

*Powder Dissolution.* The powder dissolution experiment was conducted in a RC-6 dissolution test analyzer using the paddle method at a rotation speed of 50 rpm at 37 °C (n = 2). Accurately weighed powders of 500 mg LDM were added to dissolution vessels containing 500 mL of pure water. To minimize the size effect on dissolution results, samples of forms 1, α, β and DH were sieved through 100-mesh sieves. For dissolution test in water, sampling was performed at 1, 2, 5, 10, 15, 20, 30, 40, 60, 80, 100, 120, 150, 180, 210 and 240 min. All the withdraw suspensions were filtered with 0.45 μm PTFE filters prior to being detected by UV spectrophotometer and analyzed using the UV standard curve.

1. **Figure Contents**

**Figure S1**

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**Figure S1.** PXRD patterns of the reported forms 2-6.

**Figure S2**

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**Figure S2.** Preparation process of new form α in nitromethane.

**Figure S3**

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(a)



(b)

**Figure S3.** The overlaid DSC and TGA profiles of (a) the reported form 1 and (b) new form β.

**Figure S4**

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**Figure S4.** Transformation process of form α when heating.

**Figure S5**

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**Figure S5.** The transformation process of **LDM** in water: Reported form 1 → Reported form 7 → DH.

**Figure S6**

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**(a)**

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**(b)**

**Figure S6.** FTIR patterns of **LDM** polymorphs.

**Figure S7**



(a)



(b)



(c)



(D)



(e)



(f)



(g)



(h)

**Figure S7.** The results of **LDM** forms monitored by PXRD under accelerated conditions (a) form 1 at 25 °C/P2O5, (b) form 1 at 40 °C/75% RH, (c) DH at 25 °C/P2O5, (d) DH at 40 °C/75% RH, (e) form α at 25 °C/P2O5, (f) form α at 40 °C/75% RH, (g) form β at 25 °C/P2O5, (h) form β at 40 °C/75% RH.

**Figure S8**

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**Figure S8.** UV standard curve.

1. **Table Content**

**Table S1**

**Table S1.** The results of **LDM** forms monitored by PXRD under accelerated conditions.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Form 1 | DH | Form α | Form β |
| 40℃/75% RH | 4 weeks | 4 weeks | 4 weeks →form 1 | 1 week →form 1 |
| 25℃/P2O5 | 4 weeks | 4 weeks →form 7 | 4 weeks | 4 weeks |