

## Crystal Form of Olmutinib

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**ABSTRACT.** Olmutinib, N-[3-({2-[4-(4-methylpiperazine-1-yl)aniline]thieno[3,2-d]Pyrimidin-4-yl}oxy)phenyl]prop-2-enamide dihydrochloride monohydrate, Olita<sup>TM</sup> is an oral, third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) that was developed by Boehringer Ingelheim and Hanmi Pharmaceutical Co. Ltd for the treatment of non-small cell lung cancer (NSCLC). The aim of this work was to investigate the existence of polymorphs and pseudopolymorphs of olmutinib. Three crystal forms of olmutinib have been isolated by recrystallization and characterized by differential scanning calorimetry (DSC), thermogravimetric (TG) analysis and powder X-ray diffractometry (PXRD). From the DSC and TG data it was confirmed that Form 1 is monohydrate, Form 2 is dihydrate, Form 3 is 1.5 hydrate. The PXRD patterns of three crystal forms were different respectively. After storage of 1 month at 2 °C, 24% RH (Relative Humidity), Form 1, Form 2, and Form 3 were not transformed.

**Key words:** Olmutinib, Crystal form, DSC, TG, PXRD

### INTRODUCTION

Prior to the development of major dosage forms with a new drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information dictates many of the subsequent events and possible approaches in formulation development.<sup>1</sup> This first learning phase regarding a drug is known as preformulation.<sup>1,2</sup> In the case of a new drug substance, it is important that crystal form data should be generated prior to the initiation of pivotal clinical studies and primary stability batches. Thus, the thorough investigation of new solid states of a drug molecule is recognized as an essential and very important part of preformulation studies.<sup>3</sup>

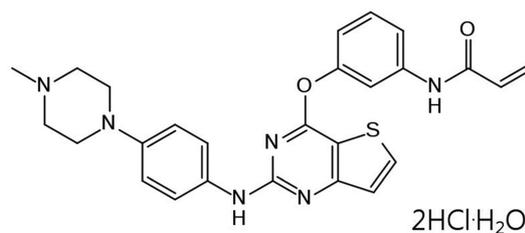
It is well known and recognized that pharmaceutical solids can exist in multiple crystalline solid forms.<sup>3</sup> Crystal forms include polymorphs, solvates, and amorphous forms as defined in the International Conference on Harmonization (ICH) Guideline Q6A.<sup>4</sup>

Polymorphs share the same chemical composition but have different crystal structures. Because of their structural differences, polymorphs may have different physicochemical properties. For example, polymorphs can have different densities, habits, melting properties, vapor pressures, solubilities, dissolution rates, tableting, and mechanical properties.<sup>5-7</sup> The crystal form affects properties such as drug

absorption, rate of dissolution, elimination rate, and stability in galenic preparations.<sup>8-10</sup>

Solvates are molecular complexes that have incorporated the crystallizing solvent molecule in their lattice. When the solvent incorporated in the solvate is water, it is called a hydrate. To distinguish solvates from polymorphs, which are not molecular compounds, the term pseudopolymorph is used.<sup>5,6</sup> Identification of possible hydrate compounds is also important since their aqueous solubilities can be significantly less than their anhydrous forms.<sup>11-14</sup>

Olmutinib (Fig. 1) N-[3-({2-[4-(4-methylpiperazine-1-yl)aniline]thieno[3,2-d]pyrimidin-4-yl}oxy)phenyl]prop-2-enamide dihydrochloride monohydrate, Olita<sup>TM</sup> is an oral, third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) that was developed by Boehringer Ingelheim and Hanmi Pharmaceutical Co. Ltd for the treatment of non-small cell lung cancer (NSCLC). Third-generation EGFR TKIs with covalent binding to the receptors



**Figure 1.** Chemical structure of olmutinib dihydrochloride monohydrate.

demonstrate irreversible enzymatic inhibition of activating EGFR mutations and T790M mutation (a common reason for acquired EGFR TKI resistance), while sparing wild-type EGFR.<sup>15</sup> In December 2015, olmutinib was granted breakthrough therapy designation in NSCLC by the US FDA. In May 2016, olmutinib received its first global approval in South Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

The aim of this study was to investigate the existence of polymorphs and pseudopolymorphs of olmutinib.

## EXPERIMENTAL

### Materials

Olmutinib was supplied by Hanmi Pharmaceuticals Co. Ltd. (Seoul, Korea). Solvents were analytical reagent grade or HPLC grade, used without further purification.

### Preparation of Crystal Forms

**Form 1.** Form 1 is the donated sample and standard. The standard was always stored at 0–2 °C.

**Form 2.** A suspension of Form 1 in methanol/water (1:9) was heated to 45 °C for ten min. The solution was filtered to remove most of the precipitates, and then left undisturbed for one week at 4 °C. The resulting solid was filtered and dried for one week in a desiccator to produce Form 2.

**Form 3.** A suspension of Form 1 in water was left undisturbed at room temperature for three weeks. The suspension was filtered and dried for one week in a desiccator to produce Form 3.

### Methods

**Thermal analysis.** Thermal analysis methods used in this study included differential scanning calorimetry (DSC) and thermogravimetric (TG) analysis. The DSC data were collected using a Mettler-Toledo DSC 1 STAR<sup>®</sup> system (Mettler-Toledo AG, Schwerzenbach, Switzerland) within the temperature range of 30–270 °C at a heating rate of 10 °C/min. Five mg of sample was analyzed using aluminum cells and an empty cell was used as reference. Nitrogen was used as purged gas with a flow rate of 50 mL/min. The TG was carried out using a Mettler-Toledo TGA 1 STAR<sup>®</sup> system (Mettler-Toledo AG, Schwerzenbach, Switzerland). Five mg of sample was analyzed within the temperature range of 30–270 °C at a heating rate of 10 °C/min under nitrogen purging (50 mL/min).

**Powder X-ray diffraction.** Powder X-ray diffraction

(PXRD) patterns were collected under ambient conditions on a D8 focus- Bruker AXS (Bruker AXS GmbH, Karlsruhe, Germany) diffractometer using graphite monochromatized CuK $\alpha$  radiation ( $\lambda=1.54178$  Å). The isothermal measurement conditions were: target Cu, voltage 30 kV, current 10 mA. The PXRD patterns of the samples were compared based on peak position and relative intensity, peak shifting, and the lack of peaks in certain angular regions.

**Transformation.** An aliquot (100 mg) of each crystal form was placed in a weighing dish and stored at 20 °C in 24% relative humidity (RH). The transformation behavior of the crystal forms was monitored by PXRD, DSC, and TG.

## RESULTS AND DISCUSSION

The DSC and TG curves of Form 1 - 3 are illustrated in Fig. 2 - 7. The DSC curve of Form 1 shows two endothermic peaks at 99 and 235 °C. The DSC curve of Form 2

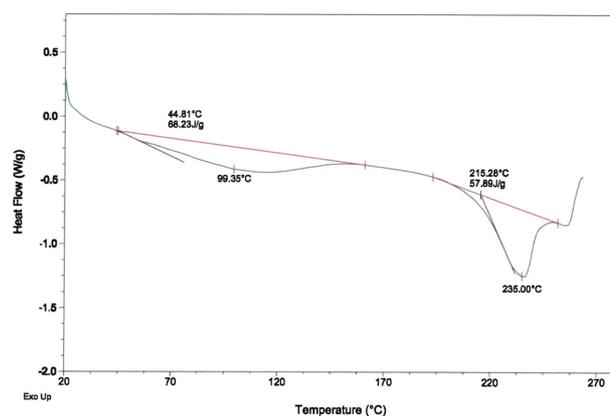


Figure 2. DSC curve of Form 1.

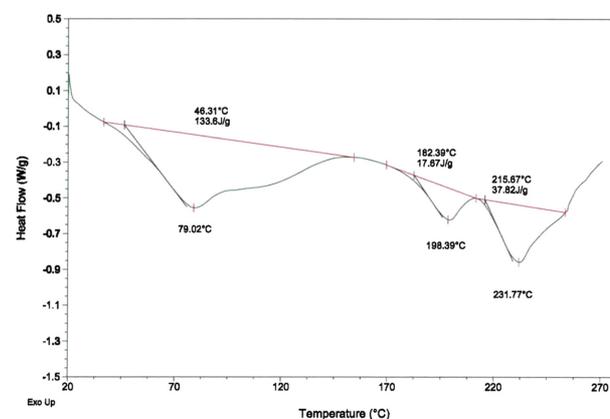


Figure 3. DSC curve of Form 2.

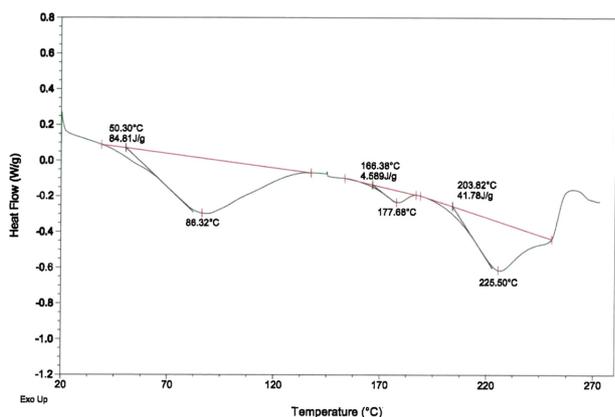


Figure 4. DSC curve of Form 3.

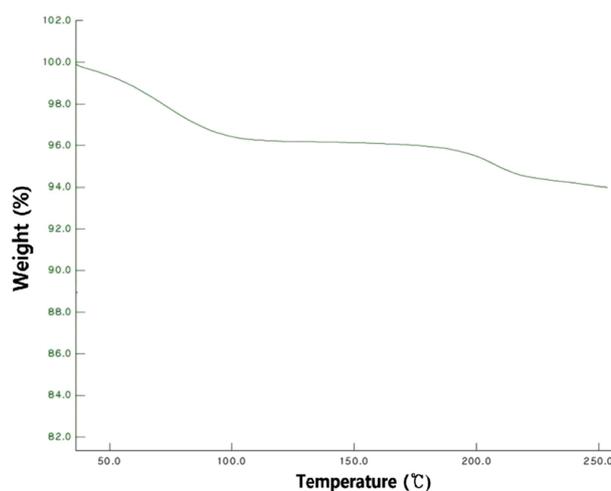


Figure 7. TG curve of Form 3.

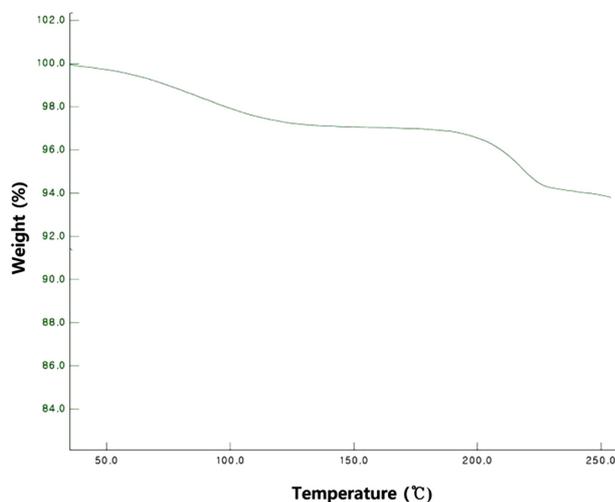


Figure 5. TG curve of Form 1.

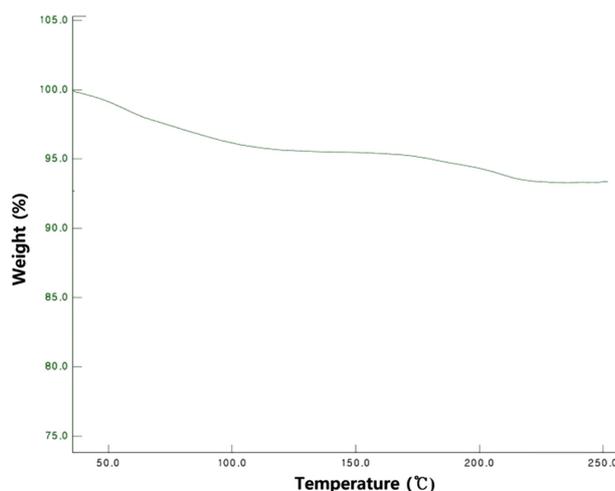


Figure 6. TG curve of Form 2.

shows three endothermic peaks at 79 °C, 198 °C and 231 °C. Form 3 shows also three endothermic peaks at 86 °C, 177 °C, and 225 °C. On TG curve of Form 1, the mass loss corresponding to the DSC endotherm at 50–150 °C was 3%, which corresponds to the loss of 0.96 mole of H<sub>2</sub>O. The TG curve of Form 2 shows the mass loss at 50–200 °C (6.1%) which corresponds to the loss of 1.96 mole of H<sub>2</sub>O. The TG curve of Form 3 shows the mass loss at 50–200 °C (4.5%) which corresponds to the loss of 1.4425 mole of H<sub>2</sub>O. TG analysis represents a powerful adjunct to the other methods of thermal analysis, since a combination of either a DTA or a DSC study with a TG determination can be used in the assignment of observed thermal events.<sup>16</sup>

The Powder X-ray diffraction patterns of Form 1 - 3 are illustrated in Fig. 8-10. The PXRD patterns of Form 1 - 3 showed differences. The PXRD pattern of the Form 1 had peaks at 5.5, 8.6, 10.6, 12.7, 13.9, 14.4, and 20.9 degrees two-theta. The PXRD pattern of Form 2 had peaks at 5.5, 6.3, 6.9, 8.8, 10.6, 11.1, 12.7, 13.9, 14.4, and 20.9 degrees two-theta. The PXRD pattern of Form 3 had peaks at 5.5, 7.4, 8.8, 10.6, 11.2, 12.7, 13.9, 14.4, and 21 degrees two-theta.

The crystal forms were characterized by DSC, TG, and PXRD. From the DSC and TG data it was confirmed that Form 1 is monohydrate, Form 2 is dihydrate, Form 3 is 1.5 hydrate.

All crystal forms were stored at 20 °C in 24% RH. After storage for one month under these conditions, none of the crystal forms showed a change in DSC, TG, and PXRD pattern (data not shown).

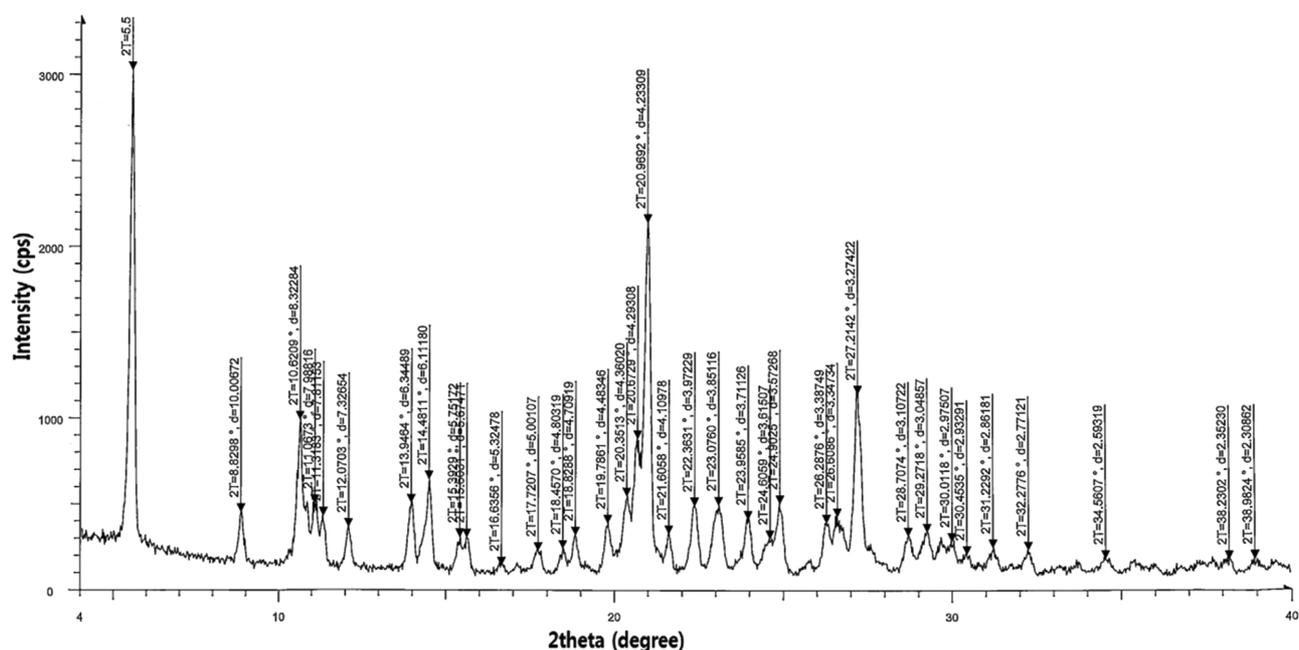


Figure 8. PXRD pattern of Form 1.

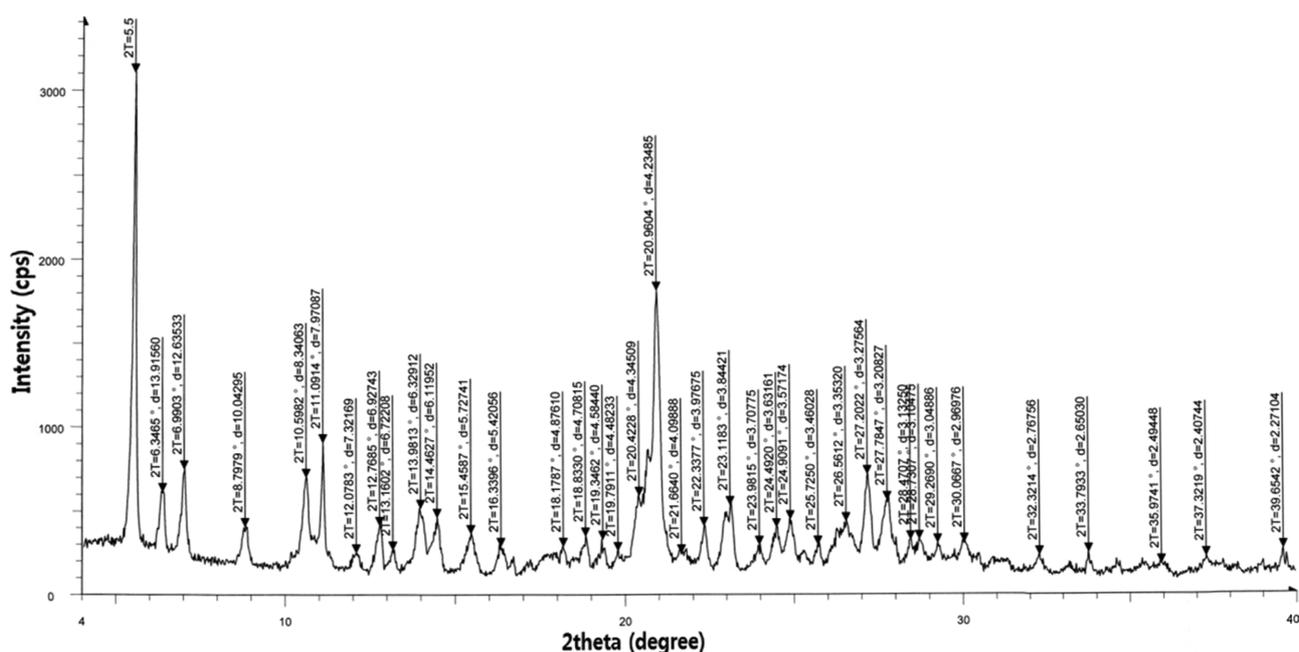


Figure 9. PXRD pattern of Form 2.

## CONCLUSION

We undertook the possible production of the new crystal form of olmutinib. The PXRD patterns of Form 1 - 3 showed differences. Three crystal forms of olmutinib were prepared by recrystallization from different sol-

vents. The crystal forms were characterized by DSC, TG, and PXRD. From the DSC and TG data it was confirmed that Form 1 is monohydrate, Form 2 is dihydrate, Form 3 is 1.5 hydrate. After storage of 1 month at 2 °C, 24% RH (Relative Humidity), Form 1, Form 2, and Form 3 were not transformed.

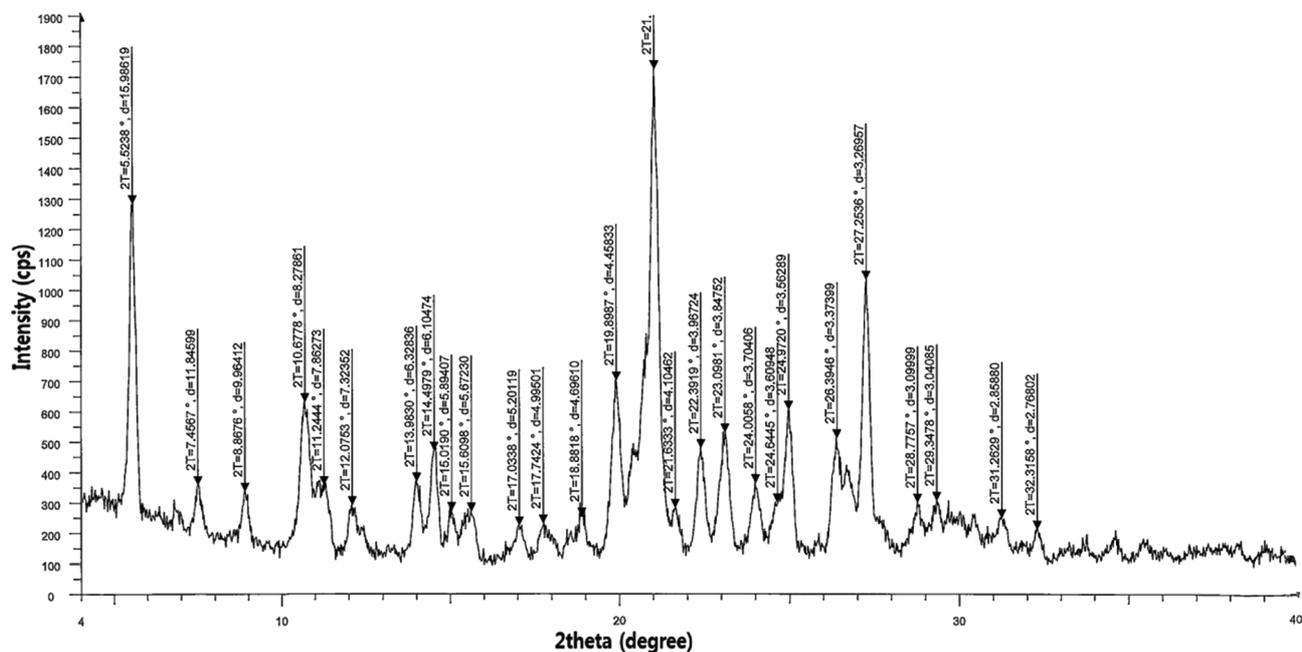


Figure 10. PXRD pattern of Form 3.

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