Indian Journal of Chemistry
Vol. 63, May 2024, pp. 464-472
DOI: 10.56042/ijc.v63i5.8497

New polymorphic forms of Lenvatinib mesylate and process for their preparation

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Received 2 February 2024; accepted (revised) 23 April 2024

This work involves creating and characterizing stable polymorphic forms of Lenvatinib mesylate while ensuring pharmaceutical purity. The process is optimized and uses various analytical techniques such as thermal analysis, powder X-ray diffraction, and differential scanning calorimetry to examine these forms. Using these techniques, these forms can be synthesized on a commercial scale with high efficiency and purity, including two new polymorphs (form 1 and 2) that are highly pure. These findings provide valuable insights into preparing and characterizing stable Lenvatinib mesylate forms, beneficial for developing new pharmaceutical products in the industry. The recognition of a newly discovered, stable polymorph of the anti-cancer molecule marks a crucial milestone in the domain of drug development. This finding not only enhances our comprehension of the molecular characteristics of the compound but also carries the potential for revolutionary effects on cancer therapy in terms of molecular stability.

Keywords: Lenvatinib mesylate, Lenvatinib, Powder X-ray diffraction, Thermal analysis, Differential scanning calorimetry

Lenvatinib Mesylate is an active pharmaceutical ingredient (API) that can be found in a variety of polymorphic forms, including amorphous and crystalline polymorphs and hydrates[1-3]. The form that will be employed as an industrial product will rely on several variables, including its stability, solubility, dissolving rate, bioavailability, production circumstances, and patent constraints. A protocol must be established for the manufacture of the active ingredient and its intermediates in the required form during the drug development process[4-8]. At every step of medication development, thorough control of the API form is important since issues can occur during the manufacturing process. The stability of various API forms can be affected by changes in temperature and humidity, which can result in phase transitions like polymorph transformations, hydration/ dehydration, and crystallization. The chemical and polymorphic purity of the API, as well as the types of important intermediates and contaminants, are all claimed in patents for Lenvatinib mesylate[9,10]. The same holds for patents on medicine formulations. To prepare and define stable polymorphic forms of Lenvatinib mesylate with high efficacy and pharmaceutical purity, which can be exploited for the development of innovative therapeutic products, in-depth research is therefore required. Mesylate salt of Lenvatinib is a kinase inhibitor having a chemical name is 4-(3-chloro-4-(cyclopropylaminocarbonyl) aminophenoxy)-7-methoxy-6-quinolinecarboxamide methane sulfonate. Lenvatinib mesylate is a white to pale reddish yellow powder[11-13]. It is slightly soluble in water and practically insoluble in ethanol. Lenvatinib, a kinase inhibitor, blocks the kinase activity of the VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 in the body (FLT4). In addition to their normal cellular functions, Lenvatinib inhibits additional kinases such as the fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, platelet-derived growth factor receptor alpha (PDGFR), KIT, and RET that have been linked to pathogenic angiogenesis, tumor growth, and cancer progression[14-20]. Moreover, Lenvatinib demonstrated antiproliferative action in hepatocellular cancer cell lines that were reliant on active FGFR signaling and concurrently inhibited the phosphorylation of FGF-receptor substrate 2 (FRS2). Differentiated thyroid cancer, renal cell carcinoma, hepatocellular carcinoma, and endometrial carcinoma are among the cancers for which Lenvatinib is licensed for medical usage[21-25]. Lenvatinib Mesylate was synthesized by the authors in two distinct polymorphic forms employing a range of solvent systems and crystallization conditions. Thermal

analysis, powder X-ray diffraction (PXRD), and infrared spectroscopy were used to describe the polymorphs. The creation of various polymorphs was shown to be highly influenced by the solvent system and crystallization conditions, according to the authors. Also, they noticed that the polymorphic forms displayed various thermal characteristics, which pointed to various thermodynamic stabilities. PXRD was used to determine the crystal structures of Lenvatinib Mesylates two polymorphism forms. The authors discovered that the primary difference in the crystal structures of the polymorphic forms was in the way the molecules were packed. To create stable and effective therapeutic formulations, the study's findings on the crystal structure and crystallization behaviour of Lenvatinib Mesylate polymorphs were useful, according to the study's authors. In conclusion, this study offers important details about the production, description, and crystal crystallization structure analysis of many polymorphic forms of Lenvatinib mesylate. The study emphasizes how critical it is to comprehend the crystal structure and crystallization behaviour of pharmacological molecules to create stable and effective medication formulations. Further research is required to determine how different processing variables and storage circumstances affect the stability and effectiveness of Lenvatinib Mesylate polymorphs.

Experimental Section

Materials

All solvents used for the experiments were of analytical grade.

Preparation of Lenvatinib Mesylate form A

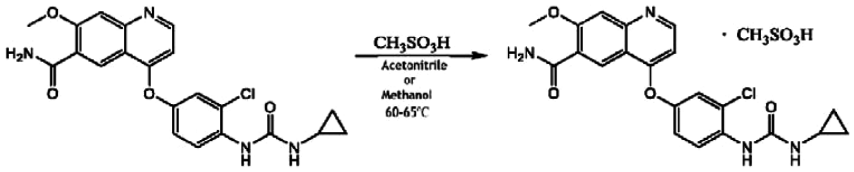
Acetonitrile (50 mL) was added into a round-bottom flask at 25-30°C. Lenvatinib Base (5gm) was added into the flask and stirred the reaction mass for 30 minutes at 25-30°C. Slowly add Methane sulfonic acid solution (1.10gm Methane sulfonic acid in 5 mL Acetonitrile at 25-30°C) into reaction mass at 25-30°C in 10-15 minutes. Stir the reaction mixture for 10 minutes at 25-30°C. Raise the temperature to 60-65°C. Stir reaction mass for 1 hour at 60-65°C. Cool the reaction mass to 25-30°C. Filter the reaction mixture at 25-30°C and wash with 10 mL acetonitrile. The obtained wet material was dried at 40-45°C under vacuum for 12 hours to get 5.95gm Lenvatinib Mesylate form-A. Form-A is also prepared by the same process using Methanol as a solvent instead of acetonitrile (Scheme 1).

Preparation of Lenvatinib Mesylate form M

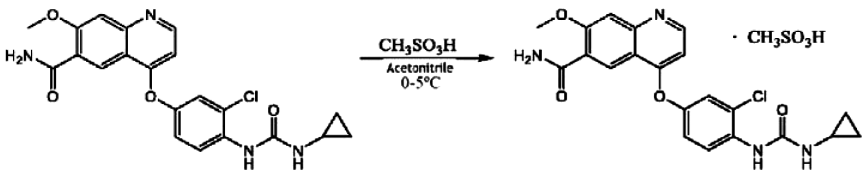
Acetonitrile (100 mL) was added into a round-bottom flask at 25-30°C. Lenvatinib Base (5gm) was added into the flask and stirred the reaction mass for 30 minutes at 25-30°C. Cool the reaction mass to 0-5°C. Slowly add Methane sulfonic acid solution (1.10gm Methane sulfonic acid in 5 mL Acetonitrile at 25-30°C) into reaction mass at 0-5°C in 10-15 minutes. Stir the reaction mixture Stir reaction mass for 2 hour at 0-5°C. Filter the reaction mixture at 0-5°C and wash with 10 mL acetonitrile. The obtained wet material was dried at 40-45°C under vacuum for 12 hours to get 5.9gm Lenvatinib Mesylate form-M (Scheme 2).

Preparation of Lenvatinib Mesylate form C

To a mixed solution of acetic acid (14 mL) and methane sulfonic acid (0.37 mL, 5.62 mmol) was added Lenvatinib Base (2. g, 4.69 mmol) to dissolve at 4°C. After confirming dissolution, 2-propanol (9 mL) and seed crystals of a crystalline form of Lenvatinib Mesylate (Form C) (1 mg), in this order, to



Scheme 1 — Preparation of Lenvatinib Mesylate form A



Scheme 2 — Preparation of Lenvatinib Mesylate form M

the reaction mixture, and the reaction mixture was stirred for 2 min. Additional isopropyl acetate (1 mL) was then added dropwise over 3 min. After the addition of the isopropyl acetate was complete, the reaction mixture was stirred for 1.5 hours and further stirred at 15°C for 14 hours (Scheme 3).

Preparation of Lenvatinib Mesylate novel crystalline form 1

Tetrahydrofuran (50 mL) was added into a round-bottom flask at 25 to 30°C. Lenvatinib Base (5gm) was added into the flask and stirred the reaction mass for 30 minutes at 25-30°C. Slowly add Methane sulfonic acid solution (1.10gm Methane sulfonic acid in 5 mL Tetrahydrofuran) into reaction mass at 25-30°C in 10-15 minutes. Stir the reaction mixture for 2 hours at 25-30°C. Filter the reaction mixture at 25-30°C and wash with 5 mL Tetrahydrofuran (Twice). The obtained wet material was dried at 35-40°C under vacuum for 12 hours to get 5.95gm Lenvatinib Mesylate Novel Polymorph-1 (Scheme 4).

Preparation of Lenvatinib Mesylate novel crystalline form 2

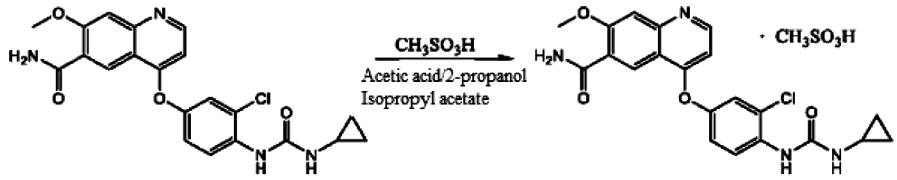
Tertiary butanol (100 mL) was added into a round-bottom flask at 30-35°C. Lenvatinib Base (5gm) was added into the flask and stirred the reaction mass for 30 minutes at 30-35°C. Slowly add Methane sulfonic acid solution (1.10gm Methane sulfonic acid in 5 mL Tertiary butanol at 30°C) into reaction mass at 30-35°C in 10-15 minutes. Stir the reaction mixture for 2 hours at 30-35°C. Filter the reaction mixture at 30-35°C and wash with 10 mL Tertiary butanol (Twice). The obtained wet material was dried at 40-45°C under vacuum for 12 hours to get 6.01gm Lenvatinib Mesylate Novel Polymorph-2 (Scheme 5).

Powder X-ray Diffraction

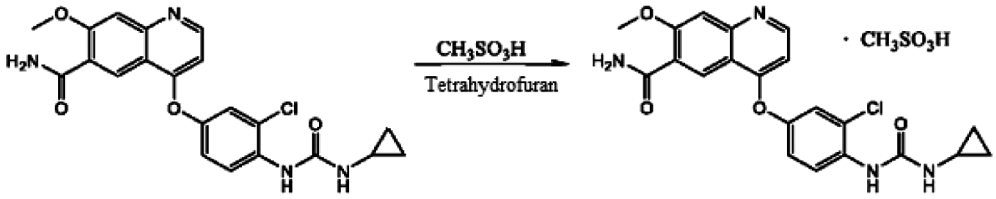
Powder diffractograms were performed on a Phillips Xpert MPD CuKα1 radiation. The samples were pressed on a glass plate. The instrument was operated in the range from 3 to 40° with the scan rate of 0.02°/min.

Differential Scanning Calorimetry

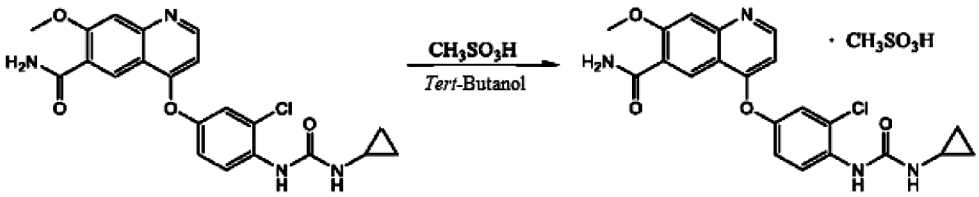
DSC measurements were performed using the Perkin Elmer DSC-4000. Samples were weighed as received, without preparation. About 5–10 mg of the studied sample was weighed into a standard aluminum pan (40 μL). The pans were hermetically sealed and perforated before measurements. The samples were heated from 25 to 300°C at 10°C/min. The measurements were performed in the nitrogen atmosphere.



Scheme 3 — Preparation of Lenvatinib Mesylate form C



Scheme 4 — Preparation of Lenvatinib Mesylate novel crystalline form 1



Scheme 5 — Preparation of Lenvatinib Mesylate novel crystalline form 2

Results and Discussion

Characterization of Powder X-ray Diffraction of various Lenvatinib Crystalline forms

A non-destructive method for examining Lenvatinib's many crystalline forms is powder X-ray diffraction (PXRD). A powder sample's crystal structure and polymorphism can be ascertained by exposing it to X-rays and observing the diffraction pattern. PXRD can be used to monitor the purity and stability of Lenvatinib crystalline forms under various circumstances, as well as to identify any contaminants in the sample. Lenvatinib and other medications must be characterized, and PXRD is a crucial technique for doing so.

Lenvatinib Mesylate Form A

PXRD of Lenvatinib Form A typically shows characteristic peaks at 2θ angles of 9.7°, 20.3°, 20.8°, 21.4°, 22.2° and 23.4°. The intensities and positions of these peaks can be used to determine the crystal structure of Lenvatinib Form A and its purity. Overall, PXRD is an essential tool for analyzing the physicochemical properties of Lenvatinib Form A and ensuring its quality and stability in pharmaceutical formulations. Fig. 1 depicts the PXRD pattern for Lenvatinib crystalline form A.

Lenvatinib Mesylate Form M

PXRD of Lenvatinib Form M typically shows characteristic peaks at 2θ angles of 6.2°, 8.0°, 11.4°, 15.3°, 19.7° and 24.9°. The intensities and positions of these peaks can be used to determine the crystal structure of Lenvatinib Form M and its purity. Overall, PXRD is an essential tool for analysing the physicochemical properties of Lenvatinib Form M and ensuring its quality and stability in pharmaceutical formulations. Fig. 2 depicts the PXRD pattern for Lenvatinib crystalline form M.

Lenvatinib Mesylate Form C

PXRD of Lenvatinib Form C typically shows characteristic peaks at 2θ angles of 6.1°, 10.2°, 10.5°, 17.6°, 23.6° and 25.6°. The intensities and positions of these peaks can be used to determine the crystal structure of Lenvatinib Form C and its purity. Overall, PXRD is an essential tool for analyzing the physicochemical properties of Lenvatinib Form C and ensuring its quality and stability in pharmaceutical formulations. Fig. 3 depicts the PXRD pattern for Lenvatinib crystalline form C.

Lenvatinib Mesylate Novel Crystalline Form 1

PXRD of Lenvatinib novel crystalline form 1 typically shows characteristic peaks at 2θ angles of

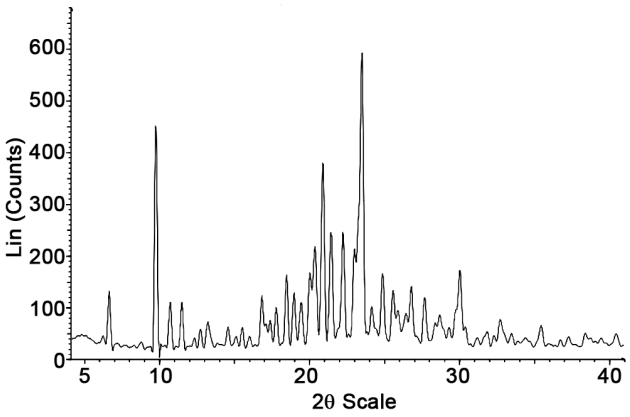


Fig. 1 — PXRD patterns of Lenvatinib mesylate form A

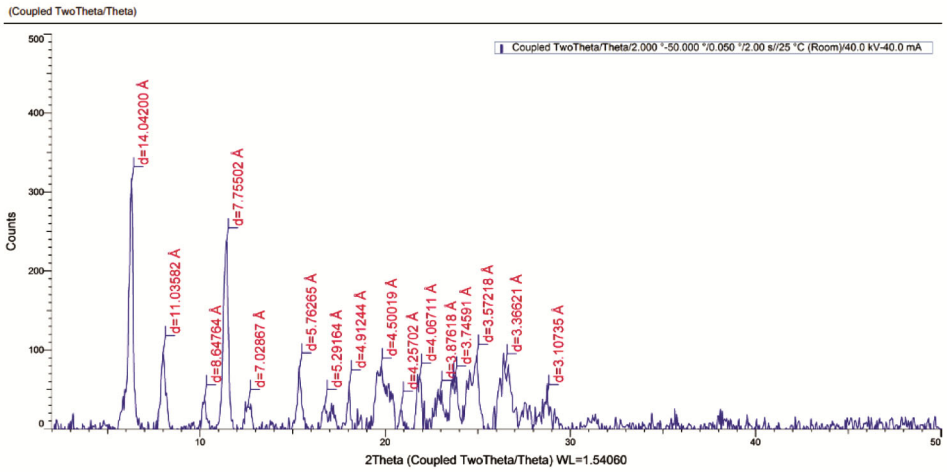


Fig. 2 — PXRD patterns of Lenvatinib mesylate form M

10.8°, 19.4°, 23.8°, 25.8°, 28.6° and 30.8°. The intensities and positions of these peaks can be used to determine the crystal structure of Lenvatinib novel crystalline form 1 and its purity. Overall, PXRD is an essential tool for analysing the physicochemical properties of Lenvatinib novel crystalline form 1 and ensuring its quality and stability in pharmaceutical formulations. Fig. 4 depicts the PXRD pattern for Lenvatinib crystalline novel crystalline form 1.

Lenvatinib Mesylate Novel Crystalline Form 2

PXRD of Lenvatinib novel crystalline form 2 typically shows characteristic peaks at 2θ angles of 4.5°, 6.1°, 9.1°, 10.5°, 17.7°, 21.7° and 23.6°. The intensities and positions of these peaks can be used to determine the crystal structure of Lenvatinib novel crystalline form 2 and its purity. Overall, PXRD is an essential tool for analysing the physicochemical properties of Lenvatinib novel crystalline form 2 and ensuring its quality and stability in pharmaceutical

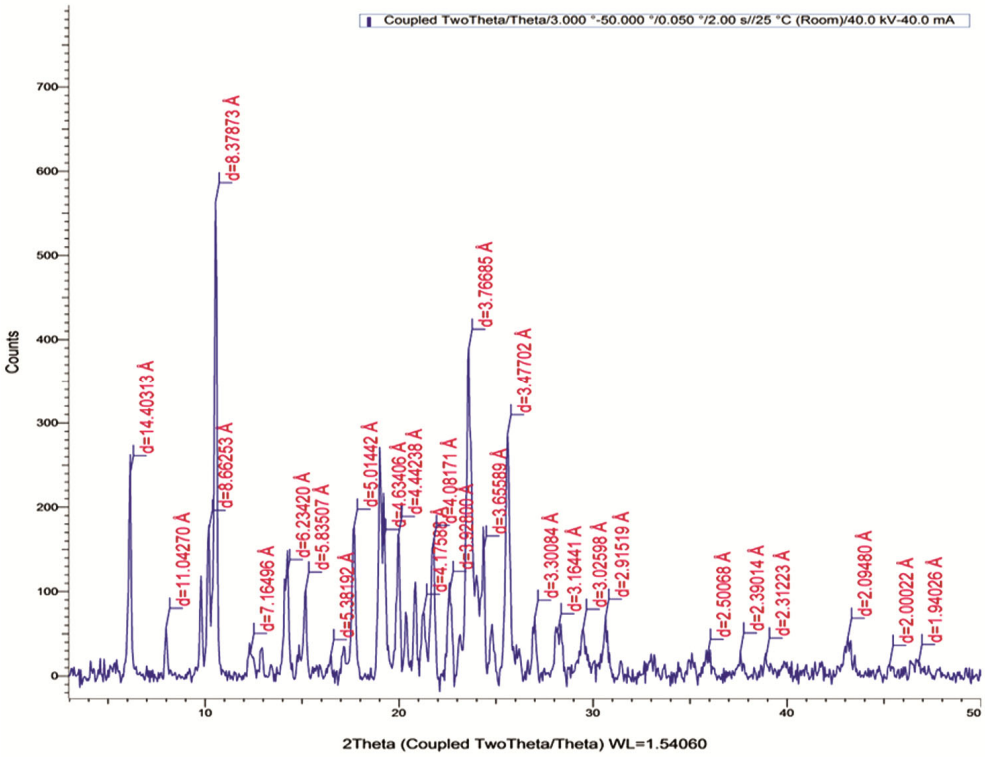


Fig. 3 — PXRD patterns of Lenvatinib mesylate form C

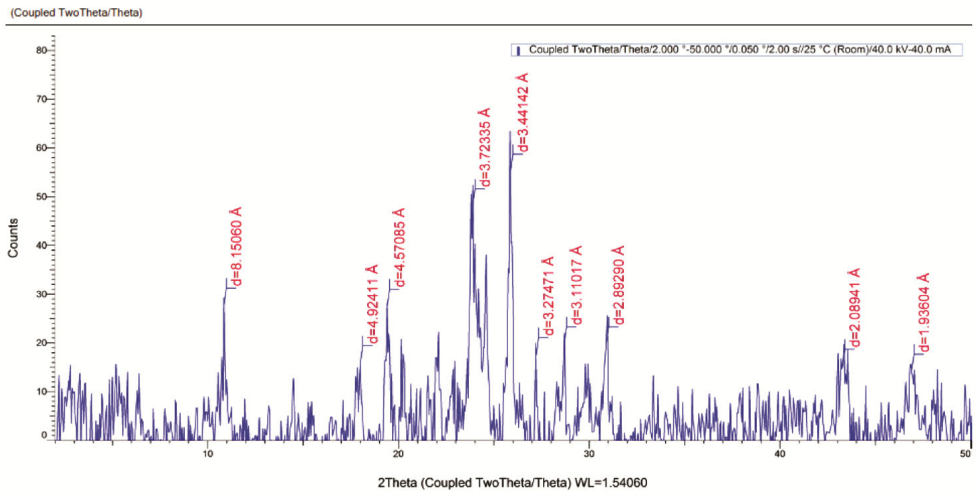


Fig. 4 — PXRD patterns of Lenvatinib novel crystalline form 1

formulations. Fig. 5 depicts the PXRD pattern for Lenvatinib crystalline novel crystalline form 2.

Characterization of Differential scanning calorimetry of various Lenvatinib Crystalline forms

A thermal analysis method called differential scanning calorimetry (DSC) is used to examine the thermal behaviour of different Lenvatinib crystalline forms. DSC can offer information regarding phase transitions, melting temperatures, glass transitions, and other thermal properties of the sample by measuring the heat flow necessary to keep the sample at the desired temperature. DSC can also be used to recognize polymorphic forms and assess their stability under various circumstances. DSC is an effective tool for figuring out the physical and chemical characteristics of Lenvatinib crystalline forms and can help with the creation of stable and effective medication formulations.

Lenvatinib Mesylate Form A

DSC curves of Lenvatinib Mesylate form A is characterized by a broad endothermic effect in the temperature range from 240 to 247°C connected with the evaporation of residual solvents (Fig. 6).

Lenvatinib Mesylate Form M

DSC curves of Lenvatinib Mesylate form M is characterized by two broad endothermic effect in the temperature range from 84 to 143°C and 156 to 166°C connected with the evaporation of residual solvents (Fig. 7).

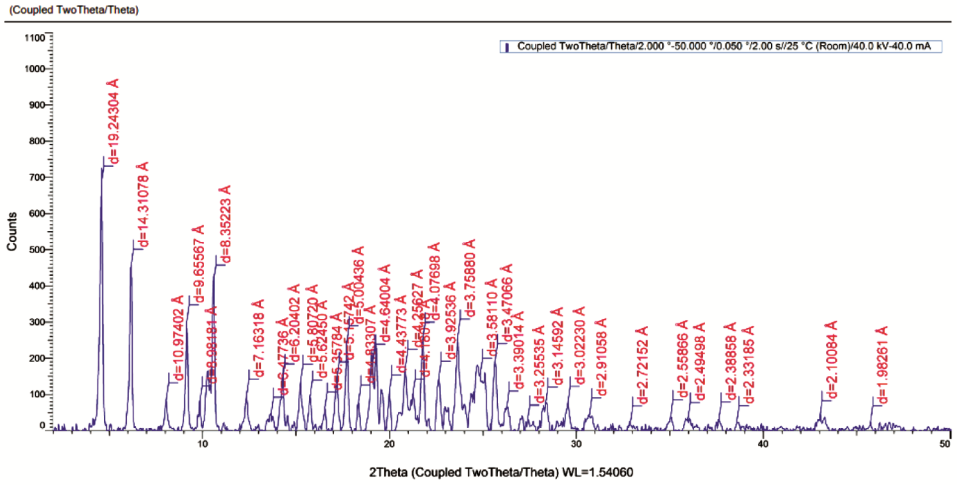


Fig. 5 — PXRD patterns of Lenvatinib novel crystalline form 2

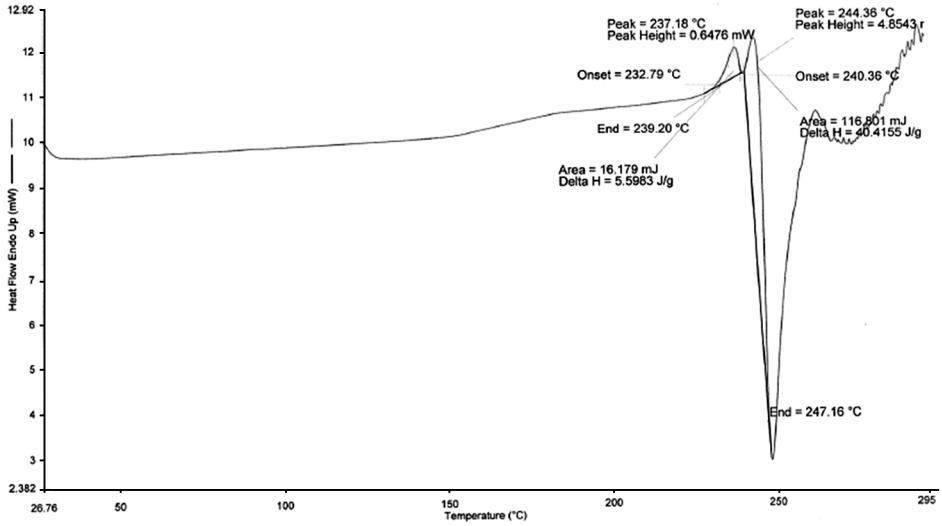


Fig. 6 — DSC patterns of Lenvatinib Mesylate form A

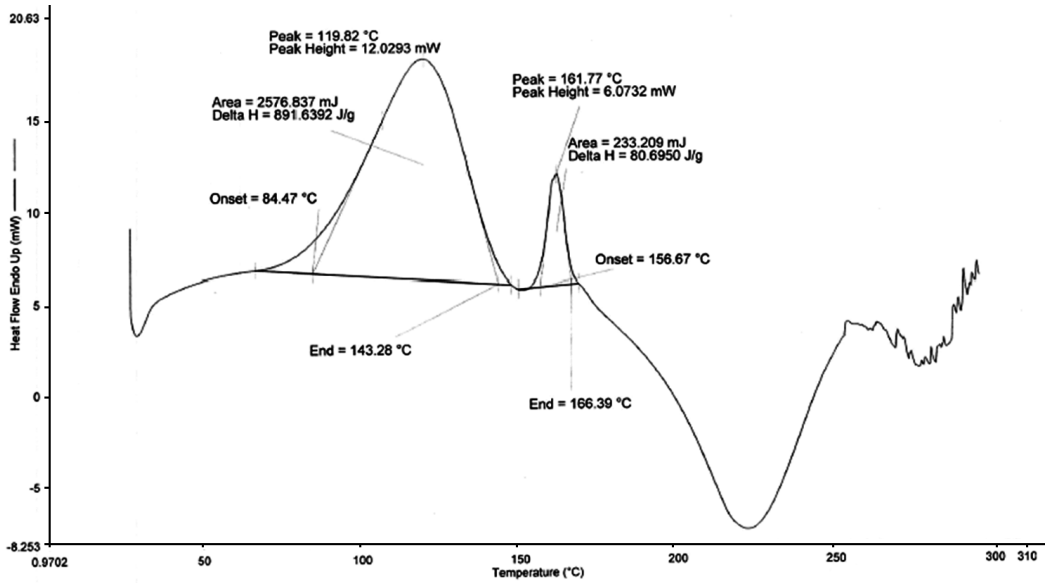


Fig. 7 — DSC patterns of Lenvatinib Mesylate Form M

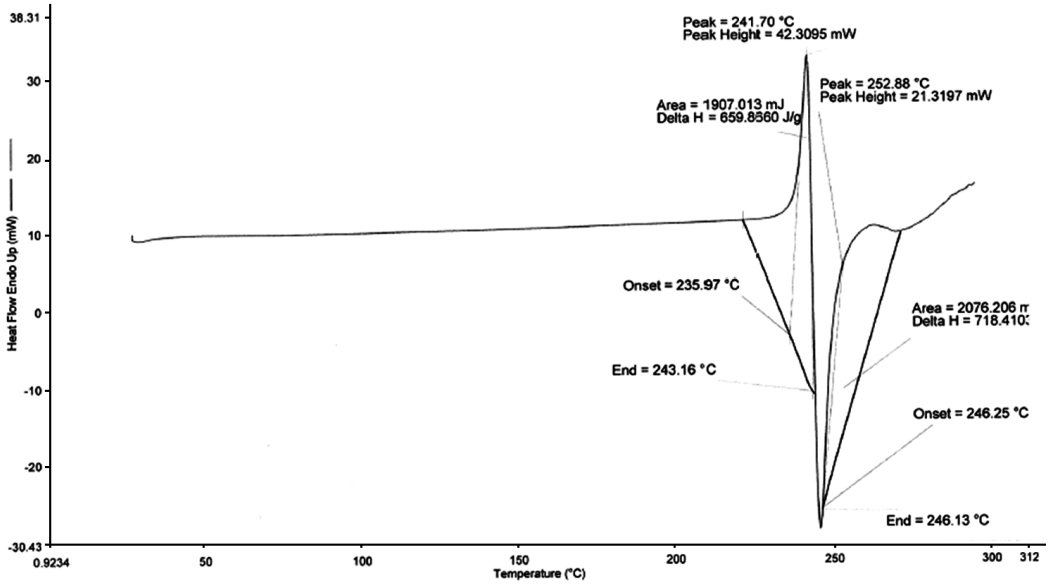


Fig. 8 — DSC patterns of Lenvatinib Mesylate Form C

Lenvatinib Mesylate Form C

DSC curves of Lenvatinib Mesylate form C are characterized by a broad endothermic effect in the temperature range from 235 to 246°C connected with the evaporation of residual solvents (Fig. 8).

Lenvatinib Mesylate Novel Crystalline Form 1

DSC curves of Lenvatinib Mesylate novel crystalline form 1 are characterized by a broad endothermic effect in the temperature range from 228 to 273°C connected with the evaporation of residual solvents (Fig. 9).

Lenvatinib Mesylate Novel Crystalline Form 2

DSC curves of Lenvatinib Mesylate novel crystalline form 2 are characterized by a broad endothermic effect in the temperature range from 229 to 239°C connected with the evaporation of residual solvents (Fig. 10).

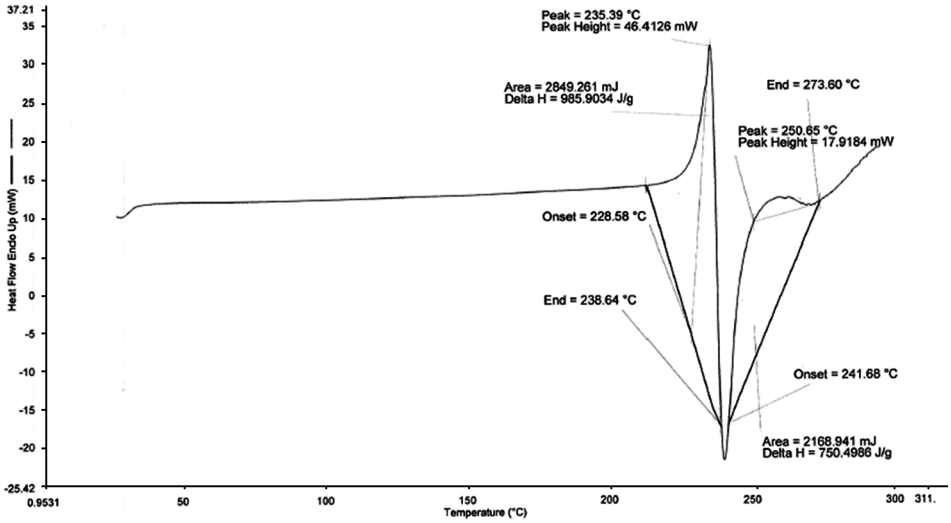


Fig. 9 — DSC patterns of Lenvatinib Mesylate novel crystalline Form 1

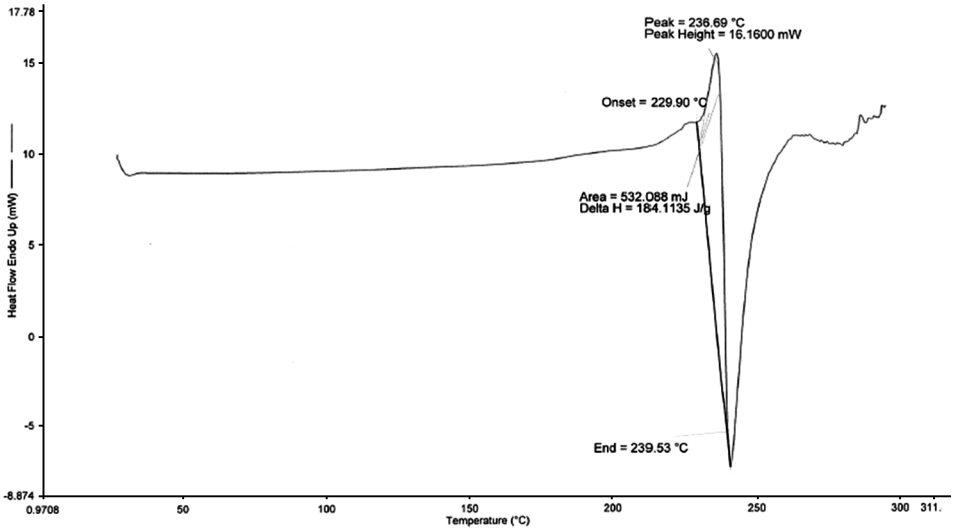


Fig. 10 — DSC patterns of Lenvatinib Mesylate novel crystalline form 2

Conclusion

The authors of this study have achieved a significant breakthrough by developing a novel method to synthesize polymorphic forms of Lenvatinib mesylate, which adhere to the rigorous purity standards mandated for active ingredients in pharmaceutical products. Along with that, the newly obtained polymorphic forms exhibit remarkable stability based on thermos-analytical techniques, rendering them suitable for incorporation into the formulation of this potent anti-cancer medication. Our investigation employed a combination of powder diffraction and differential scanning calorimetry to comprehensively characterize the physicochemical properties of these distinct crystalline forms, thereby contributing valuable insights to the field of pharmaceutical research and development. The identification of a new, stable polymorph of the anti-cancer molecule stands as a pivotal moment in drug development. This discovery not only advances our understanding of the molecular behaviour of the compound but also holds the potential for transformative impacts on cancer therapy and the conceptualization of pharmaceuticals.

Acknowledgment

The authors would like to extend sincere appreciation to BDR Lifesciences Pvt Ltd for their invaluable contributions in providing analytical and material support for the present research endeavors.

Their unwavering commitment to the scientific pursuits has been instrumental in the success of this project. The expertise and resources offered by BDR Lifesciences Pvt Ltd have significantly enhanced the quality and depth of research. Their dedication to delivering high-quality analytical services and supplying essential materials have played a crucial role in advancing the present scientific investigations. The authors are extremely grateful for their collaboration, which has not only enriched the research but also fostered a spirit of innovation and progress in the work. The authors are also thankful to RK University for creating research opportunities.

Funding

This work was not supported by any grant.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776

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