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From Solution to Solid Form: Crystallisation Methods and Their Role in Pharmaceutical Polymorphism of L-isoleucine

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ABSTRACT

Polymorphism in crystalline materials significantly influences their physicochemical properties, particularly in pharmaceutical applications. This study examined the impact of crystallisation methods on the formation of three L-isoleucine polymorphs (α, β, and γ) using polythermal and isothermal cooling, slow-solvent evaporation, and electric field-assisted crystallisation. X-ray powder diffraction confirmed their distinct crystalline structures, while differential scanning calorimetry and solubility analysis provided insights into thermal stability and dissolution behaviour. Cooling rates, supersaturation levels, and external factors such as mixing speed and electric fields strongly influenced polymorph formation. Rapid cooling favoured the metastable γ form, while controlled cooling rates led to the thermodynamically stable α form. The application of an electric field selectively promoted the β form, highlighting the role of external stimuli in directing polymorphic transitions. All L-isoleucine polymorphs exhibited identical flat hexagonal plate-like morphology and can only be distinguished by crystal apex angles. The α form, the most stable polymorph, had the highest melting point (288.6 °C) and the highest solubility. In contrast, β and γ forms are metastable, undergoing a solid-solid polymorphic transition (276.7 °C and 216.3 °C, respectively) to the thermodynamically stable α form. In aqueous solution, the β form showed the lowest solubility, indicating strong lattice stability, whereas the γ form displayed moderate solubility, compared to the a form which exhibited the highest solubility. These findings highlighted the critical role of crystallisation methods in controlling polymorphic outcomes, contributing to improved process control and formulation consistency in pharmaceutical and materials science applications.

Keywords: Polymorphism, Crystallisation Method, L-isoleucine Polymorphs, Thermal Stability, Solubility

INTRODUCTION

Polymorphism is a critical aspect of pharmaceutical sciences that influences the stability, solubility, and bioavailability of Active Pharmaceutical Ingredients (APIs). The presence of multiple crystalline forms (polymorphs) can result in significant variations in physicochemical properties, which directly affect drug efficacy and regulatory approval. For instance, polymorphism in compounds such as Ritonavir (Bauer et al., 2001; Chemburkar et al., 2000; Parent et al., 2023) and Carbamazepine (Czernicki & Baranska, 2013; Surov et al., 2023) has demonstrated its impact on drug performance and stability. Polymorphism arises from either differences in molecular packing within the crystal lattice (crystal packing polymorphism) or variations in molecular conformation within a similar packing arrangement (conformational polymorphism). In practice, these categories can overlap, especially with flexible molecules that exhibit subtle conformational variations. The presence of polymorphs is commonly identified using several characterisation techniques such as X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and optical microscopy (Ticona Chambi et al., 2024).

Understanding the factors driving polymorph formation, including the role of crystallisation methods, is essential for the industry. Although these techniques

determine polymorphic outcomes, the influence of specific processes on polymorphic transitions remains partially understood. Figure 1 presents a typical process workflow in pharmaceutical manufacturing, illustrating the interconnected steps from solution to solid form and highlighting the role of polymorphs in the solid form produced from a process. Variations in the polymorphs can lead to differences in melting points, solubility, crystal shape, mechanical properties (e.g., brittleness and colour) and downstream processing attributes such as drying, comminution, and compaction behaviour.

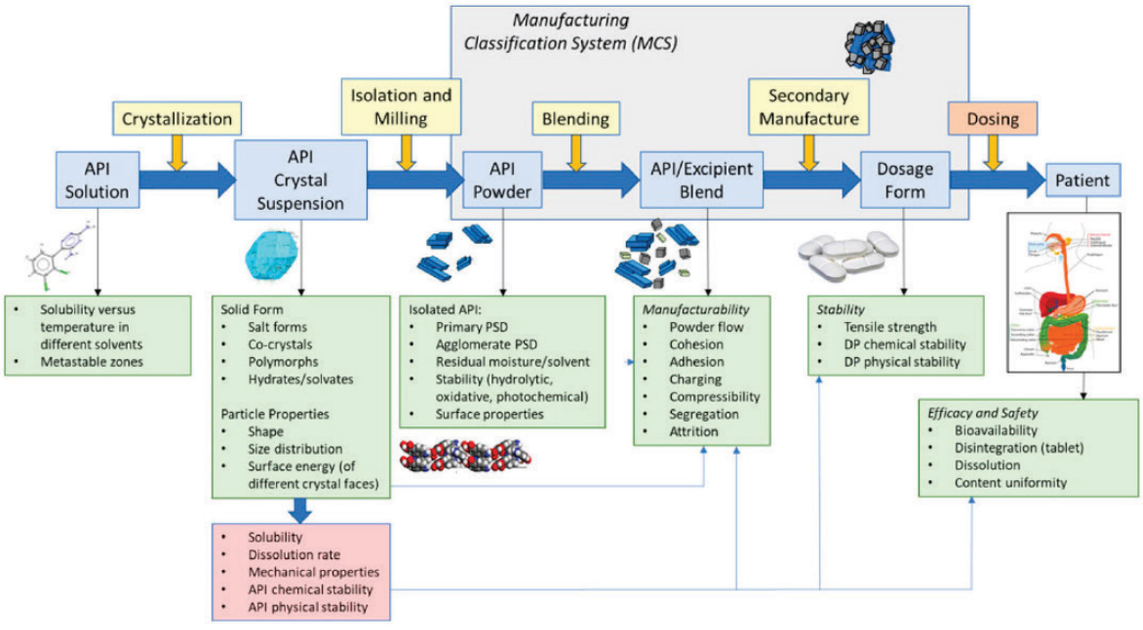

FIGURE 1. A process workflow typically used by pharmaceutical industries highlighting the interconnectivity of processes from solution to solid form. This figure was reprinted with permission from Informa UK Limited, trading as Taylor & Francis Ltd., https://www.tandfonline.com/, (Anuar et al., 2022).

TABLE 1. Variation of melting temperatures and solubility of polymorphic forms of Ritonavir (Yao et al., 2023)

Compound	Polymorphic Form and Melting point (°C)	Solubility in ethanol/water (99/1) at 5 °C (mg/mL)
Ritonavir	Form I: 120.8 Form II: 121.5 Form III: 114.6	Form I: 90 Form II: 19 Form III: 695-744

Table 1 presents the variation in physicochemical properties, specifically melting temperature and solubility, among three polymorphic forms of Ritonavir, an antiretroviral medication used for HIV treatment. Differences in melting points affect processing temperatures and product stability, while variations in solubility significantly influence bioavailability and therapeutic efficacy (Chaurasia, 2016; Mao et al., 2016).

Whilst controlling which polymorph forms during drug synthesis is critical, due to their differences in physical properties such as solubility and bioavailability, crystallisation techniques significantly influence the polymorphic outcome of APIs. Various crystallisation methods could offer distinct advantages in manipulating polymorphic controls. The solvent evaporation technique relies on the gradual removal of solvent, promoting molecular self-assembly into ordered structures. This method is often favoured for producing thermodynamically stable polymorphs with well-defined crystal morphologies due to the slow and controlled nature of the process. Conversely, anti-solvent crystallisation involves the addition of an anti-solvent to decrease API solubility, inducing nucleation. This approach can be particularly useful for generating metastable polymorphs or controlling particle size, although it requires careful optimisation to avoid uncontrolled precipitation.

Polythermal and isothermal crystallisation methods leverage temperature gradients during cooling to selectively promote the formation of specific polymorphs during

nucleation and growth. Polythermal crystallisation involves a gradual reduction in temperature, while isothermal crystallisation maintains a constant temperature to observe equilibrium crystal formation (Lu & Rohani, 2009). However, previous work on urea-formaldehyde resin, polythermal crystallisation resulted in polycrystal (Singh et al., 2014). The crystallisation process, which dictates the formation of the type of polymorphs, is governed by the interplay between kinetic and thermodynamic factors. Kinetic factors often favour the formation of metastable polymorphs, while thermodynamic control leads to a more stable form, which in turn influences the rate of nucleation and growth. Under these conditions, molecules may arrange into metastable polymorphs before they can transition into their thermodynamically stable form. Rapid nucleation rates can lead to the formation of metastable polymorphs because they allow less time for the system to reach equilibrium. According to the Ostwald step rule, the entropy of the dissolved solute is typically closely aligned with that of the metastable phase, facilitating its preferential nucleation (Lauer et al., 2023). Therefore, the nucleation rate of the metastable form is generally higher than the stable form. Taking an example presented in Table 1, Ritonavir initially crystallised in a metastable polymorph (Form I) that was soluble and bioavailable. However, a more stable but poorly soluble Form II later emerged, leading the manufacturers to opt for stable Form II (Bauer et al., 2001) despite its low solubility (in a mixture of ethanol and water) (19 mg/mL) instead of the metastable Form I (90 mg/mL) (Yao et al., 2023). In the case of Amlodipine Besylate, an antihypertensive drug, has multiple polymorphic forms. During production, metastable forms can emerge under rapid cooling or high supersaturation conditions. Controlling crystallisation kinetics by adjusting the solvent composition and cooling rates helps stabilise the desired polymorph (Koradia et al., 2010).

Conversely, thermodynamic control focuses on achieving equilibrium conditions where free energy is minimised and, hence, typically results in more stable crystalline forms. Given enough time and proper solvent conditions, the drug could crystallise in its thermodynamically stable form, ensuring consistency in tablet formulations (Chewle et al., 2020; Dathu Reddy et al., 2014; Shahrir et al., 2022).

Understanding these principles is critical for ensuring consistent production quality and optimising manufacturing efficiency. Precise control of both kinetic and thermodynamic factors is essential for modulating polymorph selection during crystallisation. To systematically investigate the influence of crystallisation techniques on polymorphism, experimental conditions must be rigorously standardised, including careful solvent selection, precise temperature regulation with a controlled water bath, and consistent agitation levels. These standardised conditions enable direct comparisons between techniques and allow manufacturers to optimise polymorphic outcomes, thereby ensuring consistent drug formulation and efficient production (Girón, 2005; Mangin et al., 2009; Threlfall, 2000).

This study aims to investigate the influence of various crystallisation techniques on the formation of L-isoleucine polymorphs: α (known as Form A (Anuar et al., 2009)), β (known as Form B (Anuar et al., 2009)), and γ, using controlled experimental conditions. By exploring the role of method selection in polymorphic behaviour, the findings contribute to improved process control and formulation consistency in pharmaceutical production.

METHODOLOGY

MATERIALS

The raw material used in this work was L-isoleucine ($C_6H_{13}O_2N$) molar mass of 131.2 g/mol, purity ≥ 99.0%), purchased from Merck. Distilled water was used as a solvent to make up the aqueous solutions.

COOLING CRYSTALLISATION

The polymorphic form of L-isoleucine was produced based on the dissolution solubility data obtained experimentally in this study, using a combination of polythermal and isothermal cooling crystallisation methods. The experiment was conducted in a 250 mL jacketed glass reactor equipped with an overhead stirrer to ensure efficient mixing. The speed of the stirrer was set at 400 rpm. Two programmable refrigerated baths were used to regulate the temperature of the solution throughout the crystallisation process (refer to Figure 2). A 3.8 g of L-isoleucine powder was added to 100 mL of distilled water to make up a 38 g/L solution concentration. The mixture of L-isoleucine solution was heated to 71 °C (15 °C above the saturated temperature for 38 g/L) for 60 minutes using the first refrigerated bath. Then, the temperature of the solution was reduced to the saturation temperature, 56 °C, at a controlled rate of 0.2 °C/min. The supply of hot water from the first refrigerated bath was stopped, and for the quench cooling process, the cold water at 20 °C from the second refrigerated bath was supplied to the jacketed reactor. The target supersaturation level for 38 g/L concentration of the solution at 20 °C was 1.65. The cooling rate (estimated at 4 °C/min) during the quench cooling period was considered a non-controlled variable. The formed crystals were harvested and dried in an oven at 40 °C for one week for further characterisation analysis.

SOLID STATE CHARACTERISATION

The recrystallised L-isoleucine powder was characterised by X-ray powder diffraction (XRPD) (Rigaku Ultima IV) with CuKα radiation (λ = 1.5406 Å), operating at 40 kV and 40 mA and scan rate of 0.1 °/s. Diffraction patterns were collected over a 2θ range of 14° to 30°, enabling the identification of polymorphic forms through the variations in diffraction peak positions. Crystal morphologies were observed using a Meiji Techno 1559 optical microscope, with image capture and analysis performed using Zarbeco software. The melting temperature of the dried crystals was measured using differential scanning calorimetry (DSC) (Metler Toledo DSC 820) under nitrogen purging. About 2 mg of the sample was weighed into 40 µL aluminium crucibles. The samples were heated from 25 °C to 400 °C at a rate of 10 °C/min, and their thermal quantities were measured.

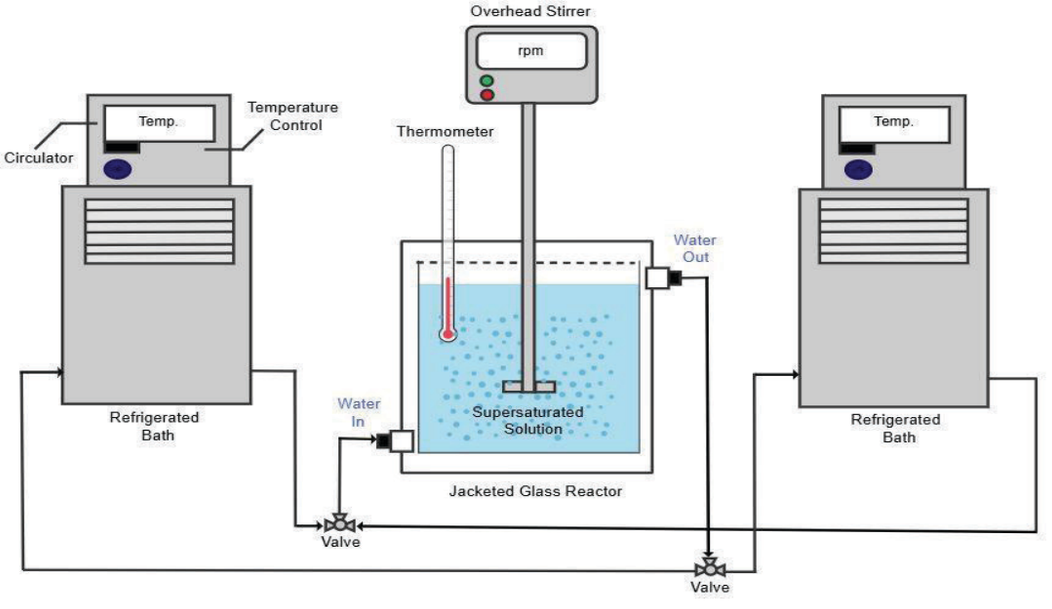

FIGURE 2. Schematic diagram of recrystallisation of L-isoleucine experimental set-up with two programmable refrigerated baths.

SOLUBILITY DETERMINATION

The solubility of the α, β and γ forms of L-isoleucine were experimentally determined using gravimetric methods. Approximately 0.1 g of a known polymorph was dissolved in distilled water, which was heated in a jacketed glass reactor at a fixed temperature (40 °C) with continuous stirring. Then, the same amount of L-isoleucine was gradually added to the solution until no further dissolution was observed. The maximum dissolved amount of L-isoleucine was recorded as the solubility point at 40 °C. The experiment was conducted in triplicate for reproducibility.

RESULT AND DISCUSSION

CRYSTALLISATION METHODS AND POLYMORPHIC FORMS

The choice of crystallisation method plays a critical role in determining the polymorphic forms of L-isoleucine. Key factors such as temperature control (polythermal and isothermal methods), slow-solvent evaporation, and the application of an electric field are particularly influential in directing crystallisation of active pharmaceutical ingredients (APIs) (Azmi et al., 2021; Shahrir et al., 2023) and hence, the route of the polymorph formation. The Polymorphic form outcomes of L-isoleucine crystallisation were demonstrably dependent on cooling rates, supersaturation levels, and initial concentrations used. Table 2 summarises the crystallisation methods with their respective grown L-isoleucine polymorphs, whilst Figure 3 illustrates the schematic representation of the crystallisation methods in recrystallising the L-isoleucine polymorphs.

In polythermal crystallisation, the crystallised form was dependent on the cooling rate. The controlled cooling of 44 g/L concentration yielded the β polymorph at rates between 0.25 and 0.75 °C/min, while a slower rate of 0.1 °C/min preferentially produced the thermodynamically favoured α polymorph (Anuar et al., 2009). The findings revealed that higher cooling rates resulted in elevated nucleation rates and promoted the formation of the metastable forms (i.e., β form) due to kinetic control.

Conversely, a low cooling rate allowed the system to approach equilibrium, hence facilitating the growth of the stable polymorph (i.e., the α form).

In isothermal crystallisation, the solution quenching method at a specific supersaturation level induced the formation of the γ form of L-isoleucine. Quenching a 38 g/L solution to 20 °C at a supersaturation of 1.65 triggered a distinct molecular transition, as evidenced by significant alterations in the diffraction pattern compared to the established α and β forms (Anuar et al., 2009). However, in this experiment, the crystallisation temperature was recorded at 31oC, i.e., within the polythermal region. When a solution is rapidly cooled from its saturation temperature, the solubility of the compound decreases, creating a highly supersaturated state. A high solution supersaturation likely favours the nucleation of metastable or kinetically favoured polymorphs instead of the thermodynamically stable form at lower temperatures (Hodnett & Verma, 2019). For instance, rapid cooling induced the formation of metastable polymorphs of L-menthol (Murugan & Karuppannan, 2024), while the controlled cooling rates in continuous crystallisation processes affected the polymorphic forms of L-glutamic acid (Achermann et al., 2023).

The experimentally grown β form of L-isoleucine exhibited a profile similar to the resolved data deposited in the Cambridge Crystallographic Data Centre (CCDC) (ref code: LISLEU03) (Curland et al., 2018). The CCDC data, representing a single crystal of the β form, was obtained through slow-solvent evaporation from a supersaturated solution at 49.85 °C. A supersaturated solution was prepared by dissolving a known weight of L-isoleucine, based on the solubility data (Anuar et al., 2009), in water under constant stirring and heating. The resulting homogeneous solution was then filtered and subjected to slow-solvent evaporation until crystal formation was observed. Electric field-assisted crystallisation was shown to promote the nucleation of β form of L-isoleucine due to the presence of the localised electric field. Notably, when an electric field (5V and 20V) was applied to L-isoleucine solution (48 g/L) through carbon electrodes (3 cm length, 1 cm × 0.1 cm × 10 cm), the β form was preferentially produced. This effect was observed under both polythermal (cooling rate: 0.7 °C/min) and isothermal crystallisation methods at controlled supersaturation levels (1.08 and 1.14) (refer to Table 2). The influence of an electric field was likely attributed to frequency-induced molecular agitation, which increases intermolecular bond formation (Pan et al., 2015), and in this case, thereby promoting β form stability in the aqueous solution.

TABLE 2. Crystallisation methods and their respective L-isoleucine polymorphic crystals formed.

Methods	Controlled variables	Solution concentration	Electric field	Polymorph formed
[a]Polythermal	Cooling rates	44 g/L	-	α, β
Polythermal (quenching) - isothermal	Supersaturation level	38 g/L	-	γ
[b]Slow-solvent evaporation	Isothermal	Not known	-	β
[c]Electric field-aided (polythermal and isothermal)	Cooling rate and supersaturation level	48 g/L 48 g/L	5V 20V	β β

[a]Anuar et al. (2009), [b]Curland et al. (2018), [c]Md Azmi et al. (2021).

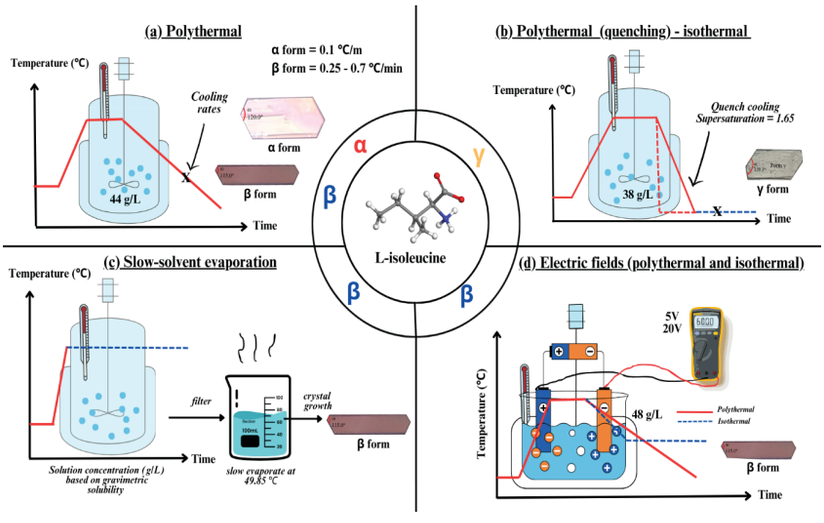

FIGURE 3. Schematic representation of crystallisation methods in recrystallising the L-isoleucine polymorphs.

CHARACTERISATION OF L-ISOLEUCINE OF POLYMORPHS

The crystallisation of L-isoleucine, conducted using both polythermal and isothermal methods, yielded consistent crystal morphologies. Optical microscopy, as depicted in Figure 4, revealed that all polymorphic forms exhibited flat, hexagonal plate-like shapes. These crystals were almost identical in appearance and are related by 2-fold crystal symmetry. However, they can be differentiated through the apex angle, w of the crystals. For α form crystals, 60 % of the observed frequency distribution of measured apex angle fell within the range of 116°–120°. Similarly, the apex angle for the β form was primarily within the 111°–115° range, accounting for 67 % of the observed frequency distribution (Anuar et al., 2009). These results highlight the distinct crystallographic characteristics of the α and β polymorphs based on their apex angle distributions. In contrast, the angle measurement of five γ form crystals harvested from the quenched cooling crystallisation exhibited a wider apex angle within the range of 121° -139°.

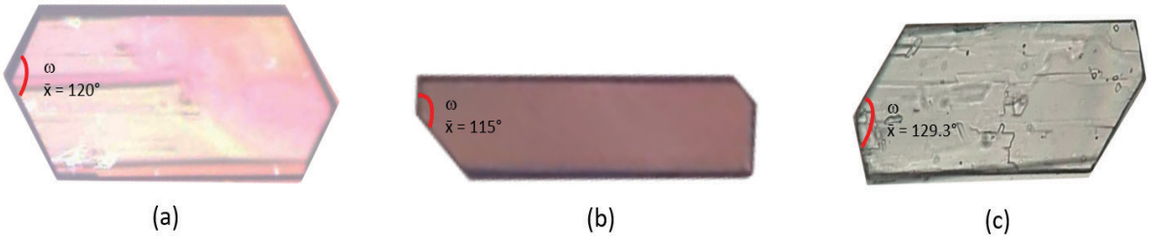

FIGURE 4. Crystal morphologies of L-isoleucine polymorphs: (a) α form, (b) β form and (c) γ form, showing almost identical morphologies and can only be differentiated through the apex angle.

The XRPD analysis confirmed the presence of the γ form using a quench-cooling approach designed to achieve a specific supersaturation level. The structural diffraction pattern of the γ form was compared with those of the α and β forms (Figure 5). The γ form was identified by eight characteristic diffraction peaks at 2θ values of 16.42°, 18.52°, 19.56°, 20.15°, 22.04°, 23.49°, 26.89°, and 27.87°. In contrast, five peaks observed in the α and β forms (2θ = 16.72°, 18.06°, 22.45°, 22.96°, and 28.88°) were either significantly broadened or absent in the γ form. However, as shown in Figure 5, the similarities in diffraction peaks at 2θ = 12.67°, 19.07°, 25.53°, 32.06°, and 38.72° across all three forms suggest no significant change in the overall crystal structure (Anuar et al., 2009). Consequently, the distinguishing peaks of all the L-isoleucine polymorphs are primarily identified through the small peaks discussed above. Additionally, the findings indicate that the increased intensity of γ form peaks at higher mixing speeds (400 rpm), which suggests a kinetic influence on its formation. However, the precise role of mixing speed in the crystallisation of L-isoleucine remains to be fully explored.

Table 3 presents the melting and solid-solid transition temperatures, along with solubility data for the three polymorphic forms (α, β, and γ) of L-isoleucine, illustrating their thermal stability and dissolution behaviour. The α form had the highest melting point (288.6 °C), indicating the most thermally stable structure, whereas the γ form showed the lowest solid-solid transition point (216.3 °C), making it the least stable. The β form fell in between, with a transition point of 267.7 °C, before transforming to **α** form. In terms of solubility in water, the α form exhibited the highest values at both 40 °C (35.23 g/L) and 60 °C (43.14 g/L), which was somewhat unexpected, as higher melting points are generally associated with lower solubility due to stronger lattice energies (Mullin, 2001). The β form, on the other hand, had the lowest solubility, remaining almost constant at different temperatures, i.e. 0.64 g/L at 40 °C and 0.74 g/L at 60 °C, indicating strong lattice stability and poor dissolution behaviour. The γ form demonstrated moderate solubility, increasing from 12.60 g/L at 40°C to 22.40 g/L at 60 °C, suggesting a positive temperature dependence.

TABLE 3. Comparison of the melting temperature and solubility for the polymorphic forms of L-isoleucine in water at 40 °C and 60 °C

Forms	Melting Point(°C)	Transition Temp. (°C)	Solubility (g/L)	
			40 °C	60 °C
α	288.6[a]	-	35.23	43.14
β	-	267.7[a]	0.64	0.74
g	-	216.3	12.60	22.40

[a]Anuar et al. (2009)

In this study, water was used as the crystallisation and dissolution medium, and the study unexpectedly showed

the high solubility of the α form, despite its high melting point, suggests that strong solute- solvent interactions may be overcoming its lattice stability. This emphasises that solubility cannot be inferred solely from melting point values and supports the importance of solvent choice in influencing dissolution behaviour (Liu et al., 2024; Wang et al., 2024). Overall, the observations aligned with recent findings that emphasise the role of solvent properties in modulating solubility and polymorphic behaviour (Chaudhary et al., 2023; Liu et al., 2023; Wang et al., 2024).

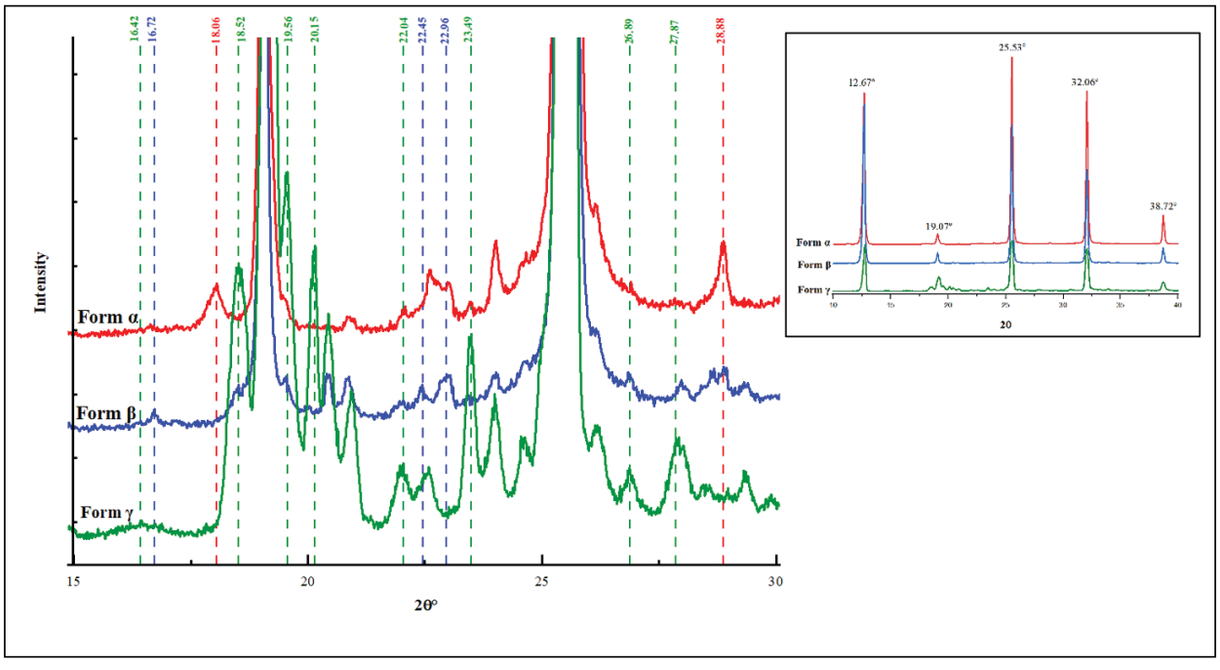

FIGURE 5. XRPD profile of the α, β and γ forms. The inset shows the similarities of the major peaks at 2θ = 12.67°, and 19.07°, 25.53°, 32.06° and 38.72°, which suggests no significant change in the crystal structure. The presence of the polymorphs can only be detected through the small peaks indicated in this figure

CONCLUSION

This study investigated the influence of various crystallisation methods on the formation of polymorphic forms (α, β, and γ) of L-isoleucine, highlighting their impact on solubility, thermal stability, and overall crystallisation behaviour. The findings demonstrated that crystallisation method selection played a crucial role in directing polymorphic outcomes through an interplay between kinetic and thermodynamic factors. The crystallisation of the thermodynamically stable α form could only be achieved through the slow-cooling polythermal method, whilst fast and rapid cooling crystallisation induced the formation of kinetically metastable β and γ forms.

The crystal morphology of all polymorphs was identical and could not be readily distinguished between them, and they can only be differentiated through their apex angle. The α form exhibited the highest melting point, whereas the β and γ forms underwent solid-solid transitions, with γ form showing the lowest transition temperature. Nonetheless, within the same temperature settings, the α form was the most soluble in water, followed by the γ form, and with the lowest solubility, the β form. These findings highlighted the importance of kinetic and thermodynamic factors in polymorph formation. Rapid cooling and high supersaturation levels favoured the formation of metastable polymorphs, whereas controlled cooling promoted thermodynamically stable forms. Additionally, the application of an electric field was observed to influence the polymorphic selection, favouring the β form. The study also suggested that increased mixing speeds could influence the formation of the γ form, suggesting a kinetic contribution to its crystallisation.

Overall, this research underscored the need for precise control over crystallisation conditions to achieve desired polymorphic outcomes. Understanding the relationship between crystallisation methods and polymorphic transformations is essential for optimising process control, ensuring formulation consistency, and improving the solubility and stability of L-isoleucine in pharmaceutical and industrial applications.

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DECLARATION OF COMPETING INTEREST

None.

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