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RECRYSTALLIZATION STRATEGIES FOR BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS) CLASS II DRUGS: IMPACT ON DISSOLUTION RATE AND ORAL BIOAVAILABILITY

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Abstract

For class II drugs of Biopharmaceutics Classification System (BCS), poor water solubility remained one the greatest challenge in modern pharmaceutical development. Notwithstanding, these drug can pass effortlessly through biological membranes due to their high permeability, their low dissolution in aqueous media prohibit them from absorption. Henceforth, dissolution rate emerges as rate limiting step for their absorption through oral route. Multiple formulation and particle engineering technologies, including solid dispersion, size reduction, lipid based delivery, complexation and recrystallization have been implemented for this purpose. Among them, recrystallization has emerged as a cos-effective, user friendly, and scalable method for refining dissolution by modifying crystal properties devoid of changing chemical structure. Although, it was considered purely as a refining method used during synthesis, recrystallization is now known as prevailing crystal engineering tool proficient for modifying the physical characteristics of active pharmaceutical ingredients without altering their chemical identity. The controlling factors such as temperature, solvent selection and recrystallization condition can be carefully controlled to modify crystal shape, size, surface properties, wettability, and polymorphic form. Ultimately, these changes directly impact dissolution rate and bioavailability of a drug. Here, we explored the scientific basis of recrystallization and discussed about the contribution of the process to enhance dissolution of BCS Class II drugs. Furthermore, the mechanism behind dissolution enhancement has also been elaborated.

1. INTRODUCTION

The oral route remains the most preferred method of drug administration due to patient compliance, convenience, and cost effectiveness [1]. However, successful oral therapy requires adequate drug dissolution in gastrointestinal (GI) fluids prior to absorption. The BCS has

categorized drugs into four classes based on intestinal permeability and aqueous solubility, where Class II includes the drugs of high permeability and low solubility, meaning that drug bioavailability is primarily controlled by dissolution rate rather than membrane transport. As current drug discovery often produces lipophilic molecules of poor water solubility, a large proportion of newly discovered drugs fall into this category [2]. Henceforth, strategies to enhance dissolution behaviour has become a primary objective in pharmaceutical formulation research [3].

Although several approaches have been trailed to enhance the drug solubility such as solid dispersion, lipid based delivery systems, particle size reduction, and nanotechnology. Although these mentioned approaches have demonstrated success but often demand specialized equipment, higher processing cost, and complex processing conditions [4]. Alternatively, recrystallization offers comparatively simple approach that permits modification of drug's solid-state properties while sustaining their chemical stability [5].

1.1. BCS Class II Drugs and Dissolution-Limited Absorption

BCS Class II drugs dissolve gradually in the GI tract, thus limits the amount of drug available at the absorption sites. Consequently, a reduced or variable systemic bioavailability ensue despite their inherent ability to permeate the intestinal membrane (Figure 1). Furthermore, several physicochemical and environmental factors, including crystal lattice energy, particle size, polymorphic form, lipophilicity, and pH-dependent solubility, all determine the rate of solid drug transitions into solution. To overcome these challenges, modern pharmaceutical research is dedicated towards formulation strategies aiming to improve dissolution and solubility, including cyclodextrin inclusion complexes, solid dispersions, self-emulsifying drug delivery systems (SEDDS), and nanoparticle-based approaches. Ultimately enhanced effective surface area, increased wettability, and reduced crystallinity ensures faster drug dissolution. Thus, crystal engineering became a widely exercised area, espacially for the BCS Class II drugs.

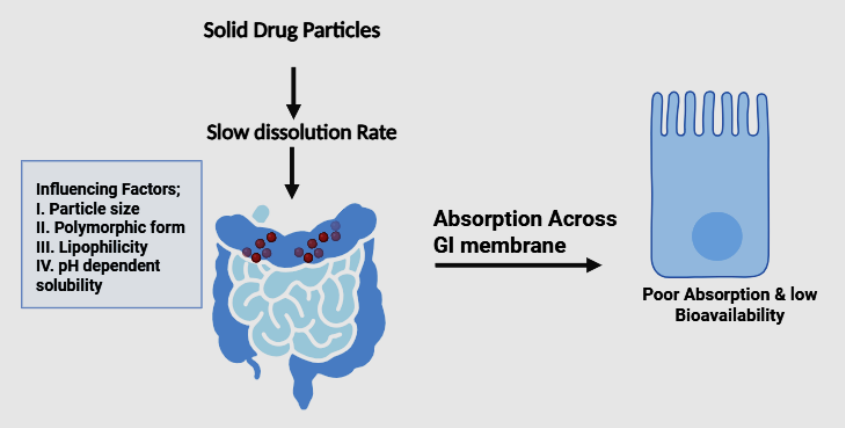

Figure 1. low solubility leading towards poor absorption and low bioavailability as shown my BCS Class II drugs.

1.2. Principles of Recrystallization

Recrystallization follow the principle that most solid compounds show better solubility in a solvent at elevated temperature. Thus, the drug is dissolved in a logical chosen solvent under heating to obtain a saturated or near-saturated condition. Meanwhile, the insoluble impurities are removed, typically by hot filtration. Subsequently, a supersaturated environment may be achieved through either addition of an anti-solvent, or slow evaporation of solvent, or a controlled cooling process. Finally, the stimulated nucleation ensues arranged crystal growth [6]. The nuclei formation stimulates deposition of additional molecules onto the nuclei, leading to crystal growth. During this

process, crystal size, size distribution, and internal lattice arrangements, depends mainly on the rate at which nucleation and growth occurs. Herein, adding anti-solvent or rapid cooling causes smaller and metastable crystals with improved dissolution characteristics [7]. Researches has proven that optimal choice of solvent plays a crucial role since solvent-solvent interactions controls molecular orientation during crystallization [8] [9]. Henceforth, controlling the recrystallization conditions warrants crystals of improved performance without altering the chemical structure of the drug [8].

1.3. Mechanisms of Dissolution Enhancement through Recrystallization

Principally, smaller crystal size enhances surface area for interaction with dissolution medium, thus a faster drug release is expected. Modification of crystal habits through recrystallization improves powder aggregation and enhance its wettability. During the process, polymorphic transition is expected, which is another salient mechanism involved in improving drug's thermodynamic stability and its performance [10]. In general, compared to stable crystalline form, metastable polymorph shows higher apparent solubility and faster dissolution. Furthermore, rapid precipitation causes production of partially amorphous structures characterized by higher free energy states and enhanced dissolution performance. These forms, however, may undergo recrystallization during storage.

1.4. Recrystallization Techniques for BCS Class II Drugs

Several techniques, both conventional and modern, have been implemented. Here, these techniques have been explained individually.

1.4.1. Conventional Solvent Recrystallization

During the conventional technique, a drug is dissolved in a suitable solvent at elevated temperature followed by controlled supersaturation through solvent evaporation or cooling (Figure 2). Here, slow crystallization may lead to thermodynamically stable polymorphs, where rapid supersaturation outcomes in metastable forms with higher solubility. However, a controlled crystal habit ensues improved powder flow and compaction. The advantages of the technique include low operational complexity, regulatory acceptance, and industrial scalability. The major disadvantages include larger crystal sizes if nucleation is not controlled, and possible formation of undesired polymorphs. However, the process remains widely applied for drugs such as fenofibrates analogs, ibuprofen, and carbamazepine [11, 12].

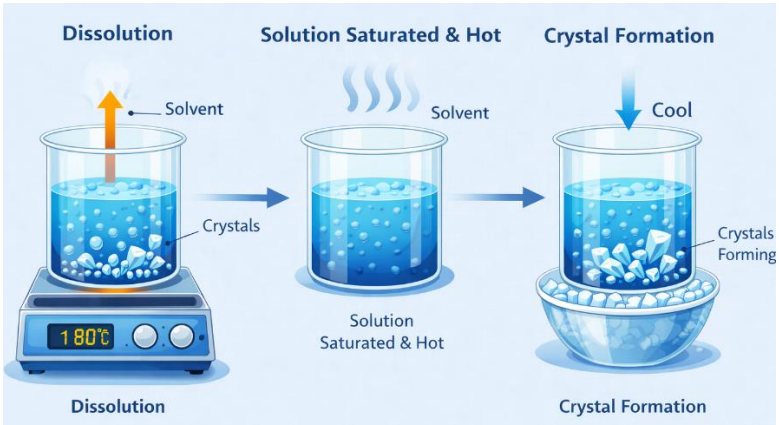

Figure 2. Dissolution of drug in hot solvent followed by cooling induces crystal formation during conventional solvent crystallization method.

1.4.2. Antisolvent Recrystallization

A miscible non-solvent (anti-solvent) is introduced into the drug solution, causing a sudden drop in solubility and rapid nucleation (Figure 3). The key mechanism of the process includes formation of microcrystals or nanocrystals following high supersaturation, and ultimately increased surface free energy enhances dissolution [13]. Multiple factors

influence the process that include injection ratio, temperature, presence of stabilizer or surfactant, and mixing hydrodynamics [14].

Figure 3. Process of nucleation, crystal formation during anti-solvent recrystallization process.

1.4.3. Temperature-controlled and Cooling Crystallization

It is an important approach in which modulation of temperature brings supersaturated condition, thus allowing predictable control over nucleation and crystal growth kinetics. Here, the drug is dissolved at an elevated temperature and crystallization is subsequently persuaded through cautiously programmed cooling profile that regulates molecular organization within crystal lattice (Figure 4). Different operational strategies include linear cooling crystallization where temperature reduces gradually at a constant rate. Second strategy is cyclic temperature crystallization, in which repeated heating-cooling cycles encourages dissolution of unstable nuclei while favouring growth of desired crystals. Thus, sudden supersaturation is prevented by adopting the above mentioned processes, resulting in uniform particle populations with narrow size distribution, reduced agglomeration, and improved process reproducibility. Controlled temperature modulation prevents sudden supersaturation, resulting in uniform particle populations with narrow size distribution, reduced agglomeration, and improved process reproducibility. Moreover, it enables selective formation or stabilization of specific polymorphic forms by controlling kinetic and thermodynamic crystallization pathway [15].

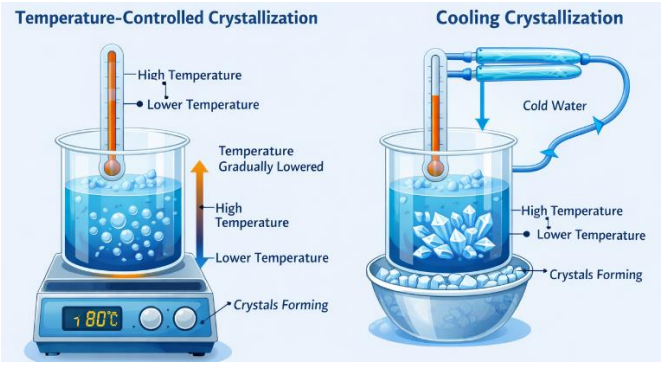

Figure 4. Comparison of cooling crystallization and temperature controlled processes.

1.4.4. Sonocrystallization

It is an advanced recrystallization technique that require ultrasonic energy to stimulate nucleation and crystal growth through phenomenon of acoustic cavitation (Figure 5). Alternating compression and rarefaction cycles generate microscopic bubbles during the process that grow and collapse quickly [16]. Consequently, the disintegration of these cavitation bubble creates localized region of high pressure,

temperature, and intense microturbulence, which intensely effect crystallization dynamics. These localized energy fluctuations generate brief regions of high supersaturation that boost the formation of multiple nucleation sites. The advantages are that the process ensures smaller sized particles of uniform distribution [17]. Many drugs such as paracetamol, carbamazepine, and indomethacin have been improved by implementing this modern technique.

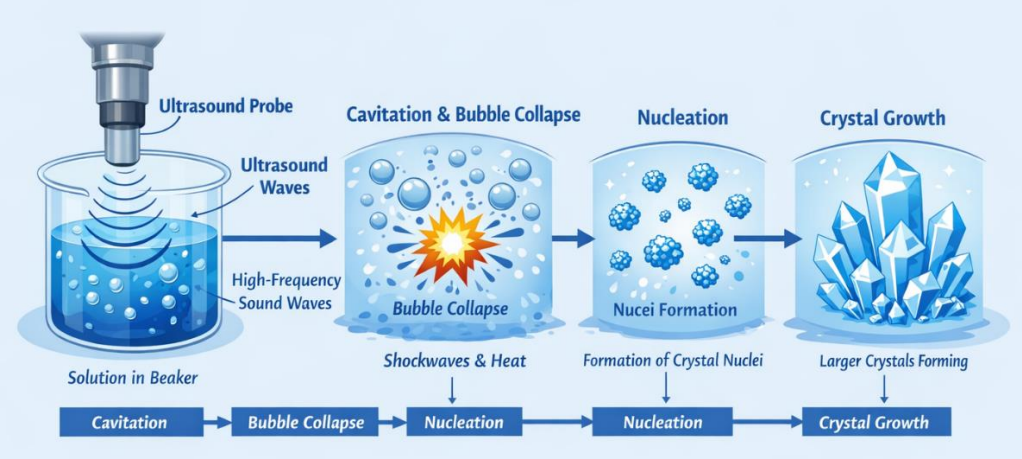

Figure 5. Sonocrystallization process illustrating cavitation, nucleation, and crystal growth under ultrasonic irradiation.

1.4.5. Supercritical Fluid Recrystallization

In the process, supercritical carbon dioxide (CO_2) is being employed becuase of its non-toxic, non-inflammable, and eco-friendly nature [18]. As these fluids behave uniquely above their critical pressure and temperature, e.g., liquid like solvating powder and gas-like diffusivity, it enables efficient dissolution and precipitation of drug molecules (Figure 6). During the process, nano- and micro range is often achievable along with narrow size distribution and improved surface area [19, 20]. Usually, use of organic solvent is not needed. Altogether, this technique represents a reproducible, scalable, and environmental friendly alternative to conventional recrystallization, making it attractive for modern drug development and industrial production of poorly soluble pharmaceuticals.

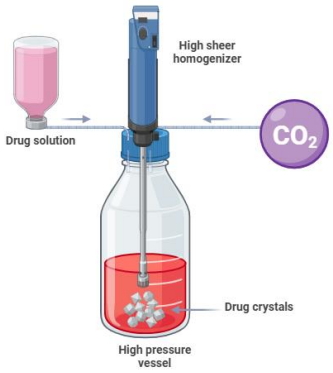

Figure 6. Process of supercritical fluid recrystallization using supercritical CO_2, where drug solution into a high-pressure vessel leads to rapid supersaturation persuaded formation of fine drug particles with controlled morphology and size.

1.4.6. Polymorph and Crystal Habit Engineering

Pharmaceutical crystal engineering represents a fundamental aspects of crystal habit engineering. It aims at optimizing the biopharmaceutical and physicochemical performance of drug substances (Figure 7). Numerous APIs, particularly BCS Class II drugs, can occur in several crystalline arrangements known as polymorphs. These polymorph, although share identical chemical composition, differ in lattice energy, hydrogen bonding interaction, thermodynamic stability, and molecular packing. These variations considerably impact critical pharmaceutical properties including melting point, mechanical behaviour, dissolution, stability, and ultimately bioavailability.

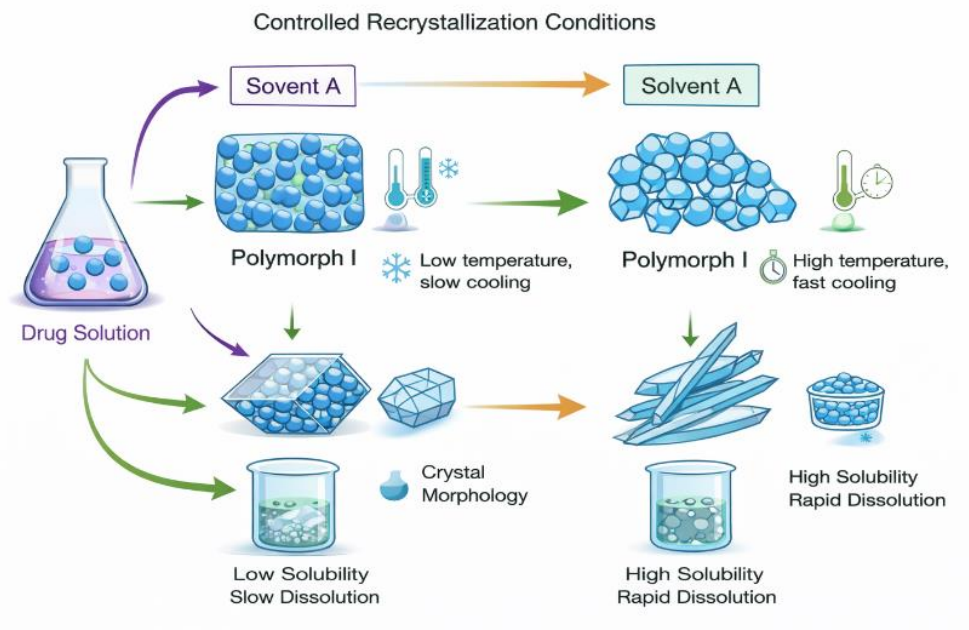

Figure 7. Controlled crystalline conditions to obtain drug crystals of optimized morphology and distinct polymorphic form

1.4.7. Co-crystallization Assisted Recrystallization

This technology involves mixing of a pharmaceutical acceptable co-former and API through non-covalent intermolecular interactions such as van der Waals forces, π–π stacking, and hydrogen bonding [21, 22]. Despite salt formation, this process does not need ionisable functional groups (Figure 8). A rationally selected co-former allow reorganized hydrogen-bonding networks within the crystal lattice, ensuring enhanced solubility, enhanced wettability, and tailored dissolution behaviour.

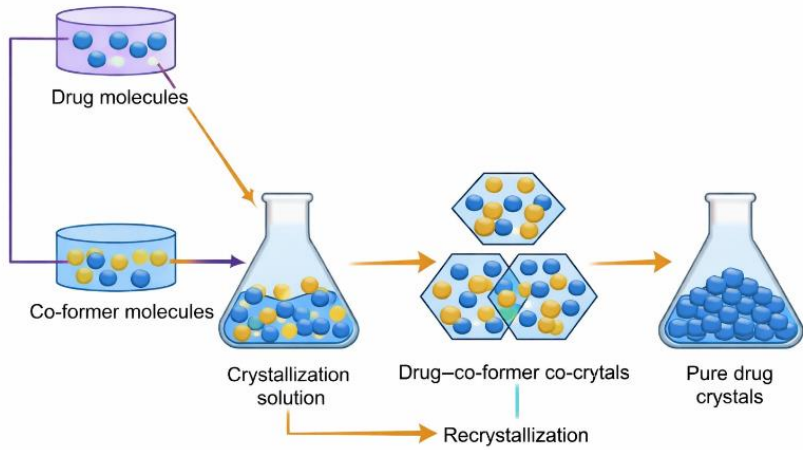

Figure 8. Mechanistic sketch of co-crystallization-assisted recrystallization display interaction between co-former and drug molecules result in formation of modified drug crystals with enhanced physicochemical characteristics

1.4.8. Green and Sustainable Recrystallization

In advanced pharmaceutical manufacturing, eco-friendly green crystallization proved as an imperative way of recrystallization because of being sustainable and having regulatory compliance [23, 24] (Figure 9). Current pharmaceutical practices encourage the technique to minimize ecological impact while maintaining product quality and efficiency. The key strategy comprises substituting harmful organic solvent with bio-based solvents or water, henceforth minimizing toxicity hazards and environmental load. These approaches cooperatively contribute to significant drop in solvent usage and waste generation.

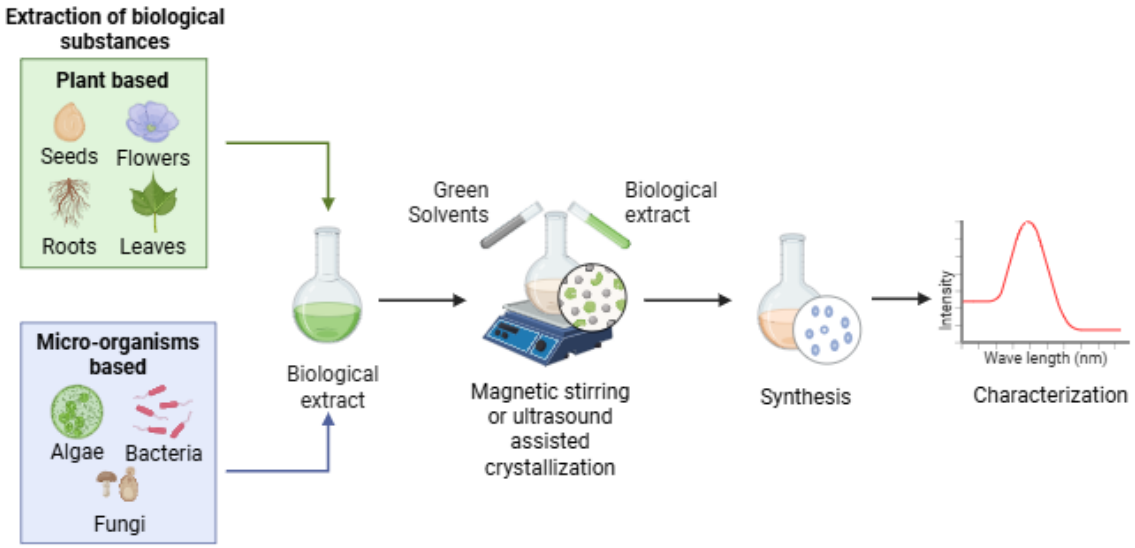

Figure 9. Green and sustainable recrystallization using energy efficient processing and eco-friendly solvents.

1.5. Process Analytical Technology for Recrystallization

To visualize the process, process analytical technology (PAT) has developed an indispensable component of modern pharmaceutical recrystallization processes, enabling control of critical crystallization parameters and real-time monitoring, thus ensuring consistent product quality [25, 26]. The variables like supersaturation temperature, pH and other attributes defining recrystallization are continuously observed, thus reducing batch-to-batch variability and minimizing risks associated with uncontrolled recrystallization events. Various *in situ* and real-time analytical techniques has been integrated into recrystallization systems. Spectroscopic methods such as Raman spectroscopy, Near-infrared (NIR) spectroscopy, and Fourier Transform Infrared (FTIR) are generally employed to monitor solute concentration, solvent interactions, and polymorphic transitions during crystallization [27]. Focused Beam Reflectance Measurement (FBRM) and Particle Vision Measurement (PVM) permit monitoring of nucleation behaviour, crystal morphology, and particle size distribution. Furthermore, process variables such as turbidity, conductivity and temperature offer valuable response regarding supersaturation generation and crystal growth evolution.

1.6. Solid-State Characterization

Broad characterisation is essential to approve structural modifications following crystallization. Powder X-ray diffraction is mostly used to identify polymorphic transitions, while differential scanning calorimetry (DSC) assesses thermal behaviour and crystallinity alterations. Scanning electron microscopy (SEM) offers visualize crystal morphology, while potential molecular interactions are identified through FTIR. Changes in surface area is identified through particle size analysis, and dissolution testing directly measures improvement in drug release profile.

1.7. Impact on Bioavailability

Pharmacokinetic performance of BCS Class II drugs is directly influenced by enhanced dissolution achieved through recrystallization [28]. Enhanced apparent solubility and better wettability supports earlier drug dissolution within gastrointestinal tract, resulting in higher concentration gradient across intestinal membranes and enhanced absorption [29, 30].

1.8. Advantage and Limitations

Low production cost, simplicity, scalability, regulatory familiarity, and compatibility are the major advantages of the method [31]. Furthermore, discovery of novel polymorphic forms through crystallization may offer prospects for intellectual property protection [32]. Protection of recrystallization while storage, controlling of solvent residue, and reproducibility during industrial scale-up necessitate cautious process optimization.

1.9. Comparison with other Solubility Enhancement Techniques

Other solubility enhancement techniques such as lipid based formulations, nanoparticle engineering are rather more complex and costly approaches [33]. Furthermore, these advanced techniques suffer from stability issue and higher production costs. Thus, before adopting more sophisticated technologies, recrystallization works as an attractive first-line strategy during early development.

FUTURE PROSPECTIVE

Future research in recrystallization is advancing towards a more design oriented approach, closely linked with crystal engineering concepts and Quality-by-Design (QbD) principles. Novel progresses are dedicated towards use of artificial intelligence for predicting polymorphic forms, microfluidic platforms, and polymorphic forms that permits rapid crystallization screening using marginal material. Furthermore, this technique is gradually being combined with nanotechnology-based systems and co-crystal formation to further optimize drug properties. Also, environmental friendly solvent is being replaced with synthetic and toxic chemicals, which are expected to play a central role in future pharmaceutical production.

CONCLUSION

Recrystallization has progressed from out-dated purification method into a versatile pharmaceutical engineering strategy capable of improving oral bioavailability and dissolution behaviour of BCS class II drugs. By governing

crystal structure, solid-state properties, morphology, it offers a scalable and cost-effective solution to overcome solubility limitations. Continued developments in crystal technology in modern drug development, proving it an essential tool for optimizing therapeutic performance of poorly soluble drug candidate.

Author's Contribution

All authors contributed equally to the conceptualization, literature review, drafting of this review, and have approved the final version of the manuscript.

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