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Review

Recent Advances in Polymorph Discovery Methods of Organic Crystals

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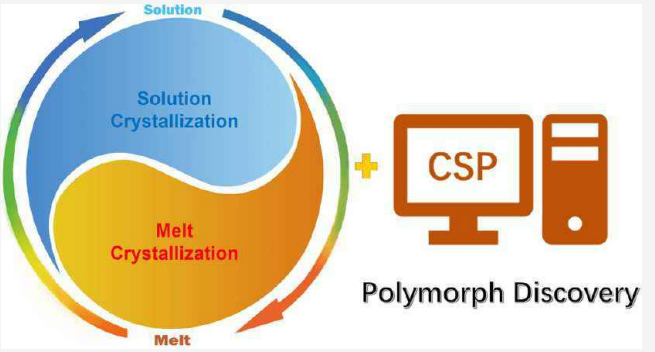
ABSTRACT: Polymorphism, the ability of the same substance to crystallize in more than one crystal structure, is a common phenomenon in organic crystals, influencing the physicochemical properties of solid materials in many important fields (foods, dyes and pigments, high energic materials, pharmaceuticals, etc.). The utilization of various polymorph discovery methods could increase the possibility of finding polymorphs with desired properties, achieving an optimal performance of the final product. Recently, there has been a steady development of polymorph discovery in both experimental and computational methods. To better guide the polymorph discovery, this paper reviews the recent advances in the polymorph screening methods of organic crystals, mainly including solution crystallization, melt crystallization, and crystal structure prediction. This paper also summarizes the nucleation theory in polymorphic systems to understand the formation of polymorphs and highlights the mechanisms of polymorph discovery by the kinds of methods. Finally, challenges of polymorph discovery are briefly discussed, aimed to shorten the screening time and make the polymorph discovery more effective.



1. INTRODUCTION

As early as 1822, polymorphism was first recognized in the inorganic compounds "arsenates and phosphates" by Mitscherlich. A decade later, the first case of the polymorphic organic compound "benzamide" was identified by Liebig and Wohler.[1] Nonetheless, until the 1990s, the polymorphism began to gain long-standing and growing interest, especially in the pharmaceutical industry. With the advancement of polymorph screening methods and characterization techniques, more and more new polymorphs have been discovered, and the number of related articles and patents is rapidly increasing. In 2020, the statistics from various databases show that 37−66% of organic molecules have polymorphs, and this percentage could be up to 80% in crystalline drugs.[2]

Polymorphism differs in molecular conformation or packing, resulting in different physicochemical properties of solid materials and influencing many aspects of our daily life (Figure 1). In foods, for example, the main ingredient of chocolate "cocoa butter" (CB) has six reported polymorphs[3,4] which could exhibit different properties of the chocolate product, such as the brittleness, thermal stability, melting point, and sensory property. Only Form V (β_2) could achieve an excellent texture and mouthfeel. In dyes and pigments, the widely used compound "quinacridone" has four polymorphs displaying different colors: red in forms α^{I}, α^{II}, and γ and yellow in form β.[5,6] In energic materials, the density and crystal packing of polymorph could greatly affect the explosion energy and sensitivity, respectively.[7,8] Four polymorphs with known structures of the explosive CL-20 (hexa-nitro-hexa-aza-isowurtzitane) have been reported in which the most compact form ε has the most insensitivity and favors the highest safety.[9] In pharmaceuticals, polymorph screening is considered as an irreplaceable step during the drug development process, since polymorph could affect the stability, solubility, and bioavailability of drugs. It could be a nightmare once the marked polymorph transforms to an unforeseen polymorph. Ritonavir, a protease inhibitor for the treatment of human immunodeficiency virus (HIV), was launched by Abbott in 1996. Unfortunately, the drug suddenly lost its efficacy after 18 months on the market, because the marked form I is a metastable form that unexpectedly transformed to the more thermodynamically stable form II with low solubility and no efficacy.[10] Abbott was forced to withdraw the drug from the market, costing the company hundreds of millions of dollars. To sum up, the choice of suitable polymorph with desired

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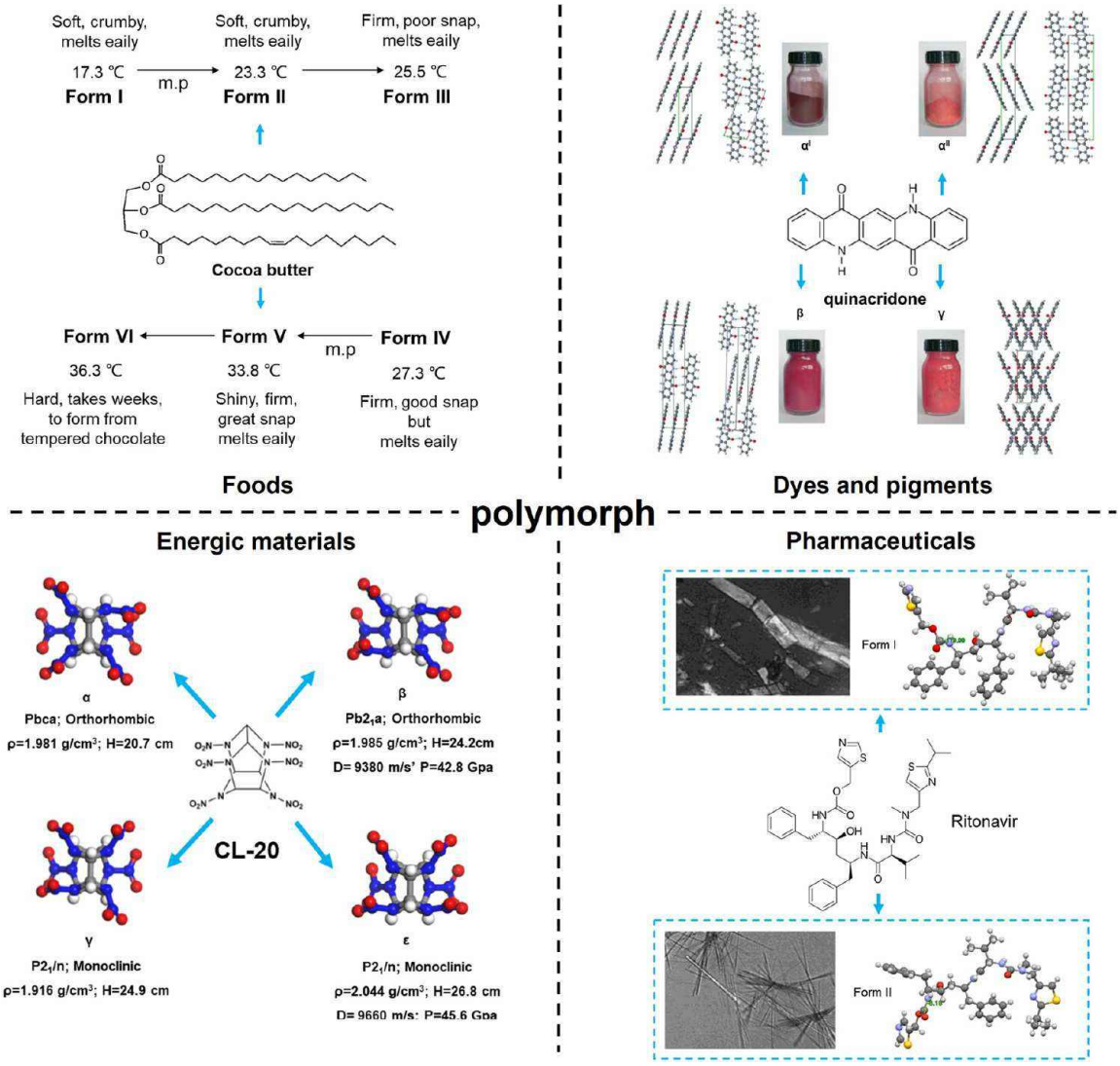

Figure 1. Influences of polymorph on foods (cocoa butter), dyes, and pigments (quinacridone, reproduced with permission from ref 6. Copyright 2016, the Royal Society of Chemistry), energic materials (CL-20, reproduced with permission from ref 8. Copyright 2021, Elsevier B.V.), and pharmaceuticals (ritonavir, reproduced with permission from ref 10. Copyright 2001, Plenum Publishing Corporation).

properties is essential to achieve optimal performance of the final product.

To obtain the suitable polymorph of organic crystals, it goes without saying that screening polymorphs is the initial step. Unfortunately, for a given organic molecule, no one method can capture all of its polymorphs. As a result, we could only rely on the combination of various polymorph discovery methods to increase the possibility of finding new polymorphs with desired properties. In 2007, Llinàs and Goodman[11] have summarized the polymorph screening methods. Nonetheless, over the past decade, there has been a sustainable and steady development of the polymorph discovery on both experimental and computational methods. Given the circumstances, to better guide polymorph discovery, this review focuses on the recent advances in the polymorph screening methods. It is worth mentioning that the underlying mechanisms of polymorph discovery by various methods are closely related to the nucleation process of crystals. So, in this review, we begin with an overview of the nucleation theories in polymorphic systems to understand the formation of polymorph. Subsequently, we summarize the polymorph screening methods, mainly including solution crystallization, melt crystallization, and crystal structure prediction. In addition, we also highlight the mechanisms of polymorph discovery by various methods and briefly discusses the challenges of polymorph discovery in the future.

2. NUCLEATION THEORIES IN POLYMORPHIC SYSTEMS

Currently, several nucleation theories are proposed to explain the nucleation mechanisms in the polymorphic systems, including Ostwald's law of stage, classical nucleation theory, nonclassical nucleation pathways, and cross nucleation.

Ostwald's law of stage describes the thermodynamic nucleation order of polymorph and assumes that the least metastable polymorph can nucleate first and then transform to a more stable one (Figure 2).[12] Although this rule has failed in some systems due to the absence of dynamics factors, most crystallization sequences follow the tendency of energy decreasing in stages. Besides, it inspires us that the polymorph with similar properties to the system will crystallize preferentially.

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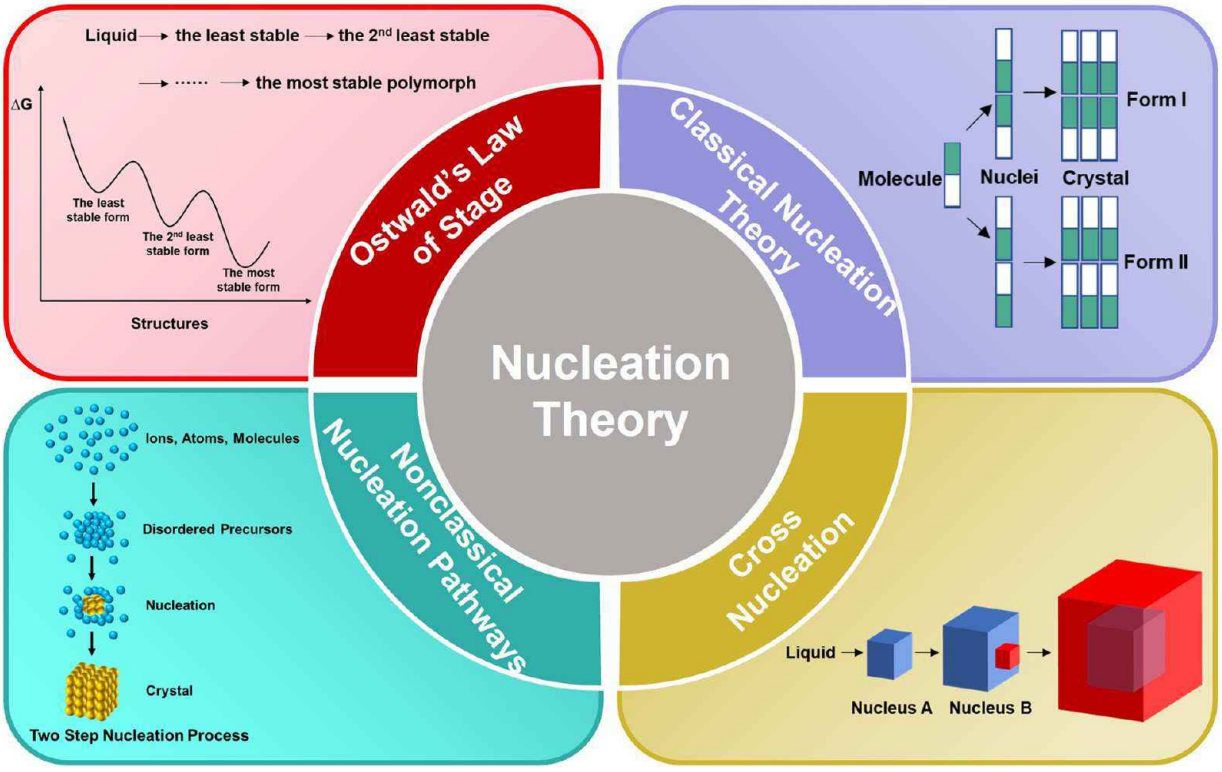

Figure 2. Nucleation theories in the polymorphic systems.

Classical nucleation theory (CNT) is the most general theoretical model for studying nucleation kinetics quantitatively. According to the CNT, if the size of prenucleation clusters exceeds the size of the critical nucleus, they can grow to be visible crystals, and their internal structure is identical with the macroscopic crystal structure. The nucleation rate is written as

$$J = k_j \exp\left(\frac{-W_c}{kT}\right) \quad (1)$$

where k_j is a kinetic parameter representing the frequency at which the molecules join to the nucleus, $W_c = \frac{16\pi}{3}\frac{\sigma^3}{\Delta G_v^2}$ is a thermodynamic term representing the free energy barrier in crystal nucleation (σ is the interfacial energy of nucleation, ΔG_v is the free energy difference between the liquid and crystal). Cassar et al.[13] and Huang et al.[14] have successfully applied the CNT to fit the nucleation rates of silicates and polyalcohols, respectively, verifying that the CNT could accurately describe the nucleation rate in the melt. Bai et al.[15] recently used narrowly distributed nanoparticles to detect critical ice nuclei, which is the first experimental confirmation of their existence. Despite its validity, the CNT does have some limitations. The CNT ideally assumes that nuclei have a spherical shape in all systems. In contrast, recent researchers[16,17] have revealed that nuclei can be irregular or rod-shaped. Furthermore, both experiments[18] and calculations[19,20] could not accurately determine the interfacial energy σ, and a small difference in σ could change the nucleation rates by orders of magnitude. In addition, the CNT also has difficulties in describing the multistep nucleation process which limits its application in polymorphic systems.

Nonclassical nucleation pathways have been continuously observed using high-resolution *in situ* technology such as *in situ* transmission electron microscopy (TEM)[21] and *in situ* atomic force microscopy (AFM).[22] According to the literature,[23−27] various intermediate states (mostly disordered precursors) could temporarily stay during the nucleation process instead of one-step nucleation descripted in CNT. Besides, the internal structures of these intermediate states could be different from that of bulk crystals.[28] Since these phenomena are incompatible with the CNT, they are referred to as nonclassical nucleation pathways. Although there is still a long way to improve the related theory about the nonclassical nucleation pathways, nonclassical crystallization offers the opportunities for understanding the formation mechanism of polymorph.

Cross nucleation is known as one polymorph nucleating on the surface of another polymorph which could be frequently observed in the melt crystallization.[29] Cross-nucleation is highly affected by the initial form, the growth rate of crystal, and crystal surface defects.[29] Interestingly, both stable-on-metastable and metastable-on-stable cases could occur during the cross nucleation, indicating that this phenomenon is unrelated to polymorph stability. Cross nucleation has revealed that the form with the faster growth rate can also dominate the final crystallization outcome, despite having a slower nucleation rate.[30]

3. POLYMORPH DISCOVERY METHODS

Polymorph discovery methods of organic crystals consist of experimental methods and computational methods. Generally, the experimental methods mainly include solution crystallization, melt crystallization, and other methods such as sublimation, solid phase transformation, high pressure crystallization, and nanoconfinement crystallization, and the computational methods mainly refer to crystal structure prediction (CSP).

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3.1. Solution Crystallization. Solution crystallization is most extensively used for polymorph discovery in industry because of its efficiency and convenience. In the solution crystallization, new polymorphs might be harvested by controlling the supersaturation, changing the solvent, and adding soluble additives or insoluble templates during the recrystallization.

3.1.1. Supersaturation. Numerous examples[31−34] demonstrate that high supersaturation of solution tends to produce the metastable forms, whereas low supersaturation of that produces thermodynamically stable forms. Sudha et al.[31] were able to prepare the most stable form I, the metastable form II, and the least stable form III of paracetamol only by increasing supersaturation. Liang et al.,[32] Yang et al.,[33] and Zhou et al.[34] found that the metastable form of L-glutamic acid, carbamazepine, and HMX (1,3,5,7-tetranitro-1,3,5,7-tetrazacyclooctane, a highly explosive compound) could crystallize at high supersaturation and the stable form could crystallize at the low supersaturation, respectively. The high supersaturation of solution facilitates the form with a higher free energy which is consistent with the Ostwald's rule. Notably, the supersaturation of solution could not only be adjusted easily and roughly by varying the cooling (evaporation) rates or antisolvent addition (vapor diffusion), but also be controlled precisely by modifying the solute-to-solvent ratio. Consequently, changing the supersaturation of solution is frequently regarded as a preferred attempt for screening polymorphs. It is worth mentioning that many thermodynamically metastable structures of organic molecules are still unlikely to crystallize even at a relatively higher supersaturation, due to the limited supersaturation (driving force of crystallization) produced in solution. For example, the solubility of ritonavir form III is estimated up to 695−744 mg/mL in 99% ethanol−1% water at 5 °C.[35] This high solubility indicates that form III can not crystallize in solution, because it is almost impossible to generate the supersaturation for form III. In contrast, melt crystallization or sublimation method (described below) has a higher driving force of crystallization which is more beneficial to discover the metastable forms.

3.1.2. Solvent. Some organic molecules exhibit solvent-dependent polymorph selectivity, facilitating the discovery of novel forms. By merely changing the solvents, Bhardwaj et al.[36] discovered five of nine galunisertib forms in the cooling crystallization. McCrone[37] states that the β form of explosive RDX (1,3,5-trinitrohexahydro-1,3,5-triazine) could only crystallize from some solvents with high boiling point. More recently, a new metastable polymorph (form IV) of piracetam was yielded in alcoholic solvents.[38] Many studies[39,40] indicated that the relations between polymorph and solvent might be established by the solvent−solute interactions. Kulkarni et al.[39] found that forms I and IV of iso-nicotinamide prefer solvents with strong hydrogen bond acceptors, while form II could crystallize in the solvents with strong hydrogen bond donors. They concluded that different solvents could form distinct hydrogen bonds with iso-nicotinamide, which influences the formation of particular structures (chain structure in forms I and IV, dimer structure in form II), thereby determining the polymorph results. The similar solvent effect on polymorph is also observed in the case of undecanedioic acid.[40] Shi et al. found that form II of undecanedioic acid yield in the solvents with high hydrogen bond donating (HBD) ability, whereas form I was accessible in the solvents with no HBD ability. They believed that the polymorph selectivity was attributed to the molecular conformation rearrangement, affecting by the HBD ability of solvent. Except for the hydrogen bond formation capabilities, other properties of solvent, such as lipophilicity, hydrophilicity, and polarity could also influence the polymorph outcomes.[41] All these properties make the selection of solvents complicated, and trial-and-error solvents results in a relatively low efficiency of this method in polymorph discovery. In addition, we also should be careful of the formation of solvates. As a result, the most challenging task is to create a guideline on quickly classifying solvents for efficient polymorph discovery, ideally based on the chemical structure of crystalline substance. To achieve this goal, the major obstacle is to deeply understand the molecular self-assembly pathways (nucleation behaviors) in kinds of solvents and make clear the link between the solvent and crystal nucleation. Some advanced technology such as *in situ* AFM and *in situ* SEM are providing opportunities to observe the nucleation process. Overall, solvents need be selected with the aid of a smarter solvent diversity mapping to increase the success rate of discovering new solid forms.

3.1.3. Soluble Tailor-Made Additives. The soluble tailor-made additives offer good opportunities for the polymorph discovery. Thomas et al.[42] discovered the form IV of piroxicam in the presence of pyrazine. Similarly, the form III of felodipine was found in the presence of maleic acid, phenacetin, or 4-hydroxybenzoic acid.[43] The soluble tailor-made additives could affect both the nucleation and growth kinetics of polymorphs via additive−solute interactions, leading to the polymorph diversity. To crystal nucleation, specifically, it is assumed that two microscopic structures, $(\alpha)_n$ and $(\beta)_n$, of the nucleation clusters exit in solution, and form α survives after competition. Adding the tailor-made additives, the additive molecules could selectively absorb on the nucleation clusters $(\alpha)_n$ and hinder the nucleation of form α, enabling the formation of form β. Zhang et al.[44] investigated the effect of soluble tailor-made additives containing a sulfonamide group on the nucleation of pyrazinamide with four polymorphs (α, β, γ, and δ). The crystal structures of forms α, β, and γ are built by dimers and form δ is built by molecular chains. The sulfonamide group of additives could form another dimer-like structure with pyrazinamide through the hydrogen bonds. That could disturb the formation of dimers in the crystal structures of forms α, β, and γ, resulting in the survival of form δ. To crystal growth, the soluble tailor-made additives could selectively influence the growth rate of particular crystal faces and further control the polymorph. In a recent study, Liu et al.[45] found that metacetamol, an analogue of paracetamol, could selectively adsorb the (011) face of form I of paracetamol and reduced its growth rate. In contrast, metacetamol has no effect on the growth rate of form II. Therefore, form II could easily crystallize in the presence of metacetamol.

Like the solvent, the selection of additive is also critical for new polymorph discovery. To make this method effective, the chosen additive must have the ability to selectively hinder the nucleation or growth of unwanted forms without affecting the crystallization of desired (new) forms. In experiments, the chemically similar additives such as molecular analogues are often first employed as the tailor-made additives to induce new polymorphs. That is because the additive−solute interactions might be readily formed if they have similar structures, finally affecting the polymorph outcomes.[46,47] Moreover, the selection of additive could be favored with the aid of theoretical simulation by computers, making this method more effective.

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For example, using the designed additives, Davey et al. selectively inhibit the crystallization of stable form β of L-glutamic acid, favoring the metastable form α. The choice of additive is based on the molecular conformation analysis of L-glutamic acid and possible additives which are computed by using semiempirical molecular orbital calculations (MOPAC).[47] These tips of both experiments and calculation indeed could give us some good suggestions on the selection of additives. However, the interfering process of additive on the nucleation of forms is still poorly understood, which should be further studied in the future. Meanwhile, more calculation methods should be developed to accurately design the additives with the aim to discover new forms effectively.

3.1.4. Insoluble Templates. As a way of heterogeneous nucleation, the insoluble templates could selectively decrease the nucleation barrier of specific polymorphs, favoring the polymorph discovery. The commonly insoluble templates employed in the polymorph screening include seeds, self-assembled monolayers (SAMs), polymers, and gels.

Seeds. The seeded method is a traditional way to grow large single crystals. Recent studies also found that the crystal seeds could be used to induce new polymorphs. Park et al. epitaxially grew a new metastable form K on the seeds of stable form F of donepezil as shown in Figure 3a.[48] The similar molecular

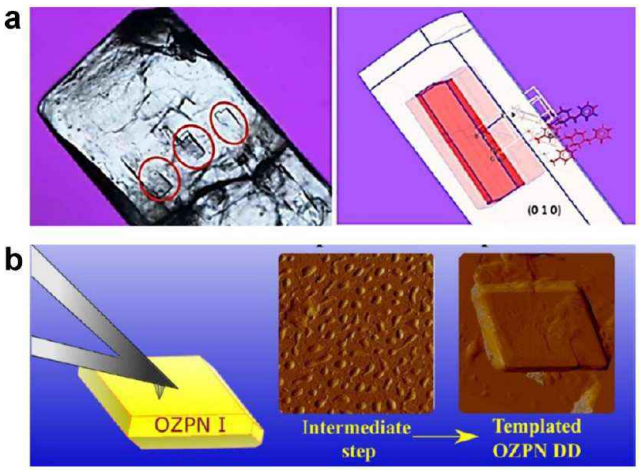

Figure 3. (a) The epitaxial growth of donepezil form K on the (010) plane of donepezil form F. (Reproduced with permission from ref 48. Copyright 2016, American Chemical Society.) (b) Olanzapine dihydrate (OZPN DD) is epitaxially grown on the (100) plane of olanzapine form I. (Reproduced with permission from ref 49. Copyright 2017, American Chemical Society.)

arrangements between the (010) plane of form F and the $(0\bar{1}1)$ plane of form K is the main reason that the form K epitaxially grows on the form F. Warzecha et al.[49] observed that the olanzapine dihydrate could epitaxially grow on the dominant $(100)_{OZPNI}$ plane of single crystals of olanzapine form I (Figure 3b), due to the structural similarity and energetic preference. In addition, the functional groups exposed on surfaces of the seed could also determine the polymorph. Yao et al.[50] found that the form II of piroxicam could selectively grow on the surfaces of piroxicam monohydrate. This is because the −S═O− (or −NH−) groups exposed on the surfaces of piroxicam monohydrate could only form a one-dimensional hydrogen bond chain (building block of form II) with piroxicam molecules. Briefly, the mechanisms of seed-induced new polymorphs mainly include the lattice match (structural similarity) and the interactions of functional group on crystal surfaces.

We note that most of new forms found by seeded methodology are occasional discovery rather than intentional actions. It implies that this method has some limitations which should be seriously considered. Commonly, the known polymorphs are used as seeds to template the new polymorph. As a result, the first factor which we should consider is the stability of seeds in the solution. If the seeds are metastable, solution-mediated phase transformation (SMPT) of these metastable seeds might occur. We should carefully observe the process of SMPT by microscope because new polymorphs might be harvested during this process. If the seeds are thermodynamically stable, the initial supersaturation also plays a crucial role in the process of new polymorph discovery. The supersaturation still offers the basic thermodynamic driving force for the nucleation of new forms, even though their nucleation barrier might decrease a lot by the seeds. That is to say, the degree of supersaturation should be adjusted to cater to the crystallization of new forms. This guideline also could be applied to other templated methods for discovering new forms. It is no doubt that the "seed" method could facilitate the polymorph discovery. However, the nucleation selectivity on the seeds is hard to predict. As a result, the nucleation mechanisms induced by the seeded template should be further studied to better understand the relations between the seeds and the new forms.

Self-Assembled Monolayers (SAMs). Self-assembled monolayers (SAMs) are ordered molecular layers, consisting of a headgroup, an intermediate molecular chain, and a tail group.[51] The tail group of SAMs exposed on the top of the substrate could be modified by fine chemical control to make the substrate have specific properties which could be used to induce new polymorphs. In 2009, Singh et al.[52] successfully obtained 6 out of 12 forms of ROY (5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, known as for its red, orange, and yellow crystals) and 4 out of 5 forms of mefenamic acid by the SAMs, demonstrating that the SAMs is an effective way for hunting polymorphs. It has been proved that the polymorph could be dominated by the intermolecular interactions between the tail group of SAMs and nuclei. Bora et al.[53] found that the form II of sulfathiazole could selectively crystallize on the mercaptosuccinic acid SAMs, a result of $O-H\cdots O_{sulfonamide}$ hydrogen bond interactions. Zhang et al.[54] reported that polymorphs of tolbutamide are highly dependent on the surface functional groups of SAMs, such as methyl, trifluoromethyl, and phenyl. Meanwhile, two-dimensional lattice matching between the SAM/crystal interface also plays an important role in polymorph discovery. Hiremath et al.[55] found that three pure forms of 1,3-bis(*m*-nitrophenyl) urea could be selectively crystallized on different SAM-functionalized gold surfaces. These results have been explained by two-dimensional lattice matching (epitaxy) and complementary functional group interactions at the SAM/crystal interfaces.

It is well-known that the preparation procedure of SAMs is complicated, mainly consisting of gold-coating (Au-SAMs), surface-washing, and film growth. The complicated procedure makes the quality of SAMs hard to control, greatly influencing the polymorph outcomes. Meanwhile, like other methods, new polymorph discovery by SAMs is still a trial-and-error process which needs constant changing of the tail groups of SAMs to increase the possibility of new forms. This blindness is also a

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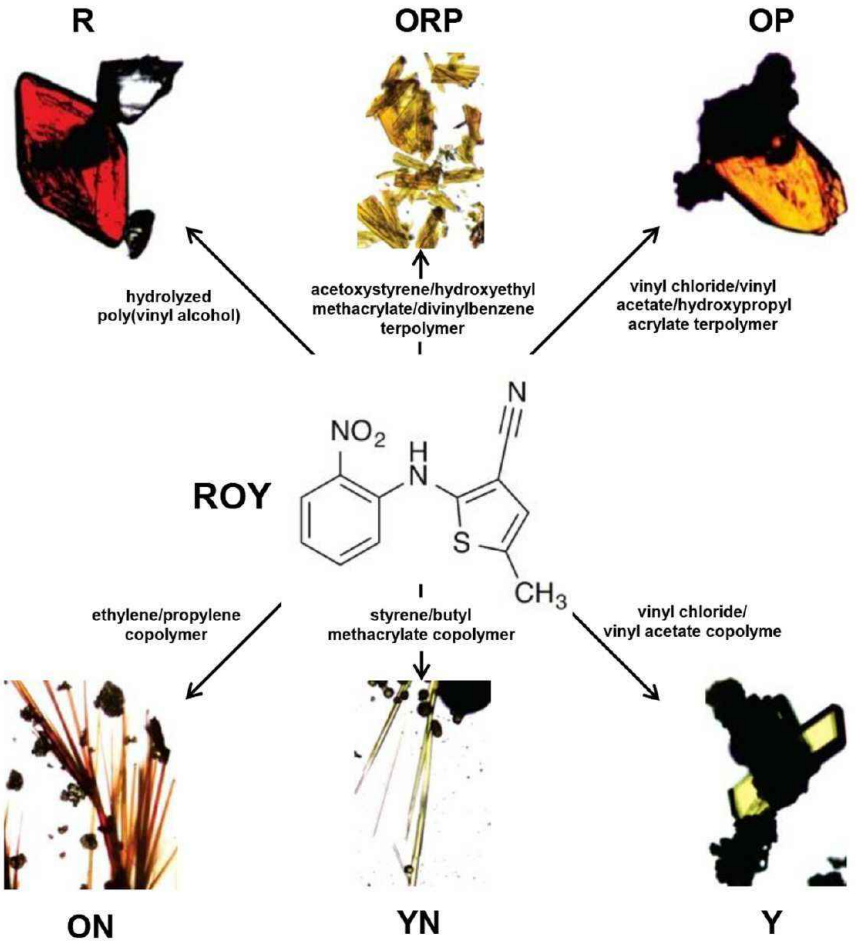

Figure 4. Photographs of ROY polymorphs crystallized in the presence of polymers, (Reproduced with permission from ref 56. Copyright 2005, American Chemical Society).

result of unclear nucleation mechanisms underlying SAMs-templated crystallization which should be further studied.

Polymer. Compared to the soluble additives, the insoluble polymer additives generally could not affect the morphology of crystals, and thus the changed morphology of crystal usually suggests the formation of a new polymorph in the presence of polymer. In 2005, Matzger et al.[56] found 6 out of 12 forms of ROY by only simply varying the polymer additives (Figure 4), confirming the highly polymorphic selectivity of this approach. Afterward, many new polymorphs were discovered in the presence of polymer additives, such as phenobarbital form V[57] and carbamazepine form IV.[58] The intermolecular interactions between the polymer and crystal were responsible for the polymorph discovery. Yao et al. reported that the pure form I of piroxicam could selectively crystallize in the presence of hydroxypropyl cellulose (HPC).[59] They found the hydroxyl groups of the HPC molecules could disturb the recognition of the hydrogen bonds in form II, leaving the form I alone during the concomitant crystallization. This method shows good compatibilities with other polymorph discovery methods, enabling its implementation along with traditional methods for discovering new polymorphs. The major topic of exploration in the future is to understand the nucleation process of polymorphs in the presence of polymers by investigating the effect of polymer alignment on crystal growth orientation.

Gels. Gels refer to a soft material with a three-dimensional spatial network structure, formed by the cross-linking of polymer molecules in solvent. The mesh sizes of pores in gels range from a few angstroms to several nanometers, which could be regulated by the chain length of the polymer. Gels such as silica or agarose have attracted initial attention in the field of protein crystallography due to their ability to improve crystal quality by delaying diffusion and restricting nucleation.[60] Several studies reported that elusive and novel forms could be grown within supramolecular gels. An unusual form of carbamazepine was supported by an amine containing dendron gelator.[61] Similarly, a novel form of chlorphenamine was crystallized from a calixarene-based gel.[61] Nowadays, two mechanisms of polymorph discovery by gels are proposed. One is the spatial confinement in which the polymer gels partition the absorbed solution and restrict the mobility of the adsorbed solute molecules. The other is that the polymer gels containing many functional groups could form the intermolecular interactions with solute molecules. The two mechanisms often work together to affect the polymorph outcome. Diao et al.[62] found that PEGDA microgels could selectively induce nucleation of carbamazepine form II and greatly increase the possibility of ROY form R, a result of the spatial confinement and the interfacial interactions. Song et al.[63] reported that agarose could selectively crystallize the pure form III or form IV of sulfathiazole by only regulating the concentration of

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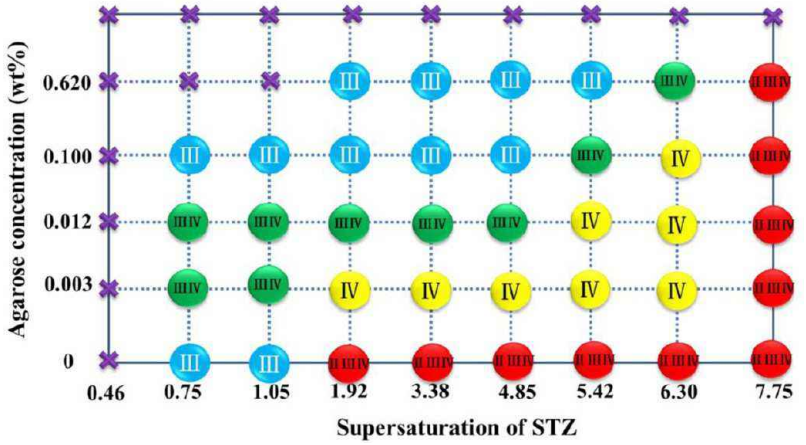

Figure 5. Influence of agarose concentration and sulfathiazole supersaturation on the crystallization outcomes of sulfathiazole polymorphs. (Reproduced with permission from ref 63. Copyright 2019, American Chemical Society.)

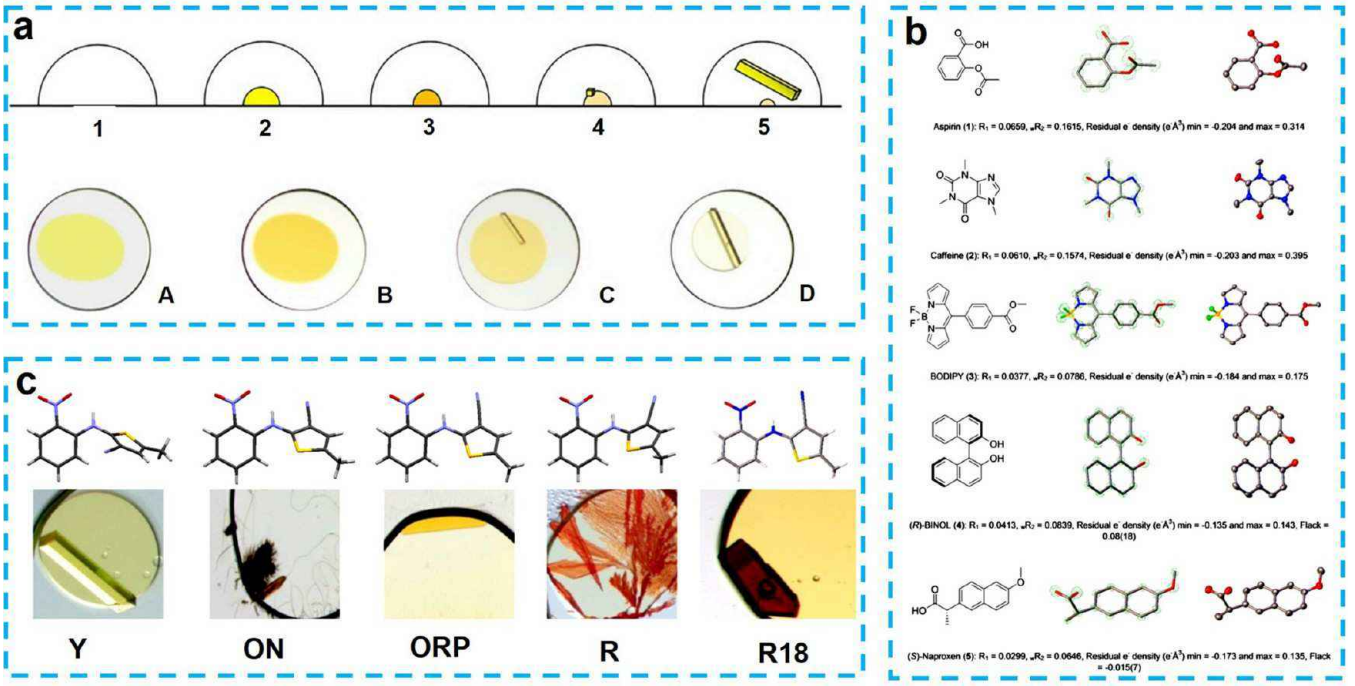

Figure 6. (a) Cross-section schematic illustration of an ENaCt experiment (top) and the crystallization process of a ENaCt experiment with 50 mg/mL ROY in DMSO and 200 nL mineral oil (bottom). (b) Molecular structures, electron density maps, and refined crystallographic molecular models derived from SCXRD analysis of single crystals of compounds (aspirin, caffeine, bodipy, (*R*)-binol and (*S*) naproxen) prepared via the ENaCt protocol. (c) Five forms of ROY obtained by the ENaCt method. (Reproduced with permission from ref 65. Copyright 2020, Elsevier.)

agarose at a certain supersaturation (Figure 5), also due to both the spatial confinement and intermolecular interactions.

Although the gels are beneficial to increase the polymorph diversity, there are some disadvantages. For the hydrogels, they could only adsorb water during heating, indicating that water is the only choice to be used to dissolve the crystalline molecules. As a result, the crystalline molecules must have a relatively high solubility in water which at least could dissolve in the water during heating, so that they could crystallize after cooling. Meanwhile, it is a challenge to separate the crystals from the hydrogels. These problems have been successfully solved in the organic gels. More importantly, the organic gels could also be incorporated with various functional groups to influence the polymorph outcomes. Of course, to make the choice of organic gels reasonable, it is necessary to understand the detailed reaction coordinates in the nucleation process.

Other Templates. Interestingly, some inorganic templates (glass, metal, and plastic) could also be utilized to increase the polymorph selectivity. Yang et al.[33] found that form II or form III of carbamazepine could selectively grow on the glass (or polytetrafluoroethylene) and the metal tin, respectively. Mohammed et al.[64] reported that the form II of acetaminophen preferentially crystallize on the silver films instead of the glass slides. Unfortunately, the mechanistic understanding of polymorph discovery by these inorganic templates is still insufficient.

3.1.5. Encapsulated Nanodroplet Crystallization (ENaCt). In 2020, Tyler et al.[65] created a robot-assisted and high-throughput method of solution crystallization for a combina-

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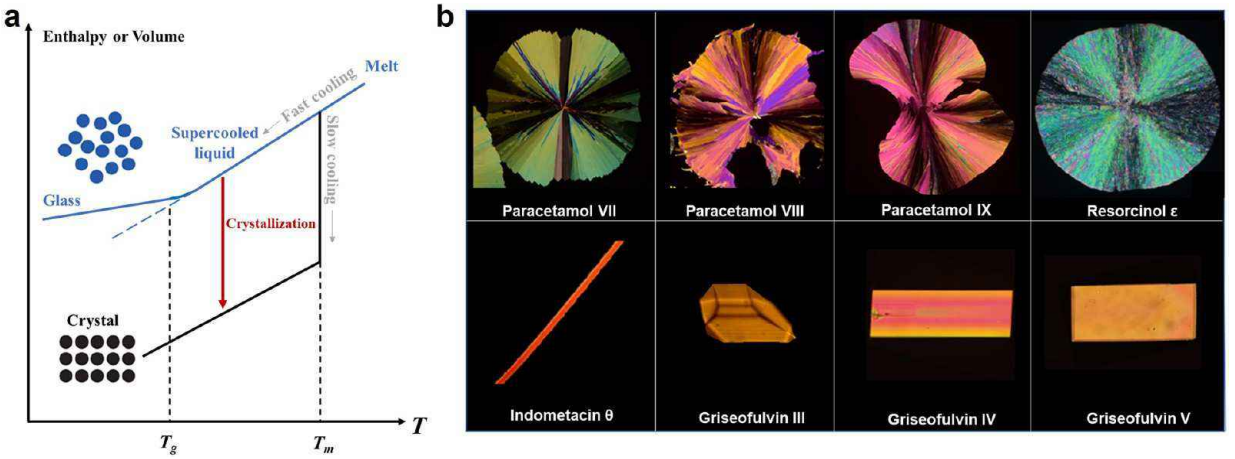

Figure 7. (a) Schematic representation of the enthalpy or volume of a liquid and its different solids as a function of temperature. (b) Representative photographs of new polymorphs harvested by melt crystallization. Paracetamol VIII, VIII, and IX (Reproduced with permission ref 78. Copyright 2019, American Chemical Society); Resorcinol ε (Reproduced with permission from ref 76. Copyright 2016, American Chemical Society); Indometacin θ (Reproduced with permission ref 83. Copyright 2021, Wiley-VCH); Griseofulvin III Reproduced with permission ref 84. Copyright 2018, the Royal Society of Chemistry); Griseofulvin IV and V (Reproduced with permission ref 82. Copyright 2022, American Chemical Society).

tion of polymorph discovery and single-crystal preparation, named as encapsulated nanodroplet crystallization. In detail, as shown in Figure 6a, the viscous inert oil (mainly mineral oil) is first dispensed onto a well of a 96-well glass plate (1), and then analyte solution is injected into a mineral oil droplet (2, A), solvent evaporates (3, B) to make the nucleation (4, C) and growth (5, D) of the crystal. This method allows hundreds of polymorph screening experiments to be performed simultaneously in parallel with minimal overall sample requirements, greatly saving the labor cost and shortening the development cycle. Besides, the single crystals grown directly from nanoliter droplets are suitable for SCXRD (Figure 6b). In this method, they successfully discovered a new (R18) polymorph of ROY and cultivated its high-quality single crystal, as shown in Figure 6c. Significantly, the ENaCt method could obtain 5 out of 12 forms of ROY by ENact, demonstrating its high efficiency in polymorph discovery. Nowadays, the automated crystallization technology has been successfully applied in the field of solid-state research, partially replacing manual screening experiments. However, pharmaceutical companies still mainly rely on the results of manual polymorph screening experiments, especially for important drug molecules. It is because the automated crystallization technology still has some problems which restrict its further developments. For example, the automated crystallization technology is not flexible, and all the crystallization conditions are identical for one batch of experiments in the 96-well glass plate. The only parameter which could be adjusted in experiments is solvents, affecting the diversity of experiments. In addition, the quality of the PXRD data collected directly from the glass substrate is poor due to the tiny crystals crystallized in each "island". Meanwhile, the small amount of sample used in this method also makes the experimental results difficult to reproduce when we scale it up manually in the lab. As a result, a flexible automated crystallization technology which considers more crystallization parameters should be developed to solve these problems and better help the polymorph discovery.

3.1.6. Other Methods of Solution Crystallization. We note that the methods such as pH control, ultrasonic crystallization, and laser-induced polymorph are often utilized to isolate the desired polymorph in concomitant crystallization, rather than polymorph discovery.

pH-Controlled Polymorph. In some cases, polymorphs are highly sensitive to the solution pH. For example, four forms (I–IV) of felodipine could be subsequently produced by pH adjustment.[43] Similarly, two forms of tianeptine were isolated by varying pH.[66] Han et al.[67] resolved the riddle of γ-glycine preferential crystallization over α-glycine in the acidic or basic solution. They believed that the glycine ions produced in the acidic or basic solution could induce head-to-tail molecular packing which matches the crystal structure of γ-glycine, mainly facilitating the nucleation of γ-glycine.

Ultrasonic Crystallization. Sonication is often considered an intensified crystallization technology to improve the quality of product such as the particle size, because it can decrease metastable zone width, shorten induction time, and increase nucleation rate, finally affecting the crystallization process.[68,69] Meanwhile, sonication can also be used to obtain the metastable forms such as form II of sulfamerazine[70] and form II of acetaminophen,[71] which may be correlated to the frequency and power of sonication.

Laser-Induced Polymorph. Zaccaro et al.[72] reported that the polar γ form of glycine could crystallize by an intense laser pulse of 1.06 μm. In a similar way, Wang et al.[73] found that the percentage of the elusive form III of acetaminophen was greatly increased through femtosecond laser irradiation with an optimal pulse energy and double-pulse delay. Studies revealed that the selective crystallization by the laser might be relevant to a laser-induced shock wave (pressure gradient) and cavitation events. As shown above, the entire changed external crystallization environment could affect the polymorph outcomes. However, it is tricky to understand how the crystallization parameters influence the nucleation process to determine the final polymorph. The unclear nucleation mechanism is a common question for all these polymorph discovery methods, restricting their effective search for new polymorphs. It is a matter of the utmost important to develop nucleation theories to further guide the polymorph discovery.

In fact, various methods in solution crystallization are usually jointly adopted to improve the efficiency of polymorph discovery. Undoubtedly, solution crystallization is the most

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commonly used method for polymorph discovery. Solution is a two-phase system containing solute and solvent molecules, and the solute−solvent interactions provide a significant challenge for the study of nucleation and growth of crystals, which determine the outcome of polymorphs. In contrast, melt crystallization is typically a single-component system, making it easier to study crystallization, particularly for homogeneous nucleation. In addition, melt crystallization is playing an important role in polymorph discovery.

3.2. Melt Crystallization. The enthalpy or volume of a substance at different states (melt, crystal, or glass) as a function of temperature is shown in Figure 7a.[74] Melt crystallization could spontaneously occur below the melting point, and more and more polymorphs[75−84] are being harvested during this process, as shown in Figure 7b.

As early as 1971, the excellent ability of melt crystallization on polymorph discovery has been demonstrated by Maria Kuhnert-Brandstätter.[85] In her book, she has listed 1000 polymorphs grown from the melt. However, the tricky question at that stage was that all these new polymorphs were only identified by morphology or melting point rather than single-crystal diffraction, because no effective methods could be employed to prepare single crystals for structural solution after the new polymorph discovery in the melt. In 2005, Chen et al.[75] discovered the Y04 and YT04 forms of ROY by melt crystallization. Inspiringly, they successfully cultivated the single crystals of one (YT04) of the two new forms by seeding a saturated solution and solved its structure by single-crystal diffraction. Recently, the melt microdroplet method for cultivating single crystals developed well, achieving the integration of polymorph discovery and single crystal preparation only by melt crystallization. Using this technique, Gui et al.[79] cultivated single crystals of nifedipine γ' for structural solution, and Ou et al.[80,82,84] applied it to many other systems with success, including forms II, III, IV, and V of griseofulvin and Y04 of ROY. Meanwhile, Shtukenberg et al. developed a method for combining X-ray powder diffraction analysis and crystal structure prediction algorithms without the need for the preparation of single crystals and successfully solved the melt-discovered polymorphs (form IV of aspirin,[77] forms VII, VIII, and IX of paracetamol[78]). These enhancements revitalized the melt crystallization in polymorph discovery. Studies[86,87] showed that new polymorphs discovered by melt crystallization appeared to be thermodynamically less stable which was confirmed by the energy comparison of piroxicam polymorphs harvested from the solution crystallization and melt crystallization,[81] as shown in Figure 8. It makes the melt crystallization become a complement to solution crystallization in polymorph discovery.

3.2.1. Spontaneous Crystallization. New forms might be found directly by spontaneous crystallization in the melt, such as form VI of piroxicam,[81] form γ' of nifedipine,[79] and forms VII, VIII, and IX of paracetamol[78] (Table 1). Owing to the different crystallization rates of forms in the melt at different temperatures, some forms might appear within a narrow temperature range. For example, the γ' form of nifedipine could only be observed at temperatures between 353 and 383 K (30 K range) and the forms VII, VIII, and IX of paracetamol might crystallize at temperatures between 323 and 343 K (20 K range) under ideal conditions with RH < 30%. Therefore, multiple temperature ranges should be selected to increase the probability of discovering new polymorphs.

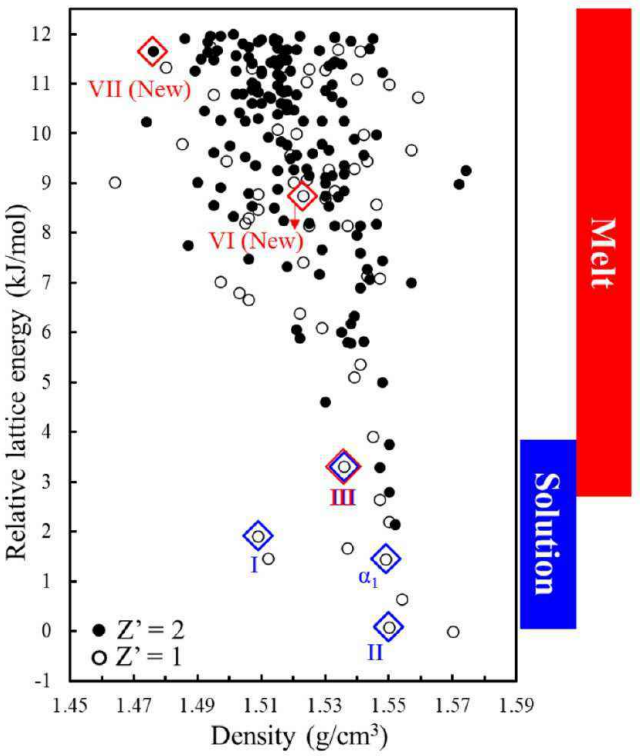

Figure 8. CSP landscape (relative lattice energy vs density) of piroxicam with $Z' = 1$ (open circle) and $Z' = 2$ (solid circle) structures within 12 kJ/mol relative to the global minimum. The bule and red open diamonds indicate experimental crystal structures discovered by the solution crystallization and melt crystallization, respectively. (Reproduced with permission from ref 81. Copyright 2020, American Chemical Society.)

Table 1. Summary of Polymorphs Discovered by Melt Crystallization (Spontaneous Crystallization, Cross Nucleation or Pseudoseeding) In Recent Years

Methods	Compound	Form	Ref
Spontaneous Crystallization	ROY	Y04/R05	75,86
	Griseofulvin	II/III/IV	87
	Paracetamol	VII/VIII/IX	78
	Nicotinamide	$\delta/\varepsilon/\eta/\theta$	95
	Imidacloprid	V/VIII/IX	96
	Coumarin	II/IV/V	97
	Nifedipine	γ'	79
	Piroxicam	VI	81
	Indometacin	θ	83
	Deltamethrin	II	98
	L-Lactic acid	II/III	99
	Tuberculosis	II/III	100
	Aspirin	IV	77
	Resorcinol	ε	76
Cross-nucleation	Nicotinamide	ζ	95
	Imidacloprid	VI	96
	Piroxicam	VII	81
Pseudoseeding	ROY	Y19	94
	Nicotinamide	ι	95
	Nifedipine	δ	79

The selective mechanism of polymorphs by spontaneous crystallization in the melt is still obscure. As is well-known, crystallization involves nucleation and growth. It appears that

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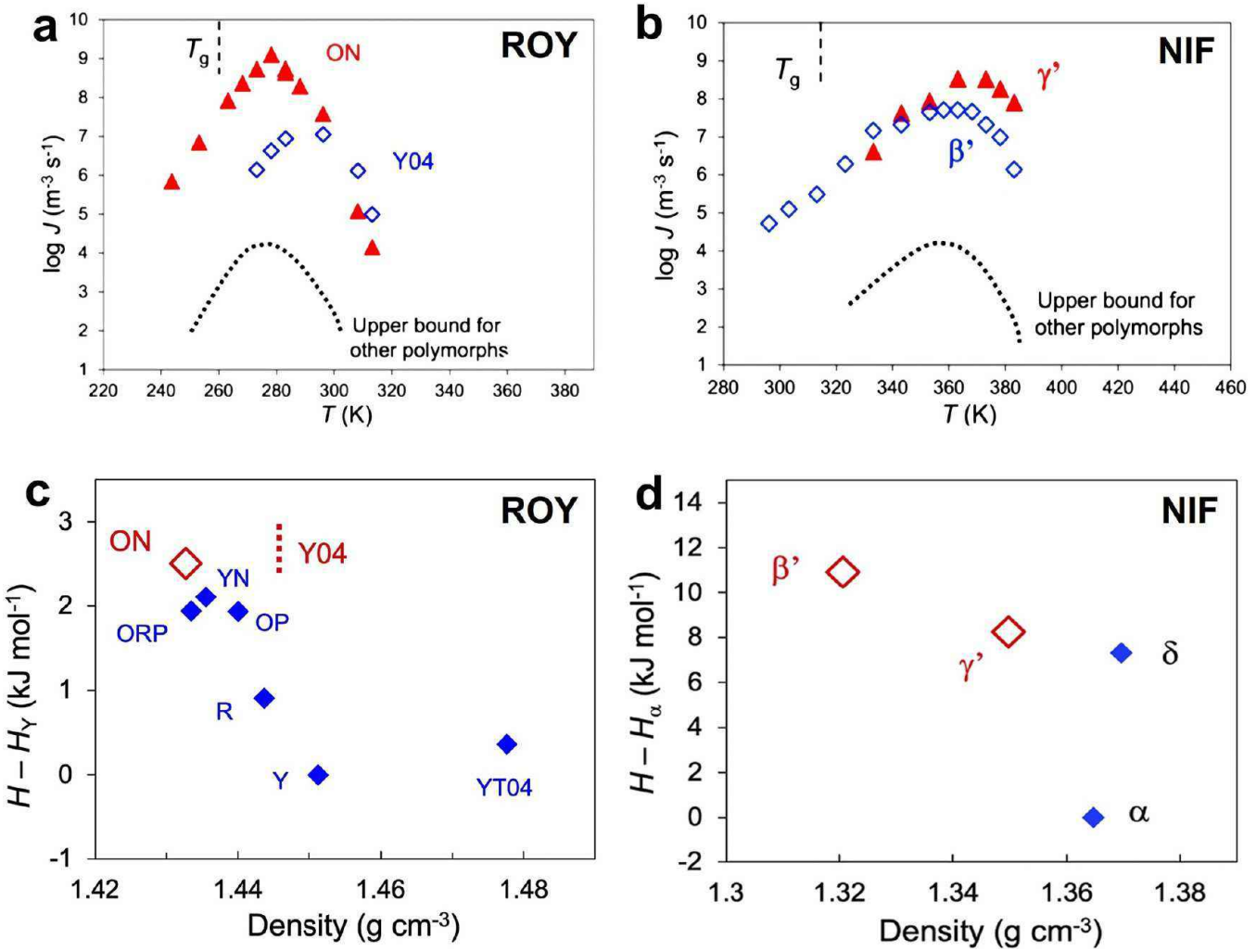

Figure 9. Nucleation rates of (a) ROY and (b) nifedipine (NIF) in its melt or glass; Polymorphs with a faster nucleation rate indicated in red diamonds on the energy/density map of (c) ROY and (d) nifedipine. (Reproduced with permission from ref 91. Copyright 2022, AIP Publishing.)

the selectivity of nucleation determines the polymorphic outcomes, as the growth rates of polymorphs differ by no more than 2 orders of magnitude.[87−90] Recently, Gui et al.[91] measured the bulk nucleation rates of ROY and nifedipine in their melt or glass along a wide temperature range. Both two polymorphic systems show vastly different spontaneous nucleation rates of polymorphs with at least a 5-decades span, as shown in Figure 9a and b. They believed that the polymorphs with a faster nucleation rate were not established from the lowest-energy conformers, while they usually own lower densities and higher energies and thus much similarity to the liquid phase as illustrated in Figure 9c and d. At present, it is still necessary to quantitatively assess polymorphic selectivity and develop the related theory to predict polymorphic selectivity in crystal nucleation process.

3.2.2. Cross Nucleation. Cross nucleation is an effective way to produce new polymorphs in the melt. Many polymorphs are discovered by cross nucleation: The R05 forms of ROY[29] were found by cross-nucleation on the Y04 form, and the form α of D-mannitol[92] was born on the surface of form δ, as shown in Figure 10.

Chen et al.[29] have systematically investigated the cross-nucleation mechanism by the cross-nucleation between the ROY polymorphs. They found that many factors could affect the cross-nucleation, such as the initial form, the growth rates of polymorphs, crystal surface defects, and temperature. Specifically, (a) the cross-nucleated polymorph can only nucleate on the specific forms. Surprisingly, evidence indicates that there is no structural similarity between the initial form and the cross-nucleated form. (b) The cross-nucleated form tends to have a faster growth rate than that of the initial form. From the perspective of free energy, it is reasonable because the cross-nucleated form with a faster growth rate can decrease the system's free energy rapidly. (c) Defects on crystal surface can induce cross-nucleation; thus the decease of surface defects by annealing can decrease the cross-nucleation rate. (d) The phenomenon of cross-nucleation is highly temperature dependent. That is, it can only occur within a certain temperature range. Temperature may influence the relative growth rate of polymorphs, resulting in cross-nucleation. Above all, to discover polymorphs through cross-nucleation more effectively, we should carefully observe the cross-nucleation of various polymorphs at different temperatures.

3.2.3. Pseudoseeding Method. Recently, studies have shown that the polymorphic diversity could be increased by the pseudoseeding method which is a similar way to cross nucleation. Herein, the pseudoseed is a crystal with a chemically similar foreign substance. Lévesque et al.[94]

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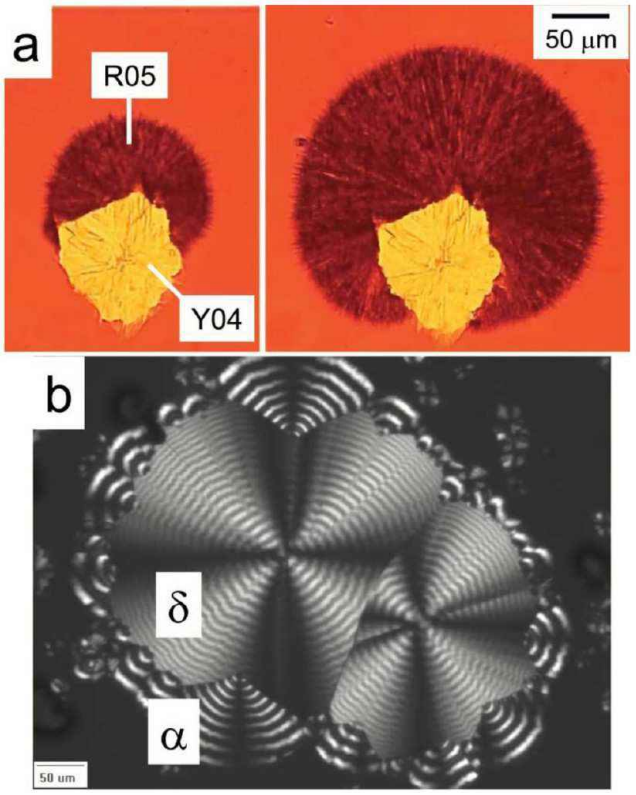

Figure 10. Cross nucleation of (a) R05 grown on Y04 of ROY. (Reproduced with permission from ref 93. Copyright 2010, American Chemical Society) and (b) form α grown on form δ of D-mannitol. (Reproduced with permission from ref 92. Copyright 2003, American Chemical Society.)

discovered the Y19 form of ROY by seeding mixed-crystals containing both the Fu-ROY (an analogue of ROY) molecules and the ROY molecules in their crystal structures. Gui et al.[79] unveiled a new form δ of nifedipine by seeding the felodipine form I crystals in the melt of nifedipine. Intriguingly, felodipine form I has a similar molecular conformation as nifedipine form δ, which may be responsible for the discovery of nifedipine form δ. We could see that both Lévesque et al.[94] and Gui et al.[79] employed the well-designed analogues as pseudoseeds to detect the new forms. So, a reasonable design or selection for the chemical structures of the analogues plays a key role in polymorph discovery.

3.3. Other Experimental Methods. *3.3.1. Sublimation Method.* Sublimation method is frequently regarded as an effective method to grow high-quality single crystals from vapor. In several cases, sublimation is also a practical technique to enable the discovery of new forms which are not accessible by other methods, such as form β of fumaric acid,[101] forms II_P and III_P of *p*-isopropylcalix[4]arene,[102] and β-phase of *N,N′*-bis(heptafluorobutyl)-2,6-dichloro-1,4,5,8-naphthalene-tetracarboxylic diimide.[103] Studies show that sublimation temperatures and the top sublimation surface (template) are key control factors for polymorph selectivity. For example, Shen et al.[104] were able to selectively crystallize polymorphs of 5-methoxy-salicylaldhyde azine by only controlling the sublimation temperature. Arlin et al.[105] obtain the unknown form V of carbamazepine by using an isomorphous template (dihydrocarbamazepine form II). Likewise, they discovered form VI, form VII, and form VIII of tolfenamic acid by sublimation onto mefenamic acid form I, solid solution template crystals containing both tolfenamic acid and flufenamic acid, and copper, respectively.[106] So, we could change the sublimation temperatures or modify the top sublimation surface to search new polymorphs in this method. Although the sublimation method has a higher driving force which favors the discovery of the metastable forms, the polymorph selectivity mechanism of sublimation method is poorly understood. In future, more quantitative data about the nucleation and growth of crystals in this method should be measured to study the crystallization process and make the polymorph selectivity clear.

Owing to the needs of vacuum or carrier gas atmosphere, most experimental setups used by the sublimation method are complicated and costly. In 2017, Ye et al.[107] developed a sample sublimation method, namely, microspacing in-air sublimation (MAS), to grow a variety of organic crystals without the aid of a vacuum system or other special equipment. Besides, they successfully prepared a series of polycyclic aromatic hydrocarbon (PAH)−1,2,4,5-tetracyanobenzene (TCNB) complexes cocrystals in this method.[108] In the future, this method might be applied to new polymorph discovery. So far, as an emerging crystallization method, this method has not been applied to the field of polymorph discovery, and no new forms have been reported by this method. Due to its higher driving force, we believe that the first case of new polymorph found by this method will come soon.

3.3.2. Solid Phase Transformation. Solid phase transformation could be triggered by external conditions such as temperature, humidity and pressure. Solid phase transformation has two sides. On the one hand, as previously mentioned, the unexpected solid phase transformation could lead to massive losses. On the other hand, it also could be utilized in polymorph discovery. Normally, heating or cooling the sample is the most convenient way to induce solid phase transformation which could be identified by DSC or hot stage microscope. Figure 11 (a) shows the reversible solid phase transformation of nifedipine, as indicated by the changed color of crystals during heating or cooling.[79] Notably, the new form β' of nifedipine is hunted during this process. Likewise, coumarin III is also discovered through the transformation of IV, as shown in Figure 11 (b).[97] For molecules with a high propensity to form solvates, the discovery of pure polymorphs could rely on the desolvation of solvates by heating or drying, which is also a way of solid phase transformation. The extreme case is that eight new neat forms of galunisertib were discovered by desolvation of various solvates.[36] It should be noted that pressure could also induce solid phase transformation, thereby facilitating the discovery of polymorphs (see below).

In 2020, Yue et al.[79] studied the solid phase transformations between six forms of nifedipine. They found that the reversible phase transformation could occur if the nitro groups involve the hydrogen bond as acceptors and have torsional freedom. This rule is also verified by other molecular crystals having nitro groups such as nisoldipine and felodipine. However, the mechanism of this kind of reversible phase transformation is mysterious. Meanwhile, for other molecular crystals without nitro groups, it is still a riddle to know whether the solid phase transformation could occur or not. In future, a more detailed process of solid phase transformation with more cases should be observed to unravel their mysteries.

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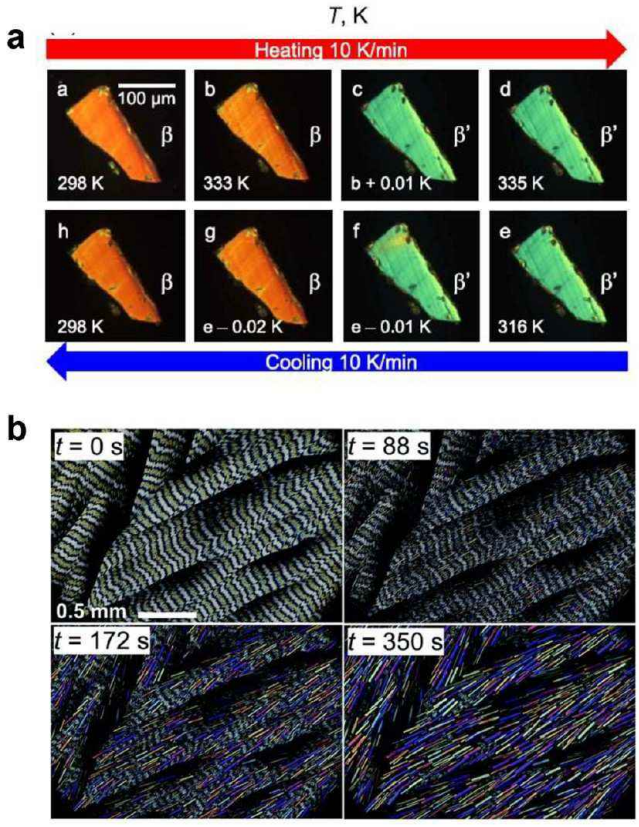

Figure 11. (a) The reversible solid phase transformation ($\beta \leftrightarrow \beta'$) of nifedipine. (Reproduced with permission from ref 79. Copyright 2020, American Chemical Society.) (b) Solid phase transformation (from IV to III) of coumarin at 57 °C observed by a polarized light optical microscope. (Reproduced with permission from ref 97. Copyright 2017, the Royal Society of Chemistry.)

3.3.3. High-Pressure Crystallization. Many new polymorphs were first observed by the high-pressure crystallization, such as forms IV and V of piracetam[109,110] and forms IV and V of paracetamol.[111] High pressure is often generated by direct compression or indirect compression (pressure pass through solution) in diamond anvil cells.[112] New polymorphs harvested by direct compression are usually a result of solid phase transformation. For example, in the high explosives, the γ form of RDX,[113] the ε form of FOX-7 (1,1-diamino-2,2-dinitroethene),[114] and the ζ-form of CL-20[115] are all first identified by high-pressure phase transition. Liu et al.[116] visualized this process by the transformation of single crystal to single crystal of CuQ2-TCNQ. As shown in Figure 12, we could clearly observe the dramatic and rapid changes in crystal dimensions in response to mechanical stimulation, suggesting that the metastable form II transforms into the stable form I. During the indirect compression crystallization, hydrates, solvates, or cocrystals might be formed due to the presence of solvents. It is worth noting that the solvent selected affects both polymorph outcomes and the pressure required to produce a given polymorph. Fabbiani et al.[109] reported that form IV of piracetam could crystallize in both methanol and water under pressure. Nevertheless, they observed that the required pressure (0.07 GPa) in methanol was significantly lower than that (0.4 GPa) in water. Additionally, the water used in the pressure crystallization easily helped to obtain a dihydrate of piracetam. Commonly, we need to rely on in situ characterization techniques such as high-pressure XRD to identify the new polymorphs produced at high pressure. Because the polymorphs discovered at high pressure might not be stable at ambient pressure. For the commercial use of these high-pressure structures, it is necessary to solve their stability problem. However, no successful work has been found in this way.

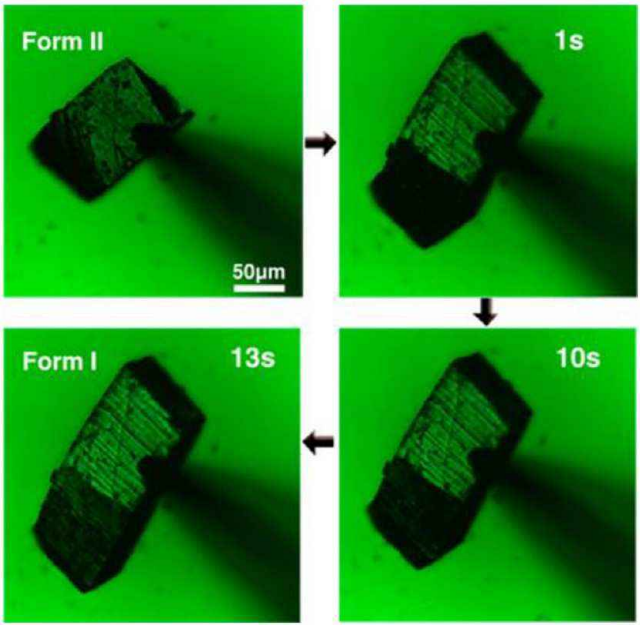

Figure 12. Solid phase transformation from the single crystal of form II of CuQ2-TCNQ to its single crystal of form I induced by pressure. (Reproduced with permission from ref 116. Copyright 2014, American Chemical Society.)

Notedly, new polymorphs with high density predicted by computers might be found under high pressure, such as dalcetrapib form C[117] and γ-aminobutyric acid monohydrate.[118] It demonstrates that the high-pressure crystallization is an effective tool to search the polymorph with a higher density.

3.3.4. Nanoconfinement. Polymorphism has different critical nucleus sizes based on the surface energies, volume free energies, and shapes of the crystals. This property could be utilized to discover new polymorphs by crystallization in nanoporous matrices (such as polymers and glass matrices) with dimensions at or near the critical nucleus size. The novel form II of the tuberculosis drug isoniazid was discovered by crystallization in controlled pore glass (CPG) with 30−100 nm pore size. The unknown polymorphs (δ form of pimelic acid, β form of suberic acid, and β form of coumarin) could crystallize in CPG with pore sizes <23 nm and poly(cyclohexylethylene) with pore sizes <40 nm.[119] Recently, Zhang et al.[120] revealed that new polymorph discovery by nanoconfinement might be relevant to the alteration of phase transformation kinetics in confined crystallization processes. Figure 13 shows the obviously different phase transition pathways of form VIII of flufenamic acid in CPG nanopores with various sizes and in bulk at room temperature. Obviously, form II and form IV of flufenamic acid emerged in the CPG with 30−50 nm and 100−200 nm, respectively, during the phase transformation. That is to say, the hidden polymorphic transformation pathways could be altered by nanoscale confinement, and new forms could be observed during this process. At present,

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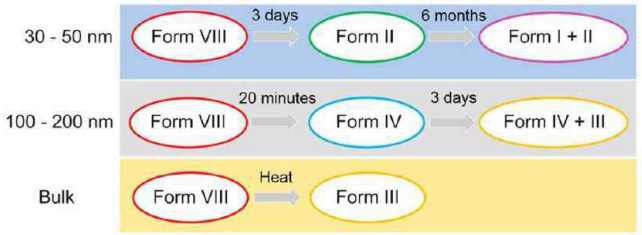

Figure 13. Phase transition pathways of form VIII of flufenamic acid confined in CPG nanopores with different sizes and in bulk under ambient conditions. (Reproduced with permission from ref 120. Copyright 2020, American Chemical Society.)

the critical size of nuclei is hard to estimate in both experiments and calculations so that we should use different sizes of controlled pore glass to detect as many polymorphs as possible. Meanwhile, we should pay more attention to the competitions between the thermodynamics and kinetics of confined crystallization. Only in this way, we could better understand the role of the pore wall on the polymorph discovery.

3.4. Crystal Structure Prediction (CSP). The well-known "ritonavir" event warned that the thermodynamically metastable form may be kinetically stable for years and then abruptly transform to a stable one. Indeed, it is not a rare phenomenon. Bučar, Lancaster, and Bernstein listed dozens of polymorphs that are unable to be reprepared, called disappearing polymorphs.[121] In 2018, a study of 41 pharmaceutical compounds revealed that 15−45% of all small-molecule drugs currently on the market do not exist in the most thermodynamically stable crystal structure.[122] These studies indicate that more ritonavir cases will appear in the future. In this context, crystal structure prediction (CSP) which uses chemical diagrams to intelligently search for possible crystal structures of organic crystalline molecules is regarded as an effective tool to avoid the recurrence of the "ritonavir" incident. This property makes the CSP gain much attention from both academia and industry, resulting in its rapid development.

Computer-predicted crystal structures mainly rely on the calculation of crystal energy, with the global minimum and a succession of local minima in the crystal energy landscape corresponding to the most thermodynamically stable form and a variety of metastable forms, respectively. It is worth noting that the free energy of some polymorphs is extremely close, with the difference being as little as 2 kcal/mol. In order to acquire the thermodynamically most stable form, it is essential to search for crystal structures with precise energy estimates. Although the methods of crystal structure prediction vary from researcher to researcher, the essential procedure often involves four steps: (a) molecular model; (b) crystal structure generation; (c) lattice energy calculations; and (d) crystal energy landscape. Specifically, the molecular configuration is initially optimized by Gaussian or molecular dynamics (MD) simulation, and the more rigid the molecule, the simpler the calculation. Second, the crystal structures with $Z' = 1$ or $Z' = 2$ in the selected space group are searched by a special algorithm such as grid search or random search (low discrepancy sequence, Monte Carlo etc.). Cambridge Structural Database (CSD) shows that the Z' of most organic crystal structures is 1 or 2, and the space group mainly involved is $P\bar{1}$, $P2_1/c$, $P2_12_12_1$, $P2_1$, $C2/c$, and $Pbca$, greatly narrowing the search for crystal structures. Subsequently, the lattice energy of crystal structures is calculated and optimized by the algorithms such as high-level quantum mechanical calculation, molecular mechanics force field, plane-wave dispersion-corrected electronic structure calculation, and hybrid model. At the end, the experimental and theoretical structures are compared in crystal energy landscape to further guide the polymorph discovery in experiments. To promote the development of CSP, the Cambridge Crystallographic Data Centre (CCDC) has organized seven most severe "blind tests" since 1999. The latest "blind test" results indicate that CSP is capable of accurately predicting the polymorphs of multicomponent crystals (cocrystals, salts, and solvates) and flexible macromolecules.[123]

Recently, the CSP has achieved tremendous progress successfully predicting crystal structures observed in experiments. A remarkable study was the ROY's CSP carried out by Vasileiadis et al. in 2012 which predicted all the experimental $Z' = 1$ structures, including both forms discovered before and after the publication.[124] In pharmaceutical science, there is an increasing number of examples in which the CSP suggests experiments to find new forms. One of the good examples is demonstrated by Neumann et al., who successfully identified a new form of dalcetrapib under the suggestion of the CSP.[117] The energy landscape indicates that a promising denser crystal structure of dalcetrapib shows better stability than that of the existing known structures with a slight increase in pressure. Under moderate pressure, a novel form of dalcetrapib is produced experimentally in a diamond anvil cell from solution or melt. This exemplifies how CSP can offer helpful information to find a novel form that was missed by conventional methods. Recently, Price's group have developed a smart strategy of employing CSP methods to identify which isostructural template should be adopted to direct the crystallization of a predicted but missing polymorph via sublimation method.[105,106] So far, they successfully directed the missed carbamazepine V and tolfenamic acid forms VI, VII, and VIII, as mentioned above.

However, CSP still needs to be further improved. One of the major challenges in CSP development is that computers create many more polymorphs which are hardly discovered in experiments, a result of the flaws of both experiments and calculations. From the experimental aspect, some polymorphs are difficult to observe, due to their slow nucleation rate, slow growth rate, and fast phase transition rate; thus not all polymorphs could be discovered by current experimental methods. From the computational aspect, the intermolecular force between atoms or molecules is often simply calculated by the potential function (force fields), instead of the more accurate quantum mechanics. Small errors in initial calculations could gradually accumulate, affecting the final results. In addition, the lattice energy in the energy landscape calculated by CSP is an approximation of the Gibbs free energy, disregarding the entropy. Nonetheless, the stability of polymorphs could be affected or even determined by entropy, especially for the polymorphs with similar lattice energy. Meanwhile, the neglect of entropy also indicates that the crystal is assumed to be a perfect static lattice, resulting in the miss of polymorphs with disordered structures. Notedly, the setting temperature in CSP is 0 K, implying that these 0 K structures may not be able to survive at ambient conditions. All these factors lead to the overprediction of CSP.

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4. SUMMARY AND OUTLOOK

This review summarizes recent experimental and computational breakthroughs in polymorph discovery of organic crystals, focusing on solution crystallization, melt crystallization, and crystal structure prediction. Meanwhile, the nucleation theories and the related mechanisms of polymorph discovery are also briefly introduced. Overall, solution crystallization is the most extensively used tool for polymorph discovery in industry, melt crystallization has become a needed complement to solution crystallization in discovery of metastable forms, and CSP is developing to guide new polymorph discovery. Currently, polymorph discovery still requires trial-and-error with a significant amount of time and energy, and no method can capture all polymorphs. So, various methods with high throughput experiments should be complementarily employed to search for new polymorphs with good properties. To make the polymorph discovery more effective, there are still some obstacles which need be overcome in the future.

The nucleation theories should be further developed to fundamentally elucidate the mechanisms of polymorph discovery. Owing to the limitations of CNT in studying nucleation kinetics, alternative strategies based on simple parameters of polymorphs such as growth rates, density, and enthalpy of melting, instead of the interfacial energy σ, should be developed to predict the nucleation rates. Compared to solution crystallization, melt crystallization could greatly simplify the parameters which influence the crystallization processes, because one does not need to consider the solvent−solute molecular interaction and solution-mediated phase transformation. Therefore, the study of homogeneous nucleation in the melt crystallization is considerably simpler than in the solution crystallization. Meanwhile, more nucleation processes should be carefully observed by advanced *in situ* technologies with high resolution, thereby improving the nucleation theory of nonclassical nucleation pathways.

Experiments and calculations should interact closely to precisely target the crystallization of new polymorphs, so resolving the "trial-and-error" issue. In experiments, for comparison with theory, it is necessary to characterize all possible polymorphs of a large variety of molecules employing multiple screening techniques in the laboratory. Moreover, more systematic works are still required for a deeper understanding of the mechanisms of polymorph discovery. In calculations, new theories should be developed to determine which polymorphs could actually be crystallized and plausible phase transformations, overcoming the "overprediction" problem, so that we can accurately predict which energetically possible structures are kinetically favored and likely to be observed.

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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