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Recent advances in drug polymorphs: Aspects of pharmaceutical properties and selective crystallization

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ABSTRACT

Drug polymorphism, an established term used to describe the phenomenon that a drug can exist in different crystalline phases, has attracted great interests in pharmaceutical field in consideration of its important role in affecting the pharmaceutical performance of oral formulations. This paper presents an overview of recent advances in the research on polymorphic drug systems including understandings on nucleation, crystal growth, dissolution, mechanical properties, polymorphic transformation, etc. Moreover, new strategies and mechanisms in the control of polymorphic forms are also highlighted in this review. Furthermore, challenges and trends in the development of polymorphic drugs are briefly discussed, aiming at developing effective and efficient pharmaceutical formulations containing the polymorphic drugs.

1. Introduction

In the field of pharmaceutical science, understanding the properties of active pharmaceutical ingredients (APIs) in the solid state is utmost important because it is the fundamental for regulating the pharmaceutical performance of oral solid formulations (Datta and Grant, 2004; Blagden et al., 2007; Shalaev et al., 2016; Fontana et al., 2018). In terms of long-range arrangement of the molecules, drugs in the solid state can be defined as either an ordered crystalline form or a disordered amorphous form (Yu, 2001; Dengale et al., 2016; Huang and Dai, 2014; Shi et al., 2020). Actually, there is a third type of solid state, which could not be straightforwardly distinguished from either crystalline or amorphous state, has been reported as liquid crystals, conformationally disordered crystal and plastic crystal in several recent studies (Shalaev et al., 2016; Teerakapibal et al., 2018).

APIs in commercial oral preparations are mainly in the crystalline form because they are superior in terms of physical stability and quality control in comparison with their amorphous counterparts (Vippagunta et al., 2001). According to the statistics, over 80% crystalline drugs exhibit the "polymorphism" phenomenon in the pharmaceutical industry in 2006 and this proportion is expected to gradually increase (Hilfiker, 2006). The phenomenon of polymorphism was firstly recognized in 1822, and a decade later Liebig and Wöhler reported the earliest example of a polymorphic organic compound benzamide, as evidenced by the different melting point and crystal habits (Bernstein et al., 1999). Until 1965, McCrone provided the most well-known definition of polymorphism as "a polymorph is a solid crystalline phase of a given compound resulting from a possibility of at least two different arrangements of the molecule of that compound in the solid state" (McCrone, 1965). Herein, crystals in different polymorphs could exhibit different lattice parameters, crystal packing or molecular conformation (Datta and Grant, 2004; Cruzcabeza and Bernstein, 2014). According to the conformational change of molecules, a polymorph could be configurational polymorph or conformational polymorph (Datta and Grant, 2004; Cruzcabeza and Bernstein, 2014). The former is mainly observed in molecular systems with a rigid structure, whose conformational change in different polymorphs is weak or negligible (Lang et al., 2002). Unlike the configurational polymorphs, molecular conformations in the conformational polymorphic systems are vastly different (Cruzcabeza and Bernstein, 2014; Bauer et al., 2001). Cruz-Cabeza and Bernstein proposed that these conformational polymorphs might exhibit more significant differences in some properties compared with the configurational polymorphs (Cruzcabeza and Bernstein, 2014). By definition conformational polymorphs are related by conformational change,

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which requires the crossing of an energy barrier. Statistics show that nearly 36% of reported polymorphic molecules in the Cambridge Structural Database (CSD) exhibit conformational polymorphs (Cruzcabeza and Bernstein, 2014). In addition, a pair of tautomers in rapid equilibrium in melt or solution are classified as tautomeric polymorphs (Bhatt and Desiraju, 2007). Similarly, crystals of isomers undergoing rapid inter-conversion in solution is also classified as polymorphs. For comparison, crystals of isomers showing slow inter-convertion is classified as different compounds rather than polymorphs (Bhatt and Desiraju, 2007).

Polymorph screening of APIs is crucial in pharmaceutical field due to different polymorphic form has its unique physical and pharmaceutical properties (Higashi et al., 2017). Ritonavir, one classical protease inhibitor of HIV, suffered a problem of drug withdrawal in 1998 because of the event of disappearing polymorphic form I, causing an enormous economic loss of Abbott Laboratories (Morissette et al., 2003). One previously unknown, more stable form II of ritonavir appears and yield a rapid polymorphic transformation, causing a decreased dissolution rate and reduced bioavailability (Morissette et al., 2003). In addition to avoiding the economic losses of appearing ineffective or poorly effective polymorph, discovering the new effective polymorph via polymorph screening would facilitate the extension of patent protection. For instance, ranitidine, whose patent protection is extended by applying a new patent of its form II due to the similar anti-ulcer effect as its form I, achieved great commercial success of an anti-ulcer drug with a total sale over 2.4 billion pound sterling (Wright, 1996).

In recent years, an increasing number of excellent reviews related to the polymorph have been published from different aspects including analysis, polymorphic phase transition, polymorph control, conformational polymorphs, etc. (Cruzcabeza and Bernstein, 2014; Higashi et al., 2017; Chieng et al., 2011; Anwar and Zahn, 2017; Llinàs and Goodman, 2008; Mangin et al., 2009). In this review, we focus on the recent advances in drug polymorphs concerning the pharmaceutical properties as oral formulations. The first part of this review discusses the formation of different polymorphs including the nucleation and crystal growth both in the solution and in the melt. The second part of this review focuses on critical issues of mechanical properties affecting the pharmaceutical manufacturing. Herein, the surface/interface properties and crystal structure-properties relationships of polymorphic drug systems are systemically discussed. Moreover, we also summarize the recent advances in polymorphic transformation and polymorph control in polymorphic drug systems. New strategies and mechanisms in the polymorph control would also be highlighted. Furthermore, we briefly discuss the challenges and trends in the development of polymorphic drugs.

2. Nucleation and crystal growth of polymorphic drugs

The final form of polymorphic drug is controlled by two crucial steps including nucleation and crystal growth. Unlike the crystal growth process, nucleation behavior remains largely unexplored despite several theories proposed to explain its mechanism, including classical and non-classical nucleation theories (Sosso et al., 2016; Karthika et al., 2016). Classical nucleation theory (CNT), developed in the first half of the 20th century, is the most famous theoretical model and dominate the field of nucleation mechanisms for nearly one century (Volmer, 1926). This theory was originally used to describe the condensation of vapors into a liquid and has already been demonstrated to successfully apply to explain the crystallizations from supercooled liquid or supersaturated solutions (Karthika et al., 2016; Mullin; Vekilov, 2010; Bai et al., 2019; Huang et al., 2018; Yao et al., 2019; Zhang et al., 2021). According to the CNT, prior to the nucleation, a prenuclei embryo with the short-range order matching the crystalline motif needs to form (Karthika et al., 2016; Mullin). Some of prenuclei would dissolve in the surrounding liquid while some could grow beyond a critical radius and become a stable nucleus (Karthika et al., 2016; Mullin; Bai et al., 2019). In a recent study, the requirement of critical ice nuclei for water freezing has been corroborated by using graphene oxide nanosheets of controlled size. Here, the observed behavior of ice formation was well consistent with that predicted by the CNT (Bai et al., 2019). However, it should be noted that the CNT does not apply in some cases including systems containing cubic shaped nuclei, polymorphic systems, etc. Moreover, the CNT also has difficulty in explaining the vanishing nucleation barrier in highly supersaturated systems (Karthika et al., 2016).

In the past decades, non-classical nucleation theories are booming and different branch theories emerged, including density functional theory (Nyquist et al., 1995; Zeng and Oxtoby, 1991), diffuse interface theory (Gránásy, 1993), two-step nucleation theory (Gebauer et al., 2014), etc. Two-step nucleation theory, one of the widely studied non-classical nucleation theories, strongly challenges the CNT by the observation of the existence of stable solute species (Gebauer et al., 2014; Gebauer et al., 2008). These solute species, also named pre-nucleation clusters, are not consistent with the CNT, which is based on a fundamental assumption that monomer association would yield a generation of unstable species (Gebauer et al., 2014). The validity of the two-step nucleation theory was firstly confirmed in the crystallization of proteins, as the pre-nucleation clusters were directly observed via dynamic light scattering and confocal depolarized spectroscopy techniques (Maes et al., 2015). In recent studies, this two-step nucleation theory could also be extended to other systems including colloidal systems (Anderson and Lekkerkerker, 2002), open framework materials (Fan et al., 2008), biomimetic mineralization (Gebauer et al., 2008; Pouget et al., 2009), etc. For instance, in the case of calcium carbonate mineralization, the precursor clusters could be observed in the early stage of nucleation, and they could be stabilized in the presence of additives (Pouget et al., 2009).

For a polymorphic system, it should be noted that direct nucleation into a stable polymorph may not be possible, therefore, the process will not be easily explained by CNT. Diffuse interface theory and two-step nucleation mechanism were reported to explain the nucleation behaviors in polymorphic systems (Karthika et al., 2016; Lu et al., 2015). According to the rule that Ostwald established in 1897, the least stable polymorph should nucleate first, then it transforms into the second least stable polymorph, and so on, finally it reaches the most stable polymorph (Fig. 1) (Ostwald, 1897). Some researchers proposed the independent nucleation theory for the polymorphic systems, stating that the final form of the crystals is a result of the competition between homogeneous nucleation of all possible polymorphs (Bernstein et al., 1999; Ter Horst et al., 2002). In 2003; Yu reported a new nucleation phenomenon, namely cross-nucleation, in the melting crystallization of two polymorphic hexitol systems D-mannitol and D-sorbitol (Yu, 2003). In the case of D-mannitol, α-polymorph could nucleate on the early nucleating δ-polymorph without undergoing polymorphic transformation (Yu, 2003). Unlike the secondary nucleation during solvent-medicated polymorphic transition, the newly nucleated polymorph in the cross-nucleation phenomenon could be less or more thermodynamically stable compared to the initially nucleated polymorph (Yu, 2003; Chen et al., 2005). Interestingly, the newly nucleated polymorph always exhibits a faster or same crystal growth rate as the initial polymorph (Chen et al., 2005).

In general, “parent” and “daughter” polymorphs could be defined in consideration of the direction of cross-nucleation (Looijmans et al., 2018). If the frequency of cross-nucleation is sufficiently high, surface of the “parent” polymorph will eventually be occupied by the cross-nuclei of “daughter” polymorph (Looijmans et al., 2018). Commonly, the cross-nucleation rate decreases with a decrease in supercooling, however, in the case of isotactic polypropylene (i-PP), the cross-nucleation of α-on-β occurs with increasing frequency above 140 °C (Looijmans et al., 2017). This anomalous behavior of cross-nucleation would also lead to a strong temperature dependency of the kinetic competition of these concomitantly growing polymorphs (Looijmans et al., 2017). For the cross-nucleation phenomenon, a model framework solely depends on the rate of cross-nucleation is proposed for predicting the final number of

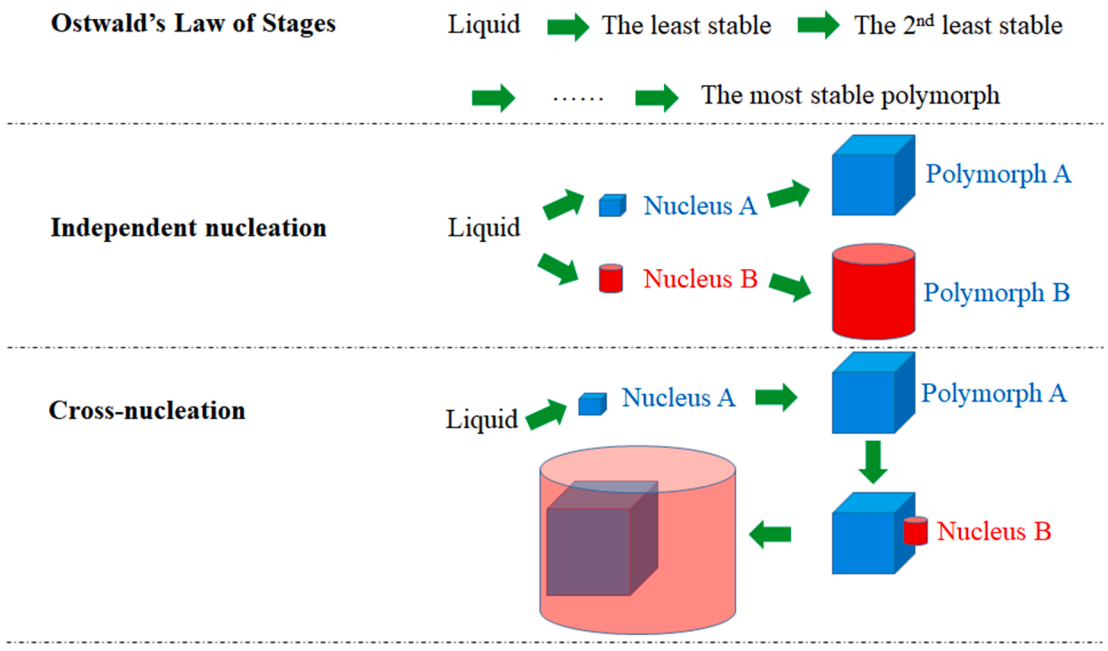

Fig. 1. Theories of crystallization in polymorphic systems.

cross-nuclei on a parent spherulite of given dimension (Looijmans et al., 2018).

In the pharmaceutical field, cross-nucleation could also be observed in several polymorphic drugs including testosterone propionate (Shtukenberg et al., 2014), paracetamol (Shtukenberg et al., 2019), sulfathiazole (Song et al., 2020), etc. For instance, Shtukenberg *et al.* found that the cross-nucleation phenomenon of form II and form III of paracetamol could reverse depending on the temperature (Shtukenberg et al., 2019). Although cross-nucleation was firstly observed in the melt of small-molecule compounds, it has also been reported in the crystallization in gels (Song et al., 2020) and polymer systems (Looijmans et al., 2017; Cavallo et al., 2017). In a very recent study, Song *et al.* investigated the crystallization of sulfathiazole in gel and find that its form III could nucleate on the initially nucleated form IV at a specific agarose concentration (Song et al., 2020). Given that seeding technique is widely used in the industry for achieving polymorph control, cross-nucleation sometimes can make this technique useless and counteract polymorph-specific crystallization.

There are many excellent reviews on the nucleation behaviors of polymorphic systems in solutions (Davey et al., 2013; Jin et al., 2020; Cruz-Cabeza et al., 2020; Blagden and Davey, 2003; Desiraju, 2013; Yu, 2010; Mahieu et al., 2013). In the past decades, in comparison with the time-consuming trial-and-error process of solution crystallization, an increasing number of new polymorphs have been discovered from the melts rather than from the solutions (Su et al., 2018; Shtukenberg et al., 2017; Shtukenberg et al., 2019; Lu and Taylor, 2016; Chen et al., 2005). Melting crystallization facilitates the discovery of some new polymorphs of the old drugs which were missed in conventional polymorph screening in solution for a long time (Shtukenberg et al., 2017; Shtukenberg et al., 2019; Lu and Taylor, 2016; Chen et al., 2005). For instance, griseofulvin, one of the classical antifungal drugs, whose first crystal structure was reported in 1977 and has been recognized to show only one polymorph for approximately half a century (Shtukenberg et al., 2017). In 2013, Mahieu *et al.* reported two new metastable polymorphs of griseofulvin during melt crystallization and further identified them by different melting points (T_m) and powder X-ray diffraction (PXRD) patterns (Shtukenberg et al., 2017). In a recent study, the third polymorph of aspirin, one of the most widely consumed drug, was also discovered in the melt (Lu and Taylor, 2016). The crystal structure of metastable polymorph (Form III) of aspirin is determined by a combination of its PXRD analysis and prediction algorithms of the crystal structure (Lu and Taylor, 2016).

Although recent studies corroborated that melt crystallization facilitates the discovery of new polymorphs, most of these studies did not solve the crystal structures (Shtukenberg et al., 2017; Ou et al., 2020; Granasy et al., 2004). This is mainly attributed to the fact that melt crystallization generally produces polycrystals, which are often unsuitable for crystal structure determination by single-crystal X-ray diffraction. Therefore, one of the main challenges to solve the crystal structure of these newly discovered polymorphs is to harvest single crystals with proper size and high quality. With the addition of low-concentration poly (ethylene oxide), Su *et al.* successfully obtained the crystal structure of griseofulvin form II *via* accelerating the crystal growth of single crystal (Shtukenberg et al., 2019). Compared to the thermodynamically stable form I, GSF form II has an anomalously large thermal expansion coefficient (Fig. 2), which is mainly attributed to its anisotropic layered crystal structure and weak layer-layer interaction (Shtukenberg et al., 2019). In a very recent study, Lu and co-workers developed a creative strategy for rapidly obtaining the single crystal of desired polymorphs

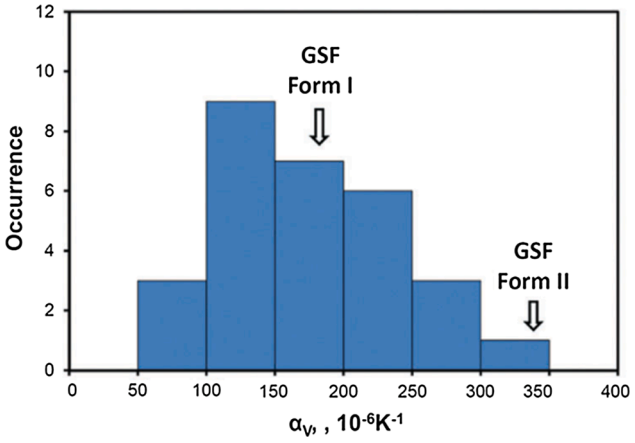

Fig. 2. Range of volumetric thermal expansion coefficients of majority of single-component crystals and the distribution of GSF form I and form II. Adapted from the Ref. 63 with the permission. (Copyright © 2017 The Royal Society of Chemistry).

from the melt microdroplets (Shtukenberg et al., 2012). This strategy of cultivating single crystals originates from the notion that polycrystals formation requires secondary nucleation and this process could be effectively suppressed near T_m (Yao et al., 2020; Li et al., 2020). In brief, the polycrystalline material was partially melted until a crystal seed was remained, subsequently, this seed was allowed to grow at the temperature very close to T_m to obtain the single crystal of proper size in the absence of secondary nucleation and interference by other growing crystals (Fig. 3) (Shtukenberg et al., 2012). This single-crystal cultivation technique *via* microdroplet melt crystallization rapidly produces a single crystal of form III of griseofulvin and it has been demonstrated in more than twenty clinical drugs (Shtukenberg et al., 2012; Li et al., 2020; Wu and Yu, 2006). By applying this melt microdroplet strategy, Li *et al.* obtained the single crystal and solved the structure of form Y04 of 5-Methyl-2-[(2-nitrophenyl) amino]-3-thiophenecabonitrile (ROY), which make ROY the largest polymorphic compound systems with twelve solved crystal structures (Wu and Yu, 2006).

Different polymorphs of a drug have been demonstrated to exhibit various nucleation rates and different nucleation temperatures (Huang et al., 2018; Yao et al., 2019; Zhang et al., 2021; Shi and Cai, 2016; Su et al., 2018). For instance, fluconazole, a classical antifungal drug, whose metastable polymorph II nucleates much faster than its stable polymorph I (Zhang et al., 2021). As shown in Fig. 4, the nucleation rate of polymorph II could be hundreds-fold faster than the estimated upper bound of the nucleation rates of polymorph I at 30 °C (2 °C below the T_g of fluconazole) (Zhang et al., 2021). Moreover, nucleation in the interior and at the free surface sometimes results in vastly different polymorphs (Shi and Cai, 2016; Su et al., 2018; Zhu et al., 2010; Gunn et al., 2011). For indomethacin (IMC), one classical model system for studying polymorphism, the main polymorph nucleates at the free surface is the γ-form, however, in the interior of deeply supercooled liquid, δ-form nucleates the fastest among all polymorphs (Shi and Cai, 2016; Su et al., 2018). In a very recent study, Su *et al.* find that nucleation of griseofulvin (GSF) could be effectively enhanced by tensile fracture (Gunn et al., 2011). As evidenced by the x-ray diffraction (XRD) patterns and T_m, the polymorphs of these enhanced nucleation are the metastable form II and III (Shtukenberg et al., 2017; Gunn et al., 2011). For comparison, the nucleated polymorph of GSF at the free surface is the thermodynamically stable form I (Zhu et al., 2010; Tian et al., 2017).

Similar to the nucleation process, crystal growth behaviors of amorphous pharmaceutical solids also exhibit strong polymorph dependence (Zhang et al., 2021; Shtukenberg et al., 2019; Chen et al., 2005; Wang and Sun, 2019; Zhang et al., 2016; Kestur and Taylor, 2013). Different polymorphs could exhibit various crystal growth rates, which has been reported in several polymorphic drug systems including fluconazole (Zhang et al., 2021), indomethacin (Shi and Cai, 2016), griseofulvin (Shtukenberg et al., 2019), itraconazole (Sun et al., 2012), carbamazepine (Wang and Sun, 2019), felodipine (Yu, 2016), etc. In the case of itraconazole, the metastable form II exhibits the fastest crystal growth rate among its three polymorphs in the deeply supercooled liquid (Sun et al., 2012). However, it should be noted that kinetics of crystal growth of different polymorphs seems to be independent on their thermodynamic stability. For instance, the crystal growth rate of thermodynamically stable form I of griseofulvin was reported to be

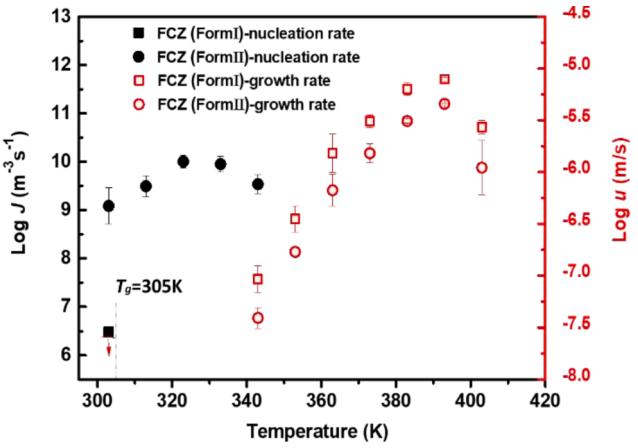

Fig. 4. Rates of nucleation and crystal growth of fluconazole polymorphs as a function of temperature. Adapted from the Ref. 33 with the permission. (Copyright © 2021 The Royal Society of Chemistry).

significantly higher than those of its metastable forms II and III (Shtukenberg et al., 2019). The difference in growth kinetics of different GSF polymorphs is quite large, and can be over two orders of magnitude different under a certain temperature range (60–90 °C) (Shtukenberg et al., 2019). Faster crystal growth rate of the thermodynamically stable form has also been reported in felodipine, and it is 1–2 orders of magnitude faster than those of its metastable form II (Yu, 2016).

Recent studies revealed that some organic systems could exhibit fast crystal growth mode below or near T_g, one occurs in the interior while the other occurs at the free surface (Shi et al., 2020; Sun et al., 2008; Hasebe et al., 2014). However, it is noteworthy that not all the polymorphs are capable of showing such fast crystal growth behaviors (Hasebe et al., 2015). In the case of ROY, Sun *et al.* found that crystal growth rates of some polymorphs would suddenly increase anomalously once the temperature decreases to near or below T_g while other polymorphs do not (Hasebe et al., 2015). They proposed that polymorphs showing this fast crystal growth (GC growth) result in a molecular packing similar to their liquid structure, as evidenced by the center-of-mass of radial distribution function analysis (Hasebe et al., 2015). Similar to GC growth in the interior, crystal growth of different polymorphs also exhibits different kinetics at the free surface (Su et al., 2018; Wang and Sun, 2019). For instance, the crystal growth rate of form IV of carbamazepine is ~5.4 and ~2.8-fold faster than that of form I and form III at 30 °C (Wang and Sun, 2019). Moreover, carbamazepine polymorphs also exhibit different ratios of the growth rate at the surface to that in the bulk (Wang and Sun, 2019). This ratio of form I could be over 100 while that of form III is ~2.4. Interestingly, crystal morphologies of different polymorphs grown at the free surface is diverse and correlate well with the surface crystal growth behaviors at the onset of liquid flow (Musumeci et al., 2016; Huang et al., 2017; Powell et al., 2013). In the case of indomethacin, α-form growing as segregated needles would be wetted and embedded by the flowing liquid as temperature increases above T_g (Powell et al., 2013). For comparison, γ-form of indomethacin

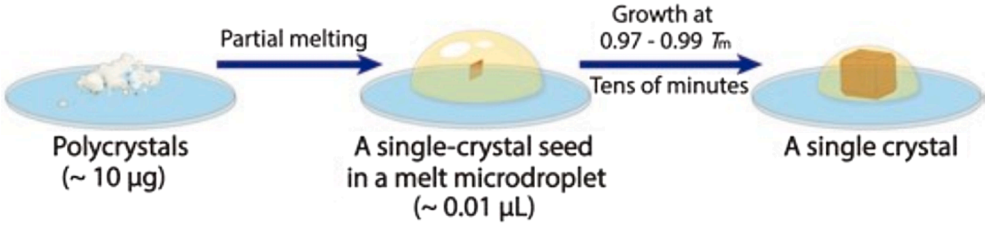

Fig. 3. The method for cultivating single crystals from melt microdroplets. Adapted from the Ref. 68 with the permission. (Copyright © 2020 The Royal Society of Chemistry).

grows into compact domains could effectively resist the disruption of liquid flow (Powell et al., 2013).

Foreign polymers can strongly influence the crystallization of amorphous pharmaceutical solids (Shi et al., 2020; Sun et al., 2008; Yao et al., 2019; Zhang et al., 2021; Shi et al., 2017; Zhang et al., 2017; Zhang et al., 2020; Madejczyk et al., 2017; Kalepu and Nekkanti, 2015; Kumar et al., 2015). In the case of polymorphic system, it is important to know that whether the polymer has the same effect on the crystallization of different polymorphs or not. Table 1 shows the recent studies focus on the effects of the polymer or additives on the crystallization of drug polymorphs. Kestur *et al.* found that the addition of 3 wt% poly (vinyl pyrrolidone) (PVP) imposed the similar inhibitory effects on the crystal growth rates of both form I and form II of felodipine, as evidenced by approximately the same ratios of crystal growth rates in the presence and absence of PVP for these two polymorphs (Yu, 2016). They proposed that this similar effect of PVP on the crystallization of felodipine polymorphs is most likely to be a result of polymer mainly affecting the amorphous matrix rather than the crystal surface (Yu, 2016). However, recent studies showed that the impacts of polymer on the crystal growth of some drugs have strong drug polymorph dependence (Zhang et al., 2016; Zhang et al., 2020; Madejczyk et al., 2017). For instance, form II of itraconazole is more sensitive to the crystal growth inhibition by polyvinylpyrrolidone-vinyl acetate copolymer (PVPVA64) and hydroxypropyl methylcellulose acetate succinate (HPMCAS) in comparison with its form I (Madejczyk et al., 2017). These selective inhibitory effects of polymer on different polymorphs of itraconazole are mainly attributed to the much stronger polymer adsorption on the crystals of form II compared with that of form I, yielding larger increase in the interfacial free energy at the crystal/melt interface (Madejczyk et al., 2017). Similar selective inhibitory effects of polymer on the crystallization of polymorphic system have also been reported in indomethacin systems doped with low-concentration PVP, HPMCAS, or hydroxypropyl methylcellulose (HPMC) (Zhang et al., 2016). In addition to the inhibitory effects, the accelerating effect of a polymer on crystallization also exhibit strong drug polymorphic dependence (Zhang et al., 2020; Kalepu and Nekkanti, 2015). For instance, 3 wt% poly (ethylene oxide) (PEO) could significantly increase the crystal growth rates of γ- and α-form of indomethacin (Zhang et al., 2020). At 70 °C, the ratio of crystal growth rates of γ- and α-indomethacin in the presence to the absence of PEO could be approximately ~50 and ~20-fold. For comparison, low-concentration PEO yields a negligible effect on the crystal growth kinetics of δ-form of indomethacin (Zhang et al., 2020). In a very recent study, the selective accelerating effect of PEO on the crystallization of indomethacin polymorphs has been demonstrated to be a result of selective enrichment of polymer at the crystal-liquid interface (Kalepu and Nekkanti, 2015). With the aid of polarized light microscopy and Raman mapping, Zhang *et al.* successfully obtained the direct evidences of selective enrichment of PEO at the crystal growth front (Fig. 5) (Kalepu and Nekkanti, 2015). They proposed that the different drug-polymer distribution at the growth front would strong affect both the thermodynamic and kinetic conditions of crystallization, thus leading to different impacts of PEO on the crystallization of indomethacin polymorphs (Kalepu and Nekkanti, 2015).

3. Pharmaceutical properties of polymorphic drugs

Various polymorphs of a drug could exhibit different physical and chemical properties including solubility, dissolution rate, bioavailability, melting point (T_m), density, compressibility, flowability, physical and chemical stability, strongly affecting the pharmaceutical performance. Solubility is one of the biggest concerns in the pharmaceutical development, particularly for the growing number of poorly water-soluble drugs discovered in recent decades (Saini et al., 2016). In 2004, Pudipeddi and Serajuddin compared the solubility of polymorphs of 55 compounds and found that solubilities of different polymorphs of most drugs are usually within a difference of 2-fold (Saini et al., 2016).

Table 1
Effects of the polymer or additives on the crystallization of drug polymorphs.

Drug & Polymorphs	Polymer or additives	Effects on the crystallization of drug polymorphs	Ref
Fluconazole (Form I and II)	Poly(vinyl pyrrolidone) (PVP), Poly(ethylene oxide) (PEO), and hydroxypropylmethyl cellulose acetate succinate (HPMCAS)	PEO could effectively accelerate the nucleation of both two polymorphs. However, it is difficult to measure the nucleation kinetics of form I, therefore, it is hard to compare the accelerating effects of PEO on fluconazole polymorphs	Zhang et al., 2021
Indomethacin (γ, α, and δ-Form)	Hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and polyvinylpyrrolidone (PVP)	Same Polymer exhibit the different inhibitory effects on the crystal growth of indomethacin polymorphs, and polymers used in this study exhibit the least inhibitory effects on the crystal growth of γ-form	Tian et al., 2017
Felodipine (Form I and II)	Poly(vinyl pyrrolidone) (PVP)	The addition of 3 wt% poly (vinyl pyrrolidone) (PVP) imposed the similar inhibitory effects on the crystal growth rates of both form I and form II of felodipine, as evidenced by approximately the same ratios of crystal growth rates in the presence and absence of PVP for these two polymorphs	Kestur and Taylor, 2013
Indomethacin (γ, α, and δ-Form)	Poly(ethylene oxide) (PEO)	The addition of 3 w/w % poly (ethylene oxide) (PEO) could significantly increase the crystal growth rates of γ- and α-form of indomethacin. For comparison, low-concentration PEO yields a negligible effect on the crystal growth kinetics of δ-form of indomethacin	Shi et al., 2017
Itraconazole (Form I and II)	Kollidone VA64 (PVPVA64) and hydroxypropylmethyl cellulose acetate succinate (HPMCAS)	The addition of PVPVA 64 and HPMCAS exhibit a much stronger inhibitory effect on the crystal growth of form II of itraconazole in	Zhang et al., 2017

(*continued on next page*)

Table 1 (*continued*)

Drug & Polymorphs	Polymer or additives	Effects on the crystallization of drug polymorphs	Ref
		comparison with that of form I	
Indomethacin (γ, α, and δ-Form)	Poly(ethylene oxide) (PEO)	The concentration of PEO enriched at the crystal-liquid interface follow the order as γ form > α form > δ form with the addition of 10% PEO at 70 °C, which is strongly correlated with the selective accelerating effects on the crystal growth kinetics of drug polymorphs	Zhang et al., 2020
Nifedipine (α, and β-Form)	Acetylated maltose (acMAL) , and acetylated sucrose (acSUC)	Activation barrier of crystal growth of β-form is not affected by these acetylated saccharides while that of α-form significantly increases	Madejczyk et al., 2017

However, in the case of premafloxacin, the solubility of form I is over two orders of magnitude higher than that of its form III in the media of ethyl acetate (Saini et al., 2016).

Solubilities of different polymorphs of a drug are closely related to their molecular stacking or molecular conformation. For instance, different molecular stacking of felodipine polymorphs decide the proportion of polar functional groups which cover the crystal surface (Zhu et al., 2016). Form II of felodipine has the highest proportion (~53%) among these four different felodipine polymorphs, leading to the improved solubility and intrinsic dissolution rate in aqueous media (Zhu et al., 2016). In addition, molecular stacking or molecular conformation could also decide the lattice energy, which is another key factor influencing the solubility and dissolution of different polymorphs of a drug (Zhang et al., 2013). Hdrochlorothiazide is one of classical diuretic and antihypertensive drugs, whose form I and form IA were reported to be conformational polymorphs (Zhang et al., 2013). Compared to form I, form IA of hdrochlorothiazide is a metastable polymorph with a lower lattice energy, leading to a lower dissolution enthalpy and a superior dissolution performance (Zhang et al., 2013). Moreover, different polymorphs of a drug could also sometimes exhibit distinct hygroscopicity (Sun, 2017). For instance, form II of apatinib mesylate exhibits a better hygroscopic stability during the dynamic vapor sorption experiment compared with its form I (Sun, 2017). Crystal structure analysis of apatinib mesylate polymorphs suggest that different hygroscopicity is most likely to be a result of discrepant molecule conformation, interaction codes, and packing arrangement (Sun, 2017). Form II of apatinib mesylate has a higher calculated density and packing efficiency in comparison with its form I, which is detrimental to the diffusion of water molecules (Sun, 2017). Moreover, as shown in Fig. 6, unlike the form II, form I of apatinib mesylate has a similar conformation and packing patterns as its monohydrate, also facilitating the water diffusion process (Sun, 2017). For comparison, if polymorphs of a drug have the similar crystal structure, little difference in hygroscopicity of these polymorphs is expected (Jain et al., 2018).

In the field of pharmaceutical science, mechanical properties of different polymorphs also need considerable attention for identifying the most suitable polymorph for manufacturing (Bhandary et al., 2017).

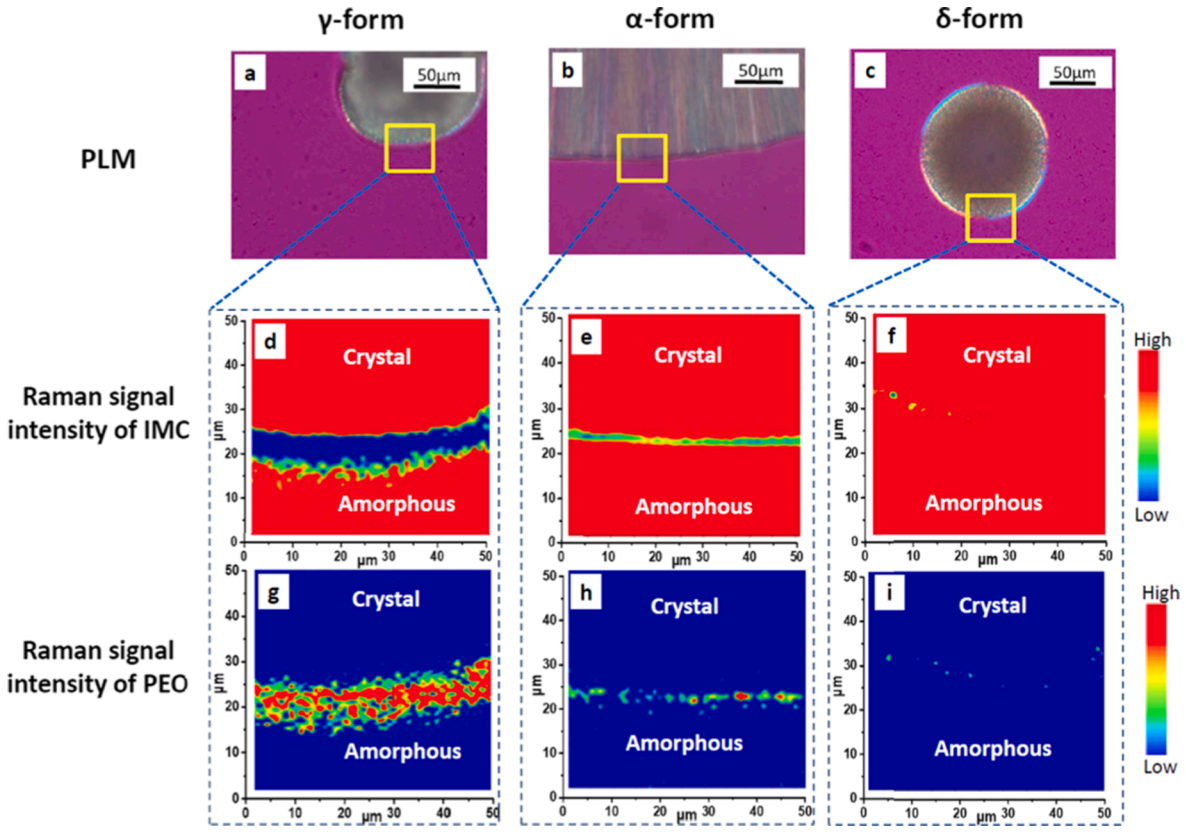

Fig. 5. Selective enrichment of PEO at the crystal growth front of indomethacin polymorphs. Adapted from the Ref. 94 with the permission. (Copyright © 2020 American Chemical Society).

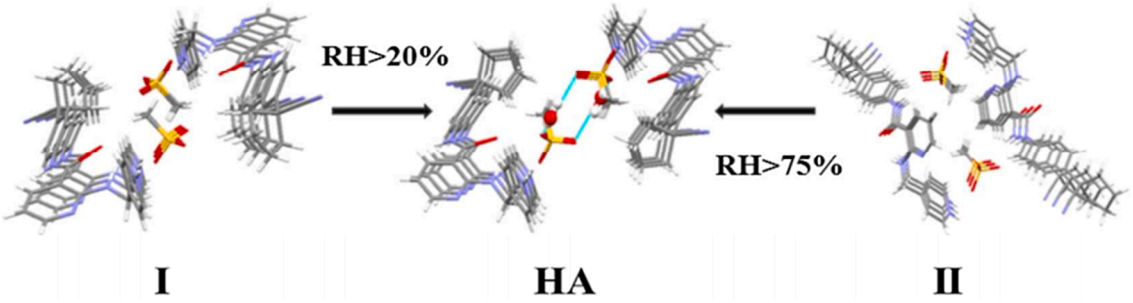

Fig. 6. Molecular conformation and packing model in forms I, form II and monohydrate of apatinib mesylate. Adapted from the Ref. 99 with the permission. (Copyright © 2016 American Chemical Society).

Recent studies have shown that mechanical properties of different polymorphs of a drug correlate well with their various crystal structures and molecular packing (Wang and Sun, 2018; Khomane et al., 2013; Yadav et al., 2017; Upadhyay et al., 2013). Crystal structure and molecular packing of different polymorphs result into different strength of molecular interaction, crystal interplanar distance, and interplanar attachment energy, leading to different slip plane and mechanical properties of a crystal. For instance, compared to its form H1, form Q of the gouty therapeutic drug febuxostat exhibits the greater compressibility, densification, and plastic deformation (Joiris et al., 1998). These superior compaction behaviors of Form Q have been mainly attributed to the presence of an active slip plane system in the crystal structure with a lower crystal hardness (Joiris et al., 1998). Similarly, form I of ranitidine hydrochloride exhibited the poorer compressibility and deformation behaviors as compared to form II (Perumalla et al., 2012). This greater tabletability of form I is mostly attributed to its more compact crystal structure in the absence of an active slip plane system (Perumalla et al., 2012). In addition, if bonding strength is comparable among different polymorphs of a drug, a polymorph containing a smoother surface of slip planes has been demonstrated to show superior compressibility and tabletability (Su et al., 2021; Young et al., 2019). In order to reveal the correlations between crystal structure and mechanical property, several established or emerging strategies have been implemented including energy framework calculations, topology analysis, crystal structure analysis based on visualization, etc. (Wang and Sun, 2018; Khomane et al., 2013; Yadav et al., 2017). In a recent study, Jain *et al.* found that form III of flufenamic acid exhibited lower overall attachment energies and larger d-spacing than those of its form I (Wang and Sun, 2018). In addition, form III also has a higher yield pressure of deformation and a lower degree of densification compared to those of form I (Wang and Sun, 2018). These microstructural and macroscopic features of form III facilitate the better compressibility and tableting performance when compared with those of form I (Wang and Sun, 2018). Furthermore, recent studies observed that mechanical properties sometimes would be an interdependent of the thermal properties in polymorphic systems (Upadhyay et al., 2018). As shown in Fig. 7, bazedoxifene acetate, a pharmaceutical salt, has three different polymorphs and their elastic moduli were demonstrated to be inversely proportional to the thermal expansion coefficients (Upadhyay et al., 2018). Interestingly, form D of bazedoxifene acetate was observed to exhibit an anomalous negative thermal expansion, which is mainly attributed to its special "spring-like" thermal motion of the structure (Upadhyay et al., 2018).

In addition, structure-mechanical property correlations of different

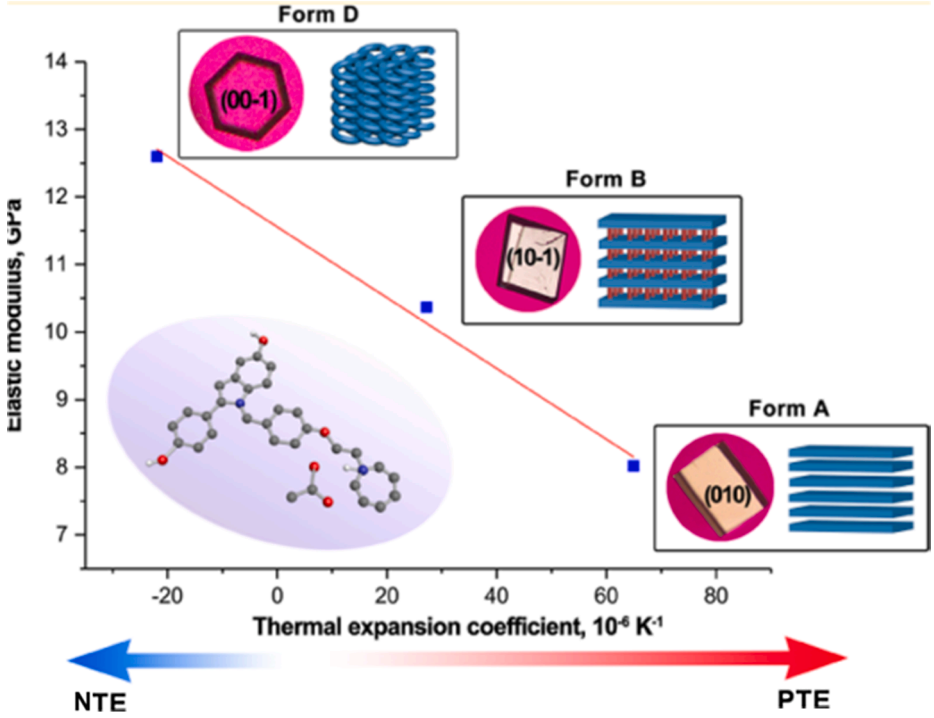

Fig. 7. Inverse relation of elastic modulus E and the thermal expansion coefficient of form A, form B and form D of bazedoxifene acetate. Adapted from the Ref. 110 with the permission. (Copyright © 2020 American Chemical Society).

polymorphs could also be revealed by the intermolecular interaction topologies from energy frameworks technique (Khomane et al., 2013; Yadav et al., 2017). For instance, form II among the three different polymorphs of N-(3-ethynylphenyl)-3-fluorobenzamide exhibits the lowest hardness and elastic modulus, as obtained from the nano-indentation experiments (Khomane et al., 2013). Structural analysis using interaction topology from energy frameworks revealed that these mechanical properties of form II can be related to the higher crystal density, stronger NH-O hydrogen bonding, and π-π stacking interactions, which could effectively impede the movement of molecular layers during indentation (Khomane et al., 2013). Similar crystal structure–mechanical property correlations have also been verified in several polymorphic systems of drugs (Yadav et al., 2017). For instance, compared to the stable γ-form, α-form of indomethacin exhibited a higher plasticity, which was explained by the existence of multiple active slip planes originating from its parallel columnar structures (Yadav et al., 2017). For comparison, γ-indomethacin exhibited a rough layer topology, which would hinder interlayer slip, and thus lead to the lower crystal plasticity (Yadav et al., 2017). In a very recent study, a specific crystal structure-tableting performance relationship of these indomethacin polymorphs was also identified by the powder Brillouin light scattering technique (Rodríguez-Hornedo et al., 1992). This optical method provided the specific acoustic frequency distributions of indomethacin polymorphs, which explained the difference in the tableting performance of γ- and α-form of indomethacin (Rodríguez-Hornedo et al., 1992). Moreover, it should be noted that the different tableting behaviors of drug polymorphs sometimes could not be fully explained from the perspective of slip planes (Wang et al., 2018). In the case of two piroxicam polytypes, in spite of the similarity in the crystal structures, form α_2 of piroxicam exhibited an inferior tabletability in comparison with its form α_1 (Wang et al., 2018). With the aid of energy-vector models, the intermolecular interaction energies of these two polytypes were analyzed and it was found that the different tableting behaviors were related to the higher dimensionality and stronger stabilizing interactions (Wang et al., 2018).

4. Polymorphic transformation

As mentioned above, different polymorphs of a drug exhibit various molecular packing, resulting in different stabilities. From the perspective of a phase diagram of energy and temperature, physical stability of a polymorph depends on its free energy, i.e., polymorph with a lower free energy would always exhibit a higher physical stability. At a specific temperature, if polymorphs in a system show different free energies, polymorphic transformation might occur and eventually lead to generation of the most stable polymorph at the expense of metastable polymorphs. However, it should be noted that this polymorphic transformation sometimes requires a long time and could be affected by both the thermodynamic and kinetic factors.

Polymorphic transformation of a drug in solution has been widely investigated due to its importance in the manufacture process for the pharmaceutical industry (Croker and Hodnett, 2010; Maher et al., 2012; Maher et al., 2014; Pallipurath et al., 2017; Zhang et al., 2002; Stoica et al., 2006; Liang et al., 2015). One phenomenon, termed as solution-mediated polymorphic transformation (SMPT), would sometimes occur if the crystal of metastable polymorph of a drug is contacted with the solvent molecules then molecular rearrangement will occur to form the more stable crystalline phase (Croker and Hodnett, 2010; Maher et al., 2012; Maher et al., 2014; Pallipurath et al., 2017; Zhang et al., 2002; Stoica et al., 2006; Liang et al., 2015). In general, the SMPT process could be divided into the following three major steps including the dissolution of the metastable crystals, nucleation of the more stable polymorph, and the crystal growth of this newly formed polymorph (Pallipurath et al., 2017; Zhang et al., 2002). A dynamic equilibrium is expected to exist between the dissolution of metastable polymorph and crystallization of the more stable polymorph (Maher et al., 2014; Pallipurath et al., 2017; Zhang et al., 2002). It should be noted that the nucleation of the more stable polymorph is often the rate-limiting step of the SMPT (Maher et al., 2014). Maher *et al.* investigated the polymorphic transformation of piracetam from the metastable form II to the more stable form III in ethanol and found that the rate of transformation correlates well with the increasing temperature (Pallipurath et al., 2017). Moreover, the nucleation of more stable form III was suggested to occur on the surface of the metastable form II at a rate proportional to the surface area of form II (Pallipurath et al., 2017). In their following work, the SMPT of piracetam from its metastable form II to the stable form III was further investigated in seven different organic solvents (Zhang et al., 2002). These rates of SMPT were found to increase with the increasing temperature, agitation rates, and the solubility of piracetam in these solvents (Zhang et al., 2002). However, in the case of 2-propanol, this trend was reversed, which was attributed to the strong interaction between piracetam and 2-propanol (Zhang et al., 2002). 2-propanol could act as a bridging ligand over the amide groups of piracetam, which participate in the formation of hydrogen bonding dimers in the crystal structure of form III, and thus retarding the nucleation and crystal growth of form III (Zhang et al., 2002).

It is well accepted that surface of the metastable polymorph could serve as the nucleation sites to facilitate the nucleation of the stable polymorph. Interestingly, some studies also found that the nucleation of the more stable polymorph exhibits a strong crystal surface dependence (Liang et al., 2016; Han et al., 2016). For instance, β-form of L-glutamic acid mainly nucleates on three preferred surfaces of α-form during the SMPT, and the nucleation probability is ranked as {011}>{111}>{001} (Han et al., 2016). Molecular simulation also showed that the adsorption energies of L-glutamic acid molecules on three crystal surface decrease follow the same order as {011}>{111}>{001} (Han et al., 2016). Moreover, the rate of SMPT of L-glutamic acid from metastable α-form to stable γ-form could also be affected by different supersaturation (Mukuta et al., 2005). In addition, in a recent study, Han et al. reported that the secondary nucleation of γ-glycine during the process of SMPT could be vastly accelerated by the addition of inorganic salts (Mnyukh, 1976). Surprisingly, some of divalent cation salts (calcium nitrate and magnesium sulfate) exhibited significant inhibition on crystal growth of γ-glycine in spite of their accelerating effects on nucleation (Mnyukh, 1976). Furthermore, recent studies also revealed that the rates of SMPT could also be affected by the solvent composition, particle size, polymer surface chemistry, existence of impurity, etc. (Maher et al., 2012; Stoica et al., 2006; Cardew et al., 1984).

Analogous to the SMPT process, polymorphic transformation of a drug could also occur in the solid state, particularly during the processing and storage of the pharmaceutical formulations. This polymorphic transformation in solid state could occur spontaneously or induced by varying the temperature (Tuble et al., 2004; Beckham et al., 2007; Kaneko et al., 1998; Beckham et al., 2008; Liu et al., 2014; Krishnan and Sureshan, 2015). In the past over two decades, a considerable number of theories have been proposed to interpret the mechanism of polymorphic transformation in solid state (Tuble et al., 2004; Beckham et al., 2007; Kaneko et al., 1998; Beckham et al., 2008; Liu et al., 2014; Krishnan and Sureshan, 2015). One of these theories is the nucleation and growth mechanism. As the name suggests, this theory proposes that nucleation is the initiation event of polymorphic transformation followed by the crystal growth process (Beckham et al., 2008; Krishnan and Sureshan, 2015; Tuble et al., 2004; Beckham et al., 2007). In the case of terephthalic acid, the polymorphic transformation in solid state has been proposed to be a surface-mediated nucleation process, i.e., nucleation occurs locally at the specific crystal edge formed by the fluctuations in the supramolecular synthons (Beckham et al., 2008). For comparison, other proposed that polymorphic transformation of some molecules is a martensitic phase transformation, whose rates are orders of the speed of sound with the topotaxy between these polymorphs (Kaneko et al., 1998; Liu et al., 2014). In solid state, single-crystal-to-single-crystal phase transition (SCTSC), one relatively rare

phenomenon could be observed in some compounds despite that changes in crystal structure would lead to the destruction of parent crystals (Srirambhatla et al., 2020; Nanubolu, 2021; Mazel et al., 2011; Jack and Dunitz, 1995). As shown in Fig. 8, form I of antihistamine drug desloratadine crystal that immersed in silicon oil undergoes a polymorphic transformation with a visible continuous transverse wave front upon heating (Mazel et al., 2011). Moreover, further investigation showed that desloratadine could exhibit a two-step reversible SCTSC phase transition among its three conformational polymorphs (Mazel et al., 2011). This two-step SCTSC phase transition strongly relates to a sequential flipping of the piperidine rings of drug molecules in the crystal structure (Mazel et al., 2011). In addition, polymorphic transformation in solid state could also occur during the milling or tableting process (Liang et al., 2015; Bobrovs et al., 2021).

5. Polymorph control

Selective crystallization of polymorphic systems was firstly proposed by Dunitz and Bernstein. They indicated that the key to obtain a particular polymorph is to find the right experimental conditions (Black et al., 2018). In their study, with the use of "tailor-made" impurities, the crystallization kinetics of various polymorphs were altered to facilitate the harvest of metastable crystal forms (Black et al., 2018). In the past several decades, the problem of polymorph control has been addressed by considerable conventional strategies including solution crystallization, melt crystallization, sublimation, milling, etc. (Anwar and Zahn, 2017; Gu et al., 2002). Moreover, in recent years, increasing emerging strategies have also been developed to obtain the desired polymorph (Liu et al., 2020).

Among these emerging strategies, it is well accepted that some additives could act as the molecular imposters, which could selectively adsorb on the growing crystal surface of an unwanted polymorph and thus effectively suppressing its growth (Liu et al., 2020). In the case of sulfamerazine, with the addition of its three structural analogs, the crystallization of its stable polymorph is effectively inhibited via adsorption of the three structural analogs on the specific crystal face, and thus facilitating the crystallization of its metastable form (Kaskiewicz et al., 2021). Interestingly, the inhibitory effects of structural analogs on the crystallization of stable polymorph of sulfamerazine correlate well with the strength of molecular interactions between these structural analogs and the crystal face (Kaskiewicz et al., 2021). Similar results were also reported in the crystallization of different polymorphs of p-amino benzoic acid in the presence of its structural analogs (Liu et al., 2020). Here, nucleation and crystal growth of α-form of p-amino benzoic acid was mainly controlled by aromatic stacking, where the additives could attach strongly, and thus facilitating a better inhibitory effect on crystallization (Liu et al., 2020). For comparison, the crystallization of its β-form exhibited a stronger resistance to the inhibitory effects of these structural analogs because its crystallization process was mainly controlled by molecular interactions rather than aromatic stacking (Liu et al., 2020). More importantly, recent studies revealed that the selective effects of these structurally analogous additives (also termed as tailor-made additives) on different polymorphs are also attributed to the issue of surrounding nucleation (Lang et al., 2002; López-Mejías et al., 2009). By combining the molecular modeling and experiments, Kaskiewicz et al. proposed that some tailor-made additives can interfere with the molecular preassembly route to the nucleation of p-amino benzoic acid by increasing the effective interfacial energy (López-Mejías et al., 2009). Besides, the addition of the tailor-made additives also changes the nucleation mechanism from instantaneous to progressive nucleation (López-Mejías et al., 2009). In a very recent study, Liu *et al.* investigated the mechanism of the effects of metacetamol on stabilizing the metastable form II of paracetamol, which is one of the representative elusive forms exhibiting difficulty in crystallization (Lang et al., 2002). Metacetamol could effectively impede the crystal growth of the most stable form I of paracetamol while it has a negligible effect on its form II, a result of the strong adsorption of metacetamol on the specific crystal face that responsible for the growth in thickness and width (Lang et al., 2002).

Polymer heteronuclei, a concept introduced nearly two decades ago, has been demonstrated to control the drug polymorphism and facilitate the finding of new polymorphs (Lopez-Mejias et al., 2012; Foroughi et al., 2011; Pfund et al., 2015; Artusio and Pisano, 2018). In 2002, Lang *et al.* systemically investigated the polymorph selection of acetaminophen in the presence of 84 different polymers (Lopez-Mejias et al., 2012). The metastable form II of acetaminophen could be obtained with the addition of certain polymers, and one of the important stabilization effects is the orientation of crystal growth from the polymer surface (Lopez-Mejias et al., 2012). Moreover, when the polymer heteronuclei method was applied to the growth of carbamazepine polymorphs, the fourth polymorph which had never been observed before was obtained with a suitable size for single-crystal X-ray diffraction (Lopez-Mejias et al., 2012). In subsequent studies, this polymer heteronuclei method was performed to successfully prepare the 5 different polymorphs of tolfenamic acid and the 9 different polymorphs of flufenamic acid (Foroughi et al., 2011; Pfund et al., 2015). In recent studies, mechanisms of polymorph selection via polymer heteronuclei were mainly attributed to the functional group interactions at the polymer-crystal interface (Nanna et al., 2018; Nanna et al., 2018). These interactions between polymer and small molecules could be investigated by several models including heterogeneous dielectric solvation model, coulomb-van der Waals model, etc. (Hamilton et al., 2012; McKellar et al., 2012).

Recent studies also find that employment of an engineered surface could also achieve polymorph selection by means of controlled nucleation (Park et al., 2016; Boyes et al., 2020; Ha et al., 2004). Nucleation and crystal growth of specific polymorph is expected to occur by controlling the chemistry and topological feature of the surface (Park et al., 2016; Boyes et al., 2020; Ha et al., 2004). For instance, indomethacin, preferentially crystallize in its δ-polymorph on an untreated surface while crystallize in its α-polymorph on certain polymer surfaces (Ha et al., 2004). In addition, surface of some crystals could also act as a template to facilitate the crystallization of other polymorphs (Nartowski et al., 2018). Park et al. found that a new metastable polymorph K of donepezil could grow on the more stable polymorph F, which could act as a template to facilitate the formation of metastable polymorph K at a relatively low supersaturation (Nartowski et al., 2018). In a very recent

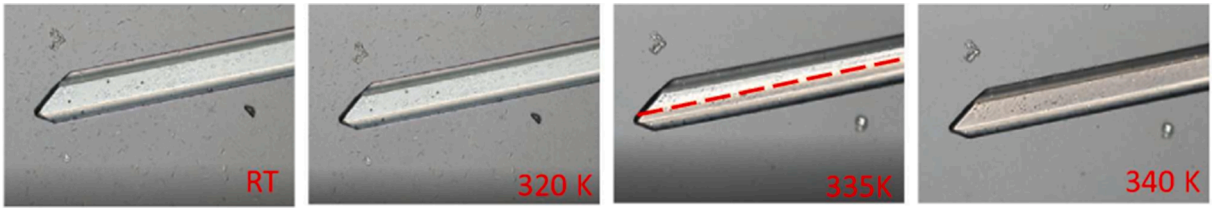

Fig. 8. Phase transition of form I of desloratadine crystal immersed in silicon oil upon heating. The red dashed line represents the movement of the visible phase boundary. Adapted from the Ref. 133 with the permission. (Copyright © 2020 American Chemical Society). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

study, graphene surface can also act as a template to induce the preferential crystallization of metastable α-glycine polymorph (Beiner et al., 2007). Computer modelling reveal that the increased stabilization of α-form is mainly attributed to the existence of oxidised moieties on graphene, facilitating the formation of hydrogen bonding interactions between graphene and glycine (Beiner et al., 2007).

Polymorph selectivity can also be affected by nanoscopic confinement imposed on the critical size (Ha et al., 2004; Hamilton et al., 2008; Zhang et al., 2020) . As described by Ha *et al.* in 2004, anthranilic acid, which has three known polymorphs, exhibited a size-dependent polymorph stability in pores with controlled sizes (Hamilton et al., 2008). With a decrease in the pore diameter, metastable form II instead of the stable form III could indefinitely persist in the pores with an average diameter of 7.5 nm (Hamilton et al., 2008). Acetaminophen, one of the classic antipyretic and analgesic drugs, was reported to exhibit a depression of melting point (T_m) under nanoscopic confinement (Diao et al., 2012). Interestingly, the relationship between T_m depression and pore diameter is consistent with what predicted by the Gibbs-Thomson equation (Foster et al., 2010). In this study, metastable form III of acetaminophen was exclusively present in the pore with an average diameter of 30 nm (Diao et al., 2012). With an increase in the pore diameter, form III and more stable form II could both be generated (Diao et al., 2012). Similarly, glycine crystallizing in nanoporous matrices was also found to be the metastable β-form, and it would slowly transform to the α-form with increasing of crystal size (Foster et al., 2010). Moreover, nanoscale confinement sometimes could also arrest and alter kinetics of phase transformation between polymorphs (Oaki and Imai, 2003). For instance, flufenamic acid, one of highly polymorphic systems, could form extremely unstable form VIII under nanoscale confinement (Oaki and Imai, 2003). Interestingly, as shown in Fig. 9, transformation pathways among flufenamic acid polymorphs strongly relate to the pore sizes (Oaki and Imai, 2003).

It is worthwhile mentioning that crystallization in gel media sometimes also exhibit strong polymorph selectivity (Song et al., 2020; Yuyama et al., 2012; Yu et al., 2021). Compared with the above-mentioned methods, crystallization in gel mimics a microgravity environment and could trap the formed crystals in the original location (Lee et al., 2005). In the case of carbamazepine, selective nucleation of its form II was achieved by using a gel of cross-linked polyethylene glycol diacrylate (Yuyama et al., 2012). For comparison, concomitant crystallization of form I and form II of carbamazepine could be observed from bulk (Yuyama et al., 2012). The polymorphic outcomes in gel media correlate well with the kinetics of gel-induced nucleation (Yuyama et al., 2012). Moreover, the polymer microstructure and chemical composition have also been demonstrated to effectively influence the polymorphic results (Yuyama et al., 2012). Mechanistic study attributed polymorph selectivity in gel mainly to the nucleation-templating effect and spatial confinement induced by polymer network (Yuyama et al., 2012). Sulfathiazole, a well-established polymorphic drug system exhibiting at least five polymorphs, could selectively grow in its form III or form IV in agarose matrix *via* only adjusting agarose concentration (Song et al., 2020). Here, the emerging of sulfathiazole correlates well with the state of agarose gel in solution (Song et al., 2020). Furthermore, polymorph control could also be achieved by other approaches including laser-induced nucleation (Yu et al., 2021), self-assembled monolayer templates (Lee et al., 2005; Artusio et al., 2021), etc. In a very recent study, femtosecond laser was demonstrated to be an effective approach for controlling the crystallization of sulfathiazole (Yu et al., 2021). The effect of polymorph selectivity was suggested to be strongly related to the laser-induced cavitation bubbles, which could act as the nucleation centers in the crystallization of sulfathiazole (Yu et al., 2021).

6. Concluding remarks and future outlook

In the past decades, drug polymorphism has attracted considerable attentions due to its great impacts on the physicochemical properties, bioavailability, therapeutic effects, etc. Increasing discoveries of new polymorphs have been reported in recent studies with greater efforts exploring this phenomenon. However, it should be noted that there are still several challenges to completely understand polymorphism in pharmaceutical drugs.

In the case of nucleation in polymorphic pharmaceutical drug systems, deeper and more systematical studies are required for elucidating the underlying nucleation mechanisms. Selective nucleation induced by interface or surface should also be further investigated and requires the establishment of the potential relevance with molecular orientation. In addition, the differences in crystal growth kinetics of drug polymorphs also remain a challenging task in mechanism interpretation. It is also promising to reveal the underlying relationship between crystal growth kinetics and molecular packing in future studies. Furthermore, more systematical investigations focusing on the impacts of additives on nucleation and crystal growth of polymorphic drug are also demanded, since they can guide a rational design of additives for controlling the polymorphism. For the pharmaceutical properties of polymorphic drugs, one of the most important issues is to explore the crystal structure-properties relationship. Special attention to the computer-assisted approaches is also urgently demanded for obtaining a deeper understanding for the structure-properties relationship.

Compared to what occurs in the solution state, polymorphic transformation in solid state is still in its early stage of study and more systematic work is especially required. In addition, it is well accepted that more stable polymorphs could sometimes nucleate on different crystal surfaces, however, underlying mechanism of this phenomenon is lacking. Moreover, it is also important to reveal the mechanism of the effects of the polymeric or small-molecular additives on the process of polymorphic transformation. Although there have been a large number of studies devoted to achieve the goal of polymorphism control, it should

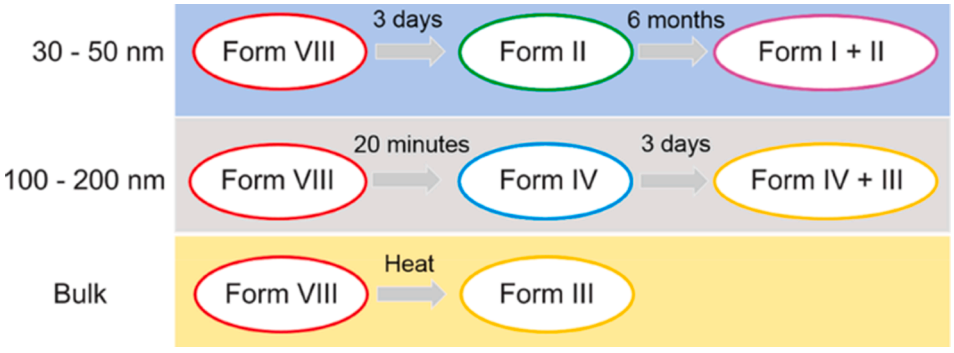

Fig. 9. Scheme for the polymorphic transition of flufenamic acid form VIII in controlled pore glasses with different pore size and in bulk. Adapted from the Ref. 159 with the permission. (Copyright © 2020 American Chemical Society).

be noted that the underlying mechanism is controversial. Consequently, more systematical work is still required for a deeper understanding and obtaining the desired polymorph. Moreover, scale-up preparation and downstream processing of the desired polymorph obtained via controlling the polymorph should also be taken into consideration. In consideration of preparation of the commercial products of the polymorphic drug, it is also meaningful to develop the technologies utilized for obtaining the desired polymorph at industrial scale. With a better understanding of pharmaceutical properties, polymorphic transformation, and selective crystallization of polymorphic drug systems, more robust pharmaceutical formulations containing the polymorphic drugs is expected to obtain a great success on the market in the future.

CRediT authorship contribution statement

Qin Shi: Conceptualization, Investigation, Writing – original draft, Supervision. **Haibiao Chen:** Resources, Writing – review & editing. **Yanan Wang:** Resources, Writing – original draft. **Jia Xu:** Writing – review & editing. **Ziying Liu:** Resources, Investigation. **Chen Zhang:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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