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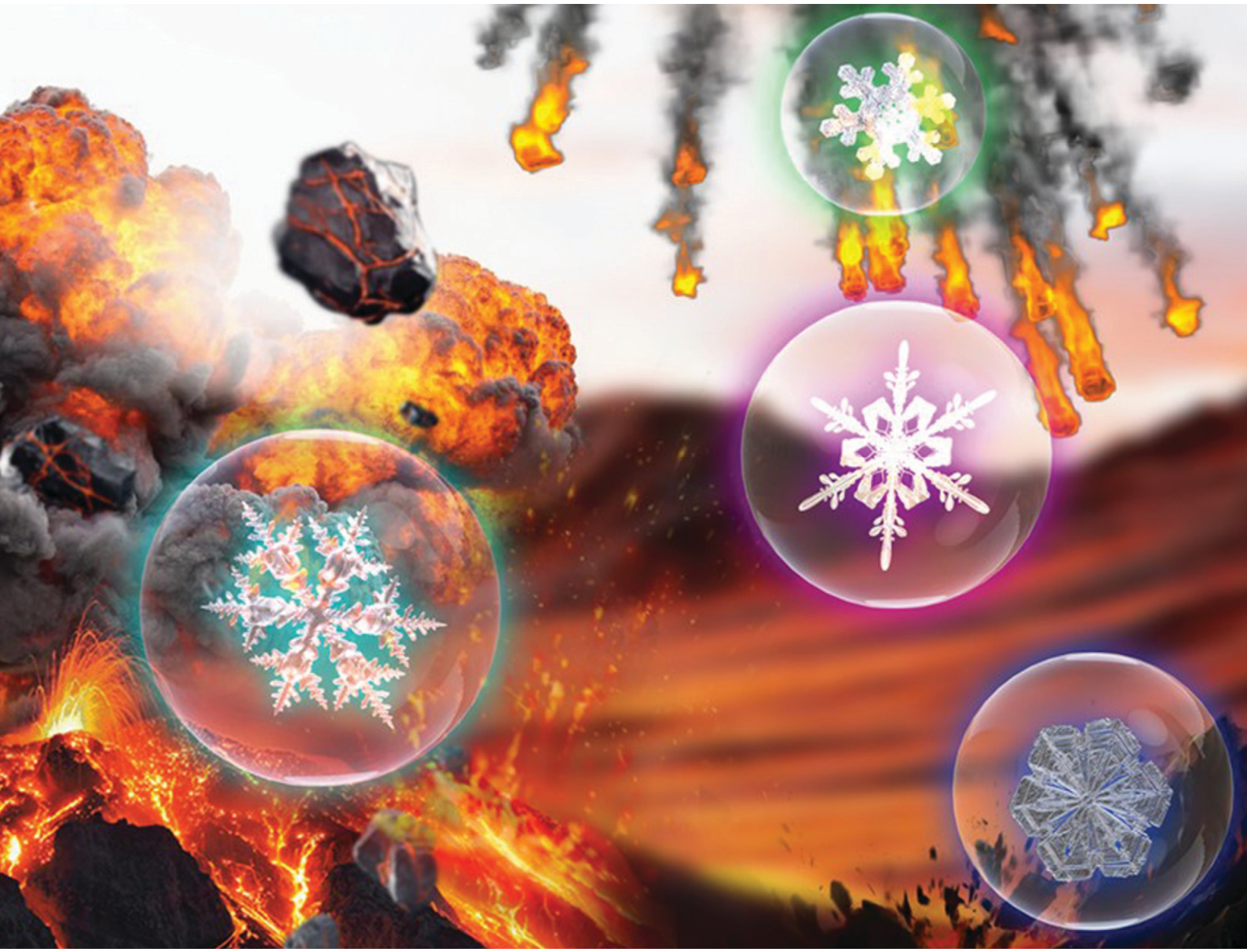

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HIGHLIGHT
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Polymorph transformation of solid drugs and inhibiting strategies

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Metastable forms and amorphous forms exhibit higher solubility and dissolution rates compared to stable crystalline forms, making them viable options for pharmaceuticals with low solubility. However, the use of metastable forms and amorphous forms may result in polymorph transformation in pharmaceutical manufacture and storage, which will reduce their bioavailability. Firstly, different polymorphic transformations were discussed. Then, the factors affecting crystals and amorphous stability, including solvent, temperature, humidity, and preparation processes were analyzed. Finally, strategies and their mechanisms to inhibit polymorphic transformation and amorphous recrystallization were also summarized, including suitable storage conditions, optimization of the preparation processes, use of additives, adjustment of formulation recipes, and surface and loading techniques.

1. Introduction

Currently, the majority of active pharmaceutical ingredients (APIs) are formulated in solid forms,[1–3] including polymorphs, hydrates or solvates, and amorphous forms.[4–6] Drug polymorphism refers to the phenomenon where the same drug molecule crystallizes into different crystal structures, and crystals of various polymorphs can exhibit distinct lattice parameters, crystal packing, or molecular conformations.[7,8] Solvates are also regarded as polymorphs when the term "polymorph" is used in a broader sense.[9,10] Hydrates are the most prevalent type of solvate, owing to the small size and polarity of water molecules, which act as both hydrogen bond donors and acceptors.[11] In contrast to the long-range ordered and periodic arrangement of crystals, amorphous (non-crystalline) forms exhibit long-range disorder and short-range ordered arrangements. Various solid forms of the same APIs often have different physical, chemical, and mechanical properties. The differences in these properties could further affect the solubility, dissolution, bioavailability, stability, compressibility, clinical efficacy, and safety of the APIs.[12–14]

The most thermodynamically stable solid forms are usually chosen for the final formulated product because of the lowest tendency to undergo polymorph transformation during processing and storage.[15] However, sometimes, stable crystals may exhibit defects, such as low solubility and bioavailability.[16–18] For example, the stable crystalline form A of chloramphenicol palmitate is biologically inactive, while the metastable crystalline form B is biologically active.[19] *In vivo* investigations of rifaximin have demonstrated that the crystalline forms δ and γ show higher bioavailability than the thermodynamically most stable crystalline form α.[20]

Therefore, some metastable crystals or even amorphous forms can be selected as commercially available solid forms of drugs to improve their bioavailability. For example, the antipsychotic drug aripiprazole has nine polymorphic crystals, of which the most common clinical form is metastable form III.[21] The antihypertensive drug valsartan is marketed in amorphous form, despite its hygroscopicity and unfavorable chemical stability.[22]

Although the use of metastable or even amorphous forms of drug formulations may increase the bioavailability, there is also a risk of polymorph transformation. A famous example is ritonavir, a protease inhibitor used for the treatment of HIV. Due to the transition from form I to a previously unknown stable form II, it was forced to withdraw from the market, causing significant economic losses for Abbott.[23,24]

Therefore, the study of drug polymorph transformation is crucial in drug development. In this review, the phenomenon of polymorphic transformation of solid drugs and its influencing factors are discussed in detail. In addition, strategies and mechanisms to inhibit the polymorphic

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transformation and amorphous recrystallization are also summarized.

2. Polymorph transformation and its influencing factors

The transition from metastable to stable state is a common phenomenon of APIs. For solvates, metastable crystals, and amorphous forms, due to their thermodynamic instability, they may undergo polymorph transformation during storage and production, which occurs as a result of solvent removal, transition to a stabilized crystalline form, and transition to a crystalline state, respectively.

The transformation of APIs may happen during different stages of the processing of solid drugs (including crystallization, drying, pulverization, sieving, mixing, granulation tableting, *etc.*) and storage process.[25–28] The main factors affecting the transformation of polymorphs include solvent, temperature, humidity, grinding, pressure, *etc.* The polymorphic transformation can be categorized into solid–solid phase transformation (SSPT) and solution-mediated phase transformation (SMPT).[29]

2.1 Solution-mediated phase transformation

In the preparation of solid drugs, solution crystallization is one of the most important methods. Solution-mediated phase transformation involves the following stages: dissolution of the metastable phase in contact with the solution, nucleation of the stable phase, and crystal growth of the stable phase.[30,31] The solvent-mediated transformation process can be affected by many factors, such as solvent, temperature, water content, pH, particle morphology, impurity or additive, *etc.*[32–35]

Zhu *et al.*[36] conducted an SMPT study using theophylline as a model compound. It was found that high temperature can facilitate the transformation, and the duration of the transformation varied with the solvent. Ding *et al.*[37] investigated the solution-mediated dehydration of sodium avibactam hydrate and found that different solution-mediated dehydration mechanisms in different solvents lead to different solid forms.

Li *et al.*[12] obtained three solvent-free forms (A, B, C) of pradofloxacin and demonstrated that form B was the most stable by SSPT experiments. This may be related to the presence of a large number of hydrogen bonds and C–H···π interactions in the crystal structure of form B. Besides, the calculated stacking coefficient of form B was largest. The study of avatrombopag maleate by Hu *et al.*[38] also showed that the stability of the crystal during SSPT can be attributed to its tightly packed structure and strong molecular interactions.

For some drugs that can form hydrates, thermodynamically stable crystalline forms can transform into hydrates in aqueous solvents. The results of the study of levofloxacin hydrochloride by Liu *et al.* showed that high water content promotes the SMPT process from form II (anhydrous) to form I (monohydrate), while high temperatures inhibit this process.[39] Li *et al.*[40] investigated the effects of particle size on the SMPT process using the anti-infective drug 5-nitrofuranone as a model drug. The results show that decreasing the particle size enhances the nucleation of stable crystalline forms because the decrease in particle size accelerates the dissolution of metastable forms and exposes more crystalline surfaces per unit mass, thus providing more possible nucleation sites on the metastable crystalline surfaces.

In a recent study, Zheng *et al.*[41] obtained eight different polymorphs of aripiprazole through suspension crystallization in 15 different solvents. They elucidated the mechanism of solvent effects on the polymorphism of

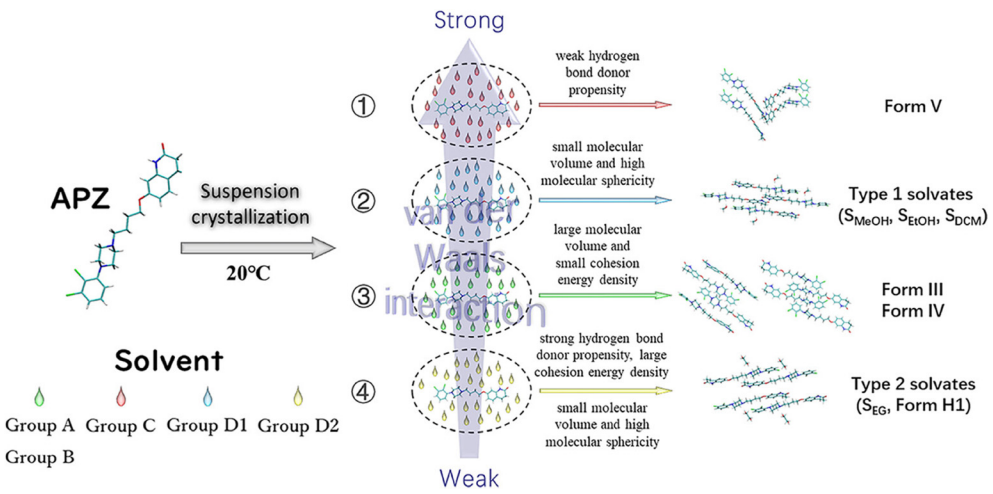

Fig. 1 Mechanism of solvent effect on aripiprazole solution-mediated phase transformation. Four scenarios based on van der Waals interaction and solvent properties. Reproduced from ref. 41. Copyright 2024 American Chemical Society.

Table 1 Selected instances of researchers conducting SMPT on pharmaceuticals in recent years

Molecule	Imposed conditions and polymorph transformation	Year	Ref.
Posaconazole	Water, form S → form A	2024	42
Aztreonam	Methanol, 10–28 °C, form C → form B Methanol, 28–45 °C, form C → form A	2023	43
Trimethoprim	Water/ethanol, form β → form α Acetonitrile + water, form α → form β	2023	44
Glutathione	Water, form α → form β	2023	45
Nitrofurantoin	Acetonitrile/nitromethane, form α → form β Ethanol/*n*-propanol/1,4-dioxane, form β → form α	2023	46
Risperidone	Methanol/ethanol/acetone, form II → form I	2023	47
Baloxavir marboxil	Acetonitrile + water, form I/form III → form II	2023	48
Acetaminophen	Water, form II → form I, trihydrate → form II	2023	49
Nilotinib	Methanol + water, amorphous → form H3, methanol, form C → form H2c/A	2022	50
Valnemulin hydrochloride	Methanol + water, dihydrate → methanol–water solvate Ethanol + water, dihydrate → ethanol–water solvate	2021	51
Erlotinib	Toluene, anhydrous form I → monohydrate form III	2021	52
Glipizide	Water, form II → form I/III	2021	53
Tolfenamic acid	2-Propanol, form IX → form II	2021	54
Piroxicam	Acetone, monohydrate → form I/II	2019	55
Acyclovir	Methanol/ethanol, form V → form I	2019	56
Lansoprazole	Water + ethanol, monohydrate → ethanol solvate	2019	57

aripiprazole's suspension crystallization by calculating solvent property parameters and employing molecular dynamics simulations. Their findings indicated that the van der Waals interaction energy between solvent molecules and aripiprazole molecules, the hydrogen bond donor tendency of solvent molecules, the volume, sphericity, and the cohesive energy density of the solvent molecules are critical factors influencing the outcomes of solvent-mediated phase transformation (Fig. 1).

In addition to the above, Table 1 lists some examples of SMPT that have been performed on drugs by researchers in recent years.

2.2 Solid–solid phase transformation

Solid-to-solid phase transitions are phase transitions that occur directly without solvent mediation, through the recombination or rearrangement of molecules, ions, or atoms into a more stable solid form.[35] Transformation of the crystalline form, including dehydration of the hydrate, may occur during heating and drying or processes such as granulation and tableting that generate mechanical and thermal energy.[58] The main factors affecting the solid–solid phase transition include temperature, humidity, pressure, crystal defects, impurities, *etc.*

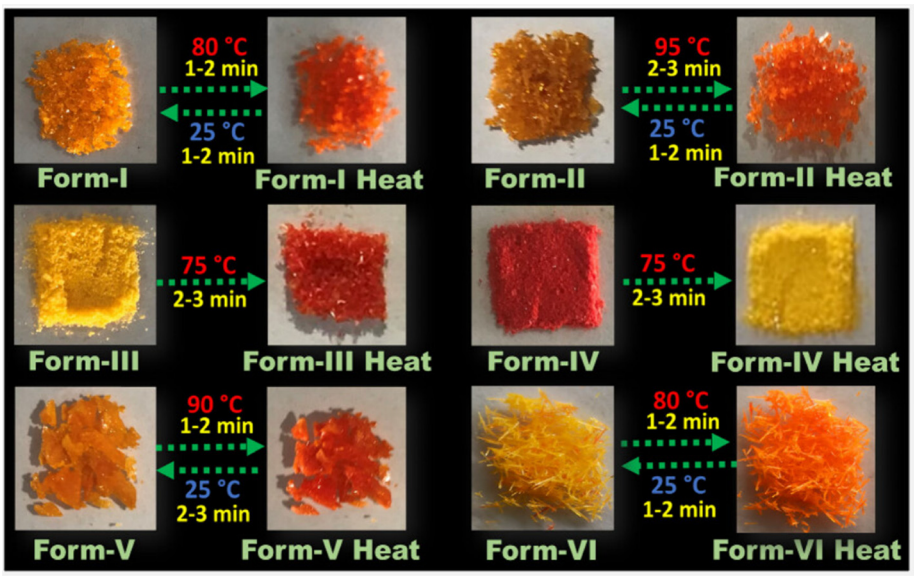

Fig. 2 Polymorph transformation and color change of sulfonamide during heating. Reproduced from ref. 62. Copyright 2024 American Chemical Society.

Zhu *et al.*[59] showed that baicalein monohydrate MH1 was converted to hemihydrate above 30 °C and to thermodynamically stable crystalline form α when heated to 125 °C. Grooff *et al.*[60] investigated the polymorph transformation of nifedipine at different storage temperatures. It was found that the amorphous form of nifedipine transformed at room temperature to its metastable form C. The rate of transformation was temperature-dependent, and it was accelerated by increasing temperature. Centore *et al.*[61] reported an abundance of solid-phase transformation of 4-hydroxybenzohydrazide, including monotropic/enantiotropic, fast/slow, diffusive/displacive, and single-crystal to single-crystal. And the transformation results can be manipulated by temperature and rate of temperature rise and fall. Mohamed *et al.*[62] reported that the weak intermolecular interactions in sulfonamide can be manipulated by heating, which may lead to polymorph transformation accompanied by significant reversible and irreversible heat-induced color changes (Fig. 2).

For the drugs that tend to form hydrates, the relative humidity (RH) of the storage environment is equally important, as changes in humidity may lead to polymorph transformation in solid drugs due to the removal or addition of crystal water. Berzins *et al.*[63] investigated the effect of humidity on the polymorph transformation of xylazine hydrochloride. It was found that, when the RH was less than 10%, all the hydrates were dehydrated and transformed into the anhydrate form, and when the RH was more than 20%, all the anhydrate forms absorbed water and transformed into hydrates. Meanwhile, the inter-transformation process between anhydrate and hydrate was also affected by the size of drug particles. As shown in Fig. 3, Kons *et al.*[64] established solid-state transformation relationships for six polymorphs of dantrolene, of which form IV, V, and VI could be obtained by solid-state dehydration of three different monohydrates (MH-I/II/III) under different humidity conditions, respectively.

Grinding or ball milling processes are common to reduce the size of drug particles in the pharmaceutical industry.[65,66] The heat and mechanical energy generated during the milling process may lead to the transformation of the crystalline form of the drug. Common grinding methods include neat grinding, variable temperature grinding, liquid-assisted grinding, ionic liquid-assisted grinding, and polymer-assisted grinding.[67] The polymorph transformation of solid drugs during milling can also be affected by many factors such as temperature, solvent, crystalline species, and additives.

Trask *et al.*[68] investigated the effect of a small amount of solvent-assisted grinding on the polymorph transformations of anthranilic acid. Form I was converted to form III and form II upon neat grinding and grinding with small amounts of *n*-heptane, respectively. No polymorph transformation was observed in neat grinding for both form II and form III. Upon the addition of a small amount of water and *n*-heptane for grinding, form III was transformed into form I and form II, respectively.

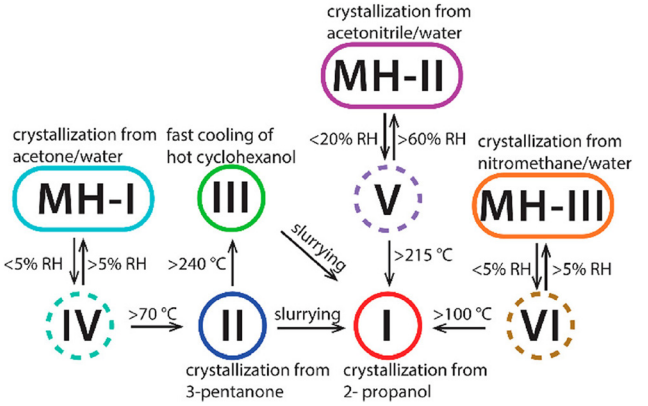

Fig. 3 Preparation of six polymorphs of dantrolene and solid phase transition relationships. Reproduced from ref. 64. Copyright 2021 American Chemical Society.

In the tableting process, compressive forces lead to shear stresses, which would distort the crystalline lattice and molecular rearrangement. In addition, the increase of temperature due to compression can also affect the polymorphic transition in the solid state.[69,70] The polymorphic transition induced by compression tablets was described in detail in a review article published in 2022 by Park *et al.*[58] Furthermore, regarding pressure-induced polymorphic transition, this phenomenon has been observed for different drug compounds by direct compression experiments using a diamond compression anvil (DAC) at pressures ranging from a few GPa to several tens of GPa. This part was described in detail in a review article by Guerain in 2020.[71]

In addition to the above, Table 2 lists some examples of SSPT of pharmaceuticals that have been investigated by researchers in recent years.

3. Inhibition strategies for polymorph transformation

Undoubtedly, polymorph transformation of solid drugs is a common phenomenon. Ritonavir and rotigotine are well-known "marketed drugs" that have been withdrawn from the market because of polymorphic transformation issues. Ritonavir, which was originally marketed for the treatment of AIDS in 1996, underwent a transition from crystalline form I to the thermodynamically stable form II, and this stable form adversely affected efficacy. In addition, since the production of ritonavir formulations requires configuration in an aqueous solution of ethanol, the production of formulations became unfeasible due to the lower solubility of form II.[96,97] Rotigotine, a drug for the treatment of Parkinson's, underwent a transition from crystalline form I to the less soluble and more stable crystalline form II, resulting in a decrease in its efficacy.[98]

Therefore, it is critical to ensure that the polymorph of a drug does not change during its life cycle. In addition, regulating the polymorph of a drug helps to prevent

Table 2 Selected instances of researchers conducting SSPT on pharmaceuticals in recent years

Molecule	Imposed conditions and polymorph transformation	Year	Ref.
Levofloxacin	Ball milling, hemihydrate → anhydrous	2024	72
Carbapenem	5% RH, form C → form C-1	2024	73
Baloxavir marboxil	Heat, form III → form II	2024	74
Spirotetramat	Heat/ball milling, amorphous → form II	2024	75
Donepezil-maleic acid	Form A/EA/DM-E → form W	2024	76
Mebendazole	75% RH, form A → form C	2024	77
Irbesartan	Milling, form A/B → amorphous	2023	78
Risperidone	Wet media milling, form B → form A → amorphous	2023	78
Creatine phosphate sodium	130 °C, form Hy4 → form Hy2	2023	79
Carbamazepine	Grinding, form III → form IV	2023	80
Glycine	Water-assisted milling, form α → stable form γ	2023	81
Furosemide	Grinding, forms I/III → amorphous	2023	82
Dotinurad	Heat, solvates → form II	2023	83
Dabigatran etexilate mesylate	150 °C, form I → form III	2023	84
Ritonavir	Grinding, form I/II → partially amorphous	2022	85
Koumine hydrochloride	105–120 °C/75% RH, amorphous → form A Room temperature, form B/C/D/E → form A	2022	86
Lenvatinib mesylate	50 °C, solvates form H-EA/form H-THF → form B	2022	87
Levofloxacin hydrochloride	80–90% RH, anhydrate form II → monohydrate form I	2022	39
Dufulin	60 °C, 92.5% RH, form IV/V/ IV/amorphous → form I	2021	88
Erlotinib	Open atmospheric, form IV → form III	2021	52
Glipizide	25 °C, grinding, form I → form II	2021	53
Valacyclovir hydrochloride	25 °C, 10% RH, form III → form SH	2021	89
Efavirenz	60–80 °C/grinding, form II → form I	2020	90
Fluconazole	70% RH, amorphous → form II 40 °C/40% RH, amorphous → form I, II and hydrate	2020	91
Avibactam	85–95% RH, form A → dihydrate form E >95% RH, anhydrous form D → dihydrate form E	2020	37
Sofosbuvir	Liquid-assisted grinding, form I → form A/amorphous	2020	92
Flibanserin	Strong light, 92.5% RH, form I → form A 60 °C, 92.5% RH, form II → form I	2020	93
Apatinib	60% RH for a month, form S3 → sesquihydrate	2019	94
Gandotinib	<8% RH, form II → form I	2019	95

infringement of intellectual property protection that may cover other polymorphs. Therefore, it is important to strictly control the polymorph of a drug to ensure its efficacy and avoid legal disputes.

The methods and strategies that have been reported for controlling the polymorph transformation of drugs include storing the drug product in a suitable environment, optimizing the preparation process and formulation, using additives or excipients, and domain-limiting techniques such as loading and coating.

3.1 Storage in a suitable environment

Temperature and relative humidity play important roles in affecting the stability of a product during storage. In general, drug molecules move more slowly when stored at low temperatures, which is beneficial in inhibiting polymorph transformation including dehydration of hydrates. It has been suggested that amorphous pharmaceutical solids are expected to remain stable at temperatures approximately fifty degrees below their glass transition temperature (T_g) because the extremely low molecular motility at that temperature condition can ensure that crystallization will not occur within a certain time scale, *i.e.*, "T_g – 50 K rule of thumb".[99–102] The stability of amorphous tauroursodeoxycholic acid at different storage temperatures was investigated by Xu *et al.*[103] After three months of storage at 4 °C, only 1.96% of the amorphous form was converted to crystalline form I. However, at 50 °C, the conversion ratio increased to 8.98%. Kissi *et al.*[104] indicated that decreasing the storage temperature significantly enhances the resistance of nifedipine amorphous to recrystallization. As shown in Fig. 4, storing nifedipine amorphous at 278 K will result in recrystallization within one day, while storing at 253 K can ensure physical stability for 136 days.

However, low temperatures are not always favorable for inhibiting polymorph transition. Cai *et al.*[105] reported extensive fracture of the amorphous of griseofulvin at temperatures of 80 °C or less below the glass transition temperature, with large cracks accelerating the nucleation and crystallization of the amorphous.

The effect of relative humidity (RH) is also equally critical. Cheng *et al.*[106] suggested that high ambient humidity may accelerate the polymorphic conversion of famotidine from form B to form A during milling. Wolbert *et al.*[107] showed that the crystallization kinetics of the amorphous form of griseofulvin increased with increasing temperature and relative humidity. At low RH, all forms of sulfathiazole exhibited kinetic stability, while at RH levels above 70%, form I transformed into mixtures of form II and form IV.[108]

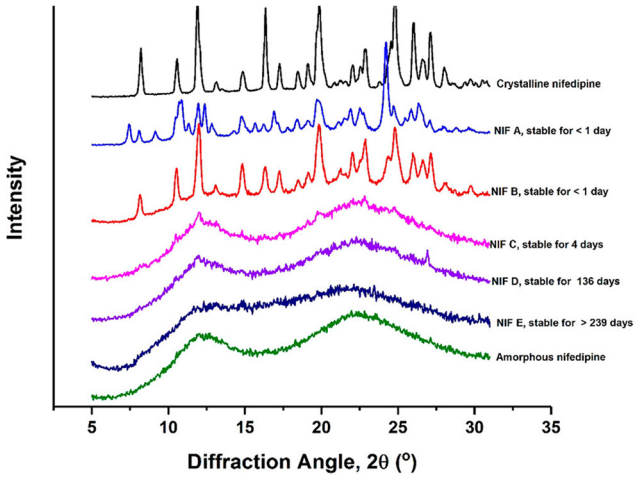

Fig. 4 PXRD of nifedipine (NIF) amorphous stored at 0% RH and different temperatures; NIF A/B/C/D/E represents storage at 313 K, 296 K, 278 K, 253 K, and 193 K, respectively. Reproduced from ref. 104. Copyright 2018 American Chemical Society.

Zhao *et al.*[109] prepared nitrendipine–polyvinyl pyrrolidone (PVP) amorphous solid dispersion (ASD), and the recrystallization tendency of ASD increased with increasing ambient humidity (Fig. 5).

Humidity-induced polymorph transformation can be mitigated by packaging design, including the type of packaging and the use of desiccants, such as the use of desiccants in the packaging of high-density polyethylene (HDPE) bottles or the use of moisture-resistant aluminum–aluminum (Al–Al) blister packs.[110] Łaszcz *et al.*[111] found that aripiprazole form III was partially converted to monohydrate after three months in the storage condition of triplex blister pack (PVC/PE/PVdC) or high-density polyethylene (HDPE) bottles vials at 40 °C and 75% RH, whereas form III stored in aluminum/aluminum blisters or HDPE bottles with desiccant remained stable under the same conditions.

In practice, temperature and relative humidity often combine to influence the polymorph transformation. All forms of clopidogrel have been reported to be very stable below 40 °C at 0% RH.[112] Caron *et al.*[113] prepared ASDs of two binary systems, sulfathiazole/PVP and sulfadimidine/PVP, and these amorphous systems remained X-ray amorphous after more than 1 year of storage at 4 °C with desiccant. Lust *et al.*[114] prepared ASDs of piroxicam and Soluplus that were stable for at least six months at 0% RH and low to moderate temperatures (6 °C and 25 °C). Aging at higher humidity (40% and 75% RH) and 25 °C resulted in recrystallization of amorphous piroxicam to anhydrous form I and monohydrate form MH within one month and two to three months, respectively Lobmann *et al.*[115] prepared amorphous simvastatin by cryo-milling, which recrystallized completely within a few days at 25 °C and 60% RH. At 25 °C and 0% RH, the amorphous started to recrystallize slightly later (11 days), whereas at 4 °C and 0% RH, it remained amorphous state for 67 days.

3.2 Optimization of the preparation process

The preparation method and process of solid drugs can significantly impact stability, and suitable preparation processes can be designed to avoid polymorph transformation. For example, dry granulation or hot melt granulation may be chosen for moisture or solvent-sensitive drugs. Hot-melt extrusion granulation may be chosen for thermally stable drugs that may undergo polymorph transformation during grinding or extrusion. For drugs that are unstable in terms of moisture and heat, a powder direct compression process can be chosen. For drugs that cannot be compacted, they can be prepared as capsules rather than tablets.

Considering that water could induce polymorph transformation from unstable form α to stable form β of imatinib mesylate, Komai *et al.* prepared imatinib mesylate tablets containing form α by dry granulation, and it was expected that the polymorph transformation from form α to form β would not take place for three years at 25 °C.[116] Thakral *et al.*[117] effectively reduced compression-induced polymorph transformation of chlorosulfonylurea by using ceramic-lined molds as well as lubricating specific sites. Zhang *et al.*[118] and Graeser *et al.*[119] reported variations in the physical stability of amorphous simvastatin prepared using different methods. Amorphous simvastatin obtained by quench cooling was more stable than amorphous milled at low temperatures. In addition, quench cooling simvastatin

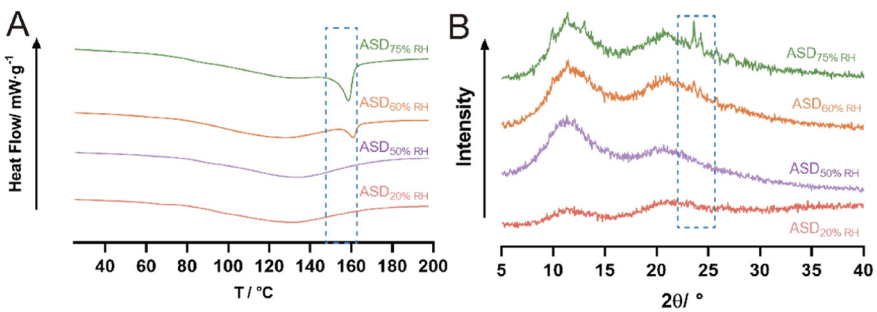

Fig. 5 (A) DSC curves and (B) PXRD patterns of the nitrendipine/PVP ASD samples after storage under various humidity conditions. Reproduced from ref. 109. Copyright 2024 The Korean Society of Industrial and Engineering Chemistry.

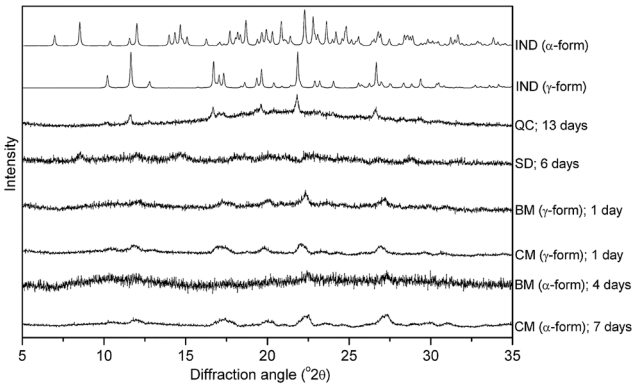

Fig. 6 Diffractograms showing the onset of crystallization of amorphous samples of indomethacin (IND) from different preparation processes. QC: quench cooled; SD: spray dried; BM: ball milled; CM: cryo-milled. Reproduced from ref. 120. Copyright © 2010 Elsevier B.V.

amorphous with a broader particle size distribution was discovered to exhibit greater stability compared to simvastatin with a narrower particle size distribution.

Karmwar *et al.*[120] prepared different indomethacin (IND) amorphous samples employing diverse preparation techniques, including melt quenching, spray drying, ball milled, and cryo-milled. Additionally, different initial polymorphs (form α and γ) were considered for the milled samples. As shown in Fig. 6, the ranking of the amorphous samples stability was: quench cooled > cryo-milled (form α) > spray dried > ball milled (form α) > ball milled (form γ) = cryo-milled (form γ). They also prepared amorphous indomethacin by transformation *via* the melt and found that the physical stability of the amorphous samples increased with the increase in cooling rate, the stability of the amorphous samples was in the order of 30 K min^{-1} > 20 K min^{-1} > 10 K min^{-1} > 5 K min^{-1} > 3 K min^{-1} ≈ 1.2 K min^{-1}.[121]

Zhang *et al.*[122] prepared various nitrendipine/PVPVA64 ASDs by microwave irradiation-quenching, solvent evaporation, and hot-melt extrusion, and the results showed that the ASDs prepared by hot-melt extrusion exhibited stronger recrystallization inhibition effect. Li *et al.*[123] generated physically stable nilotinib amorphous by adjusting several parameters, including the volume of washing water, drying duration, and anti-solvent/solvent ratio. The greatest physical stability was attained by employing a washing water volume exceeding 50 mL, prolonging the drying time to over 18 hours, and maintaining an anti-solvent/solvent ratio of more than 40. Bhujbal *et al.*[124] prepared ASDs of naproxen

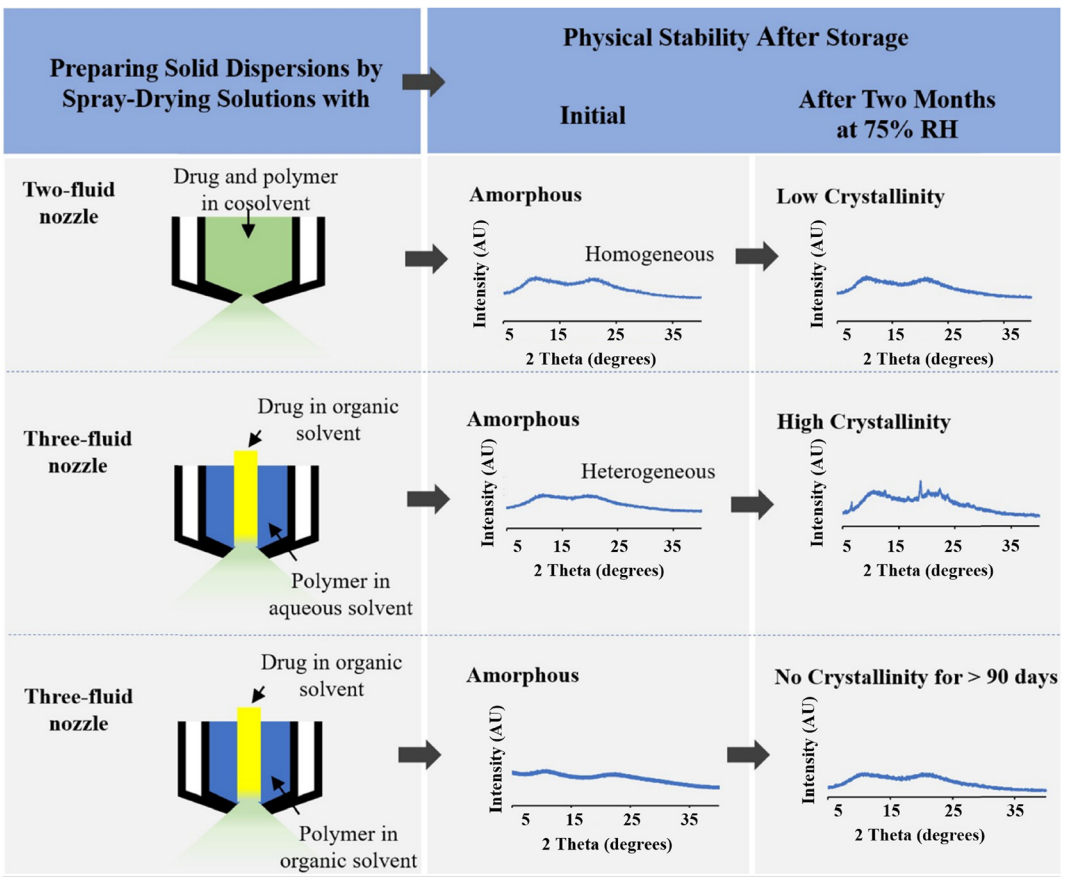

Fig. 7 Effect of spray drying process on the physical stability of naproxen amorphous solid dispersions. Reproduced from ref. 124. Copyright 2021 MDPI.

and polyvinylpyrrolidone (PVP) by spray drying using two-fluid nozzles (2FN) and three-fluid nozzles (3FN). Compared to the 2FN ASD, the faster recrystallization of naproxen in the 3FN ASD using water and acetone solution was attributed to the inhomogeneous mixing of the drug and polymer. The 3FN ASD using only acetone as solvent was the most stable one under storage conditions (Fig. 7).

The size and defects of the particles may also affect the polymorph transformation. Minkov *et al.*[125] reported that decreasing the particle size maintains the metastable form of DL-cysteine. If DL-cysteine form I was obtained as particles with the size about 1 μm through grinding, no transformation into form II was observed on cooling down even to 10 K. Thakuria *et al.*[126] prepared 1 : 1 caffeine–glutaric acid cocrystal polymorphs (form I and form II). The millimeter-sized crystals of form I showed slower conversion to form II compared to micron-sized (0.2–3 μm) powders. Svoboda *et al.*[127] prepared amorphous nimesulide powders with different particle sizes and defects. For amorphous powders of 50–125 μm and 125–180 μm, they would fully crystallize within 49 minutes and 100–200 minutes respectively. For amorphous powders with smooth surfaces, no crystals were formed even after 30 days. The effects of particle size and mechanically induced defects on the recrystallization kinetics of enzalutamide amorphous were also investigated by Svoboda *et al.*[128] The recrystallization rate of enzalutamide amorphous was primarily accelerated by the presence of processing-damaged surfaces on the powder particles. It was further noted that this detrimental effect could be prevented by annealing the material at its softening point to repair or reduce the number of defects.

3.3 Use of additives or excipients

The polymorph transformation can be inhibited by introducing additives, including polymers, organic small molecules, surfactants, structural analogs, and specific impurities.

Solvent-mediated polymorph transformations can be divided into the dissolution of the metastable form, and the nucleation and growth of the stable form. According to the literature, the mechanism of additives to inhibit solvent-mediated polymorph transformations may include the following components. The presence of certain additives can affect solubility and thus dissolution or subsequent nucleation and growth steps.[129–131] Additives may be also adsorbed on the crystal surface, affecting the adsorption of solute molecules on the crystal surface thereby hindering crystal growth.[132,133] For example, strongly hydrophobic polymers may be adsorbed on the crystal surface, affecting the binding of water to the crystal surface, thus inhibiting the formation of hydrates.[134,135] In addition, additives may be associated with solute molecules, thereby reducing the rate of nucleation.[132,136,137] Additives may also increase the viscosity of the solution system, resulting in a low mass transfer rate and hence inhibiting crystal transformation.[138]

Sonoda *et al.*[137] stabilized the substable crystalline form IV of tolbutamide through complexation by adding 6-di-*O*-methyl-β-cyclodextrin in an aqueous solution, thus inhibiting the transition to the stable crystalline form I. Ishiguro *et al.*[139] investigated the inhibition of the transformation process of chlorpropamide by the addition of 2-hydroxybutyl-β-cyclodextrin to aqueous solutions. Higher concentrations of cyclodextrin inhibited the transition from form II to form III, and at lower concentrations, cyclodextrin inhibited the transition from form III to form A. Gu *et al.*[140] showed that the structure-related additives significantly inhibited the conversion of form I to form II of sulfamerazine in acetonitrile suspension by inhibiting the nucleation and crystal growth of the more stable form II. The order of inhibition was N_4-acetylsulfamerazine > sulfadiazine > sulfamethazine. This ordering is consistent with the ordering

Table 3 Examples of solvent-mediated polymorph transformation inhibition using additives

Molecule	Additives	Inhibition process	Ref.
Nitrofurantoin	Polysorbate 80	Acetonitrile, from α ⇏ from β	46
Piroxicam	HPC[a]	Acetone, monohydrate ⇏ form II	55
L-Phenylalanine	Ammonium sulfate, dextrose	Water, anhydrate ⇏ monohydrate	131
2,4-D[b]	PVP,[c] PVPVA[d]	Aqueous methanol solution, metastable form II ⇏ form I	133
Olanzapine	PEG,[e] PVP, HPC	Water, form I ⇏ hydrate	134, 141
BMS-566394[f]	MC,[g] HPMC,[h] HPC	Water, anhydrate ⇏ dihydrate	136
Carbamazepine	MC, HPMC, HPC	Water, form I ⇏ form IV	138, 142–145
Piroxicam	SLS,[i] NaCMC[j] HPMC, Tween 80	Water, anhydrate ⇏ monohydrate	146–148
Piracetam	PEG	Water, form III ⇏ monohydrate	149
Caffeine	PAA[k]	Water, anhydrate ⇏ hydrate	150
Irbesartan	DAC[l]	Water, form A ⇏ form B	151
Cefditoren pivoxil	Sugar ester, HPMC	Water, amorphous recrystallization	152

[a] Hydroxypropyl cellulose. [b] 2,4-Dichlorophenoxyacetic acid. [c] Polyvinyl pyrrolidone. [d] *N*-Vinyl-2-pyrrolidone and vinylacetate. [e] Polyethylene glycol. [f] A poorly water soluble developmental drug intended for oral delivery. [g] Methyl cellulose. [h] Hydroxypropylmethyl cellulose. [i] Sodium lauryl sulphate. [j] Carboxymethylcellulose sodium salt. [k] Polyacrylic acid. [l] Dodecylamine chloride.

of the binding energies of the additives to the crystal surfaces.

Table 3 lists some reported examples of additives that can inhibit solvent-mediated polymorph transformations.

According to the literature, there may be interactions between the additive molecule and the drug molecule, such as hydrogen bond, that reduce the molecular mobility of the drug molecule, thereby inhibiting the solid phase transition. The interaction of additives with drug molecules also competes with water molecules for binding sites and therefore reduces the humidity-mediated solid-phase transition.[153,154] The Incorporation of excipients with low glass transition temperatures may be an effective strategy to reduce drug amorphization during milling because excipients can lower the glass transition temperature of the complex.[155,156] For mechanically induced solid-phase transformation, the addition of ductile additives or excipients can effectively reduce the interfacial shear stress, thus reducing amorphous transformation.[157] In addition, for specific additives, the acid–base microenvironment may also be altered, which also favors the stabilization of metastable form.[158]

Lin *et al.*[159] investigated the transformation behavior of gabapentin during the milling process. It was found that gabapentin crystalline form II was transformed to crystalline form III and then to crystalline form IV during the milling process. However, no transformation of form II occurred by adding some additives, such as calcium hydrogen phosphate, cyclodextrin, and mannitol, during the milling process. The effect of organic acids on the solid-phase transformation of piracetam was studied by Fan *et al.*[160] Low levels of organic acids inhibited the transition from form I to form II under heating conditions, and the inhibition followed the following order: citric acid > tricarboxylic acid > glutaric acid > adipic acid, which is consistent with the order of acidity of organic acids. The molecular simulation suggest that organic acid molecules could be adsorbed on the major crystal planes of PCM form I to form a steric hindrance layer, thereby slowing down the migration of drug molecules. They further proposed an inhibition mechanism as shown in Fig. 8, where the presence of organic acids at the grain boundaries of piracetam crystals can delay the phase separation of piracetam molecules from form I and inhibit the nucleation of form II.

Baaklini *et al.*[161] inhibited the spontaneous polycrystalline transformation of pyrazinamide form γ at room temperature by co-spray drying with 1,3-dimethylurea, and the product remained stable for storage at room temperature for up to 12 months. In contrast, the phase transition to the form δ was observed after 14 days of storage under ambient conditions without any specific treatment. Table 4 lists some reported examples of additives that can inhibit solid-phase crystal form transitions.

3.4 Amorphous solid dispersions or co-amorphous strategy

Preparation of amorphous solid dispersions (ASDs) by uniformly dispersing the drug in an amorphous state polymer matrix is an effective method to inhibit crystallization and improve amorphous stability.[170–172] In

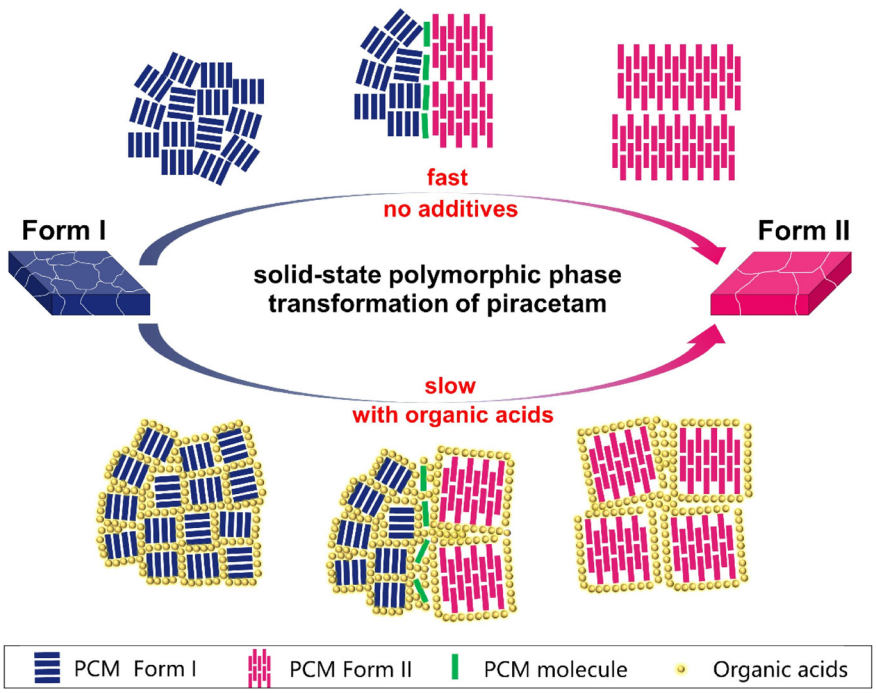

Fig. 8 Schematic illustration of the effect of organic acids on the solid phase transformation of piracetam (PCM) form I to form II. Reproduced from ref. 160. Copyright 2023 Elsevier B.V.

Table 4 Examples of solid-phase crystal form transition inhibition using additives

Molecule	Additive	Inhibition process	Ref.
Chlorpropamide	MCC[a]	Compression, form C ⇏ form A	117
Gabapentin	L-Valine	Milling, from α ⇏ from β	158
Theophylline	PVP[b]	Granulation, monohydrate ⇏ anhydrate	162, 163
Olanzapine	PVP	High humidity, anhydrate ⇏ hydrate	153
Gabapentin	Starch	Milling, form III ⇏ form II	154
Salbutamol sulphate	Glutaric acid	Milling and dry mixing, form I ⇏ amorphous	156
Posaconazole	Magnesium stearate	Compression, crystalline ⇏ amorphous	157
Flufenamic acid	Mefenamic acid	Form I ⇏ form III	164
Xylazine hydrochloride	Sucrose, lactose	Heat, form X ⇏ form A	165
Zopiclone	Sucrose, lactose	Heat, form C ⇏ form A	165
Caffeine	MCC	Compression, form I ⇏ form II	166
Sodium naproxen	PVP	Heat, dihydrate ⇏ monohydrate ⇏ anhydrous	167
Carbamazepine	PEG[c]	Grinding, dihydrate ⇏ form II ⇏ form III	168
Cytosine	Organic dye	Hydrate dehydration	169

[a] Microcrystalline cellulose. [b] Polyvinyl pyrrolidone. [c] Polyethylene glycol.

recent years, the U.S. Food and Drug Administration has approved several amorphous solid dispersing system agents for marketing, such as encorafenib–Co-povidone ASDs, apalutamide–hypromellose acetate succinate ASDs, regorafenib–povidone ASDs, *etc.*[173]

According to the literature, the stabilization mechanism of amorphous solid dispersions consists of the following components. Typically, most drugs have relatively low T_g, whereas polymeric carriers tend to have high T_g, and the "anti-plasticizing effect" of the polymeric additive can increase the T_g of ASDs and decrease the molecular mobility of drugs in ASDs, which leads to decreasing crystallization rates.[174–177] The polymer provides spatial site resistance, increases the viscosity of the system and facilitates the lowering of molecular mobility to reduce the nucleation rate and the lowering of the diffusion coefficient to affect crystal growth.[175,178,179] Drug–polymer interactions, such as van der Waals forces, ionic bond, hydrogen bond, halogen bond, *etc.*, can improve the physical stability of ASDs by reducing molecular mobility.[174,175,180–183]

A variety of polymers have been reported for use in ASD formulations. Zhang *et al.*[175] classified these polymer carriers into four categories based on their chemical structures: polyvinyl lactam polymers, cellulosic polymers, acrylate and methacrylate (co-)polymers, and various other types. (Fig. 9). In addition, proteins and poly(amino acids)s have recently been recognized as a promising class of excipients for the stabilization of amorphous solid dispersions.[184] Kabedev *et al.*[185] evaluated the stability of indomethacin-BLG (β-lactoglobulin) ASDs, along with an investigation into the mechanisms of amorphous stabilization. The ASDs could be stable for at least 12 months when stored under dry conditions. The simulation indicate that the stabilization mechanism was the reduced mobility of the drug molecules and the hydrogen bond network formed on the surface of β-lactoglobulin. Huang *et al.*[186] prepared ASDs of tadalafil and poly-l-lysine, and the ASDs can maintain amorphous state for at least 9 months at both 25 °C and 40 °C. The stability may be attributed to hydrogen bond between tadalafil and poly-l-lysine, which was confirmed by IR spectroscopy.

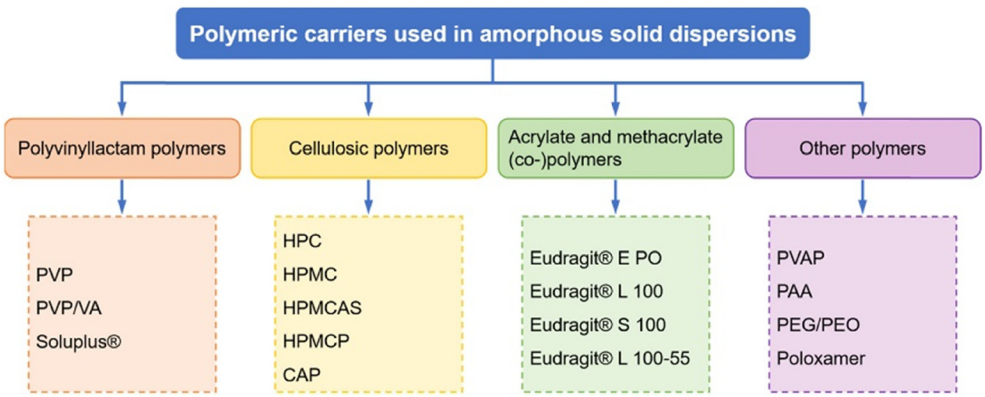

Fig. 9 Polymeric carriers in ASDs. Reproduced from ref. 175. Copyright 2023 Elsevier B.V.

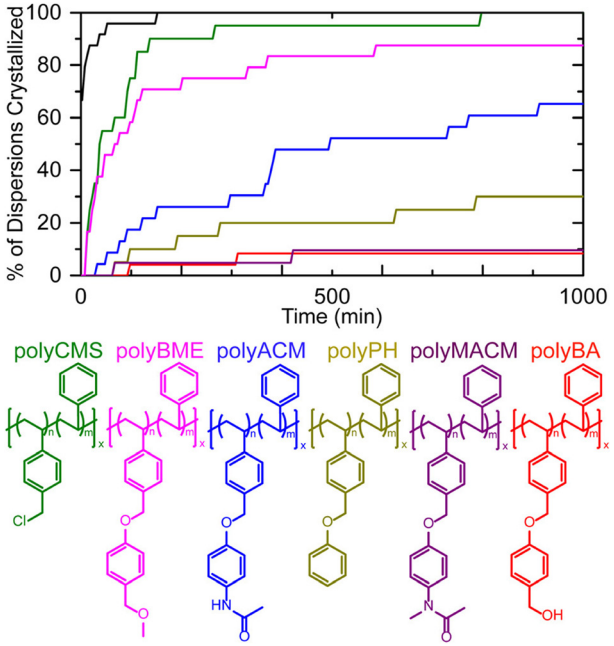

Fig. 10 Rate of nabumetone crystallization ASDs with different functionalized polymers. Black traces indicate pure nabumetone amorphous, each colored trace indicates nabumetone in the corresponding colored polymers. Reproduced from ref. 190. Copyright 2018 American Chemical Society.

Bertoni *et al.*[187] prepared an amorphous solid dispersion of indomethacin by spray solidification using the excipient Gelucire, which remained stable for 18 months without crystallization of indomethacin. In addition, its solubility and bioavailability were increased 31-fold and 2.5-fold, respectively, compared to pure indomethacin form γ. They hypothesized that indomethacin could not crystallize in ASD due to the lack of molecular mobility required for nucleation and crystal growth. Kennedy *et al.*[188] researched the amorphous solid dispersions (ASDs) of a water-insoluble VR1 antagonist (AMG 517), aiming to enhance its physical stability as well as solubility *in vivo*. AMG 517 was doped into polymer particles of HPMCAS or HPMC by spray drying. The ASDs formulation remained physically stable for at least six months under 40 °C and 75% RH. In contrast, the highly amorphous AMG 517 showed a tendency to crystallize after only 15 days of storage.

The type of polymer, molecular weight, chain length, side chain functional groups, and hydrophobicity all affect the resistance of ASDs to stabilize against crystallization.[189] In addition, the results of Frank *et al.*[190] suggested that neither the presence of polar functional groups nor hydrogen bond donating side groups are necessary to inhibit crystallization. As shown in Fig. 10, the non-polar polymer polyPH has a good crystallization inhibition effect. Besides, polyACM contains hydrogen bond donating functional groups, but is not a particularly strong inhibitor. They further hypothesized that the inhibitory ability of the polymers is also related to the polymers solubility in the drug, as well as the polymer-induced heteronucleation. In addition to the

Table 5 Some examples of the use of polymer additives to form ASDs

Drug molecules and polymers used in ASDs
Polyvinyl pyrrolidone (PVP)
Acetaminophen,[191,192] apremilast,[193] bicalutamide,[194,195] ciprofloxacin succinate salts,[196] celecoxib,[197,198] carvedilol,[199] dipyridamole,[200] felodipine,[201] indomethacin,[202,203] irbesartan,[204] itraconazoe,[203] ketoconazole,[205] myricetin,[206] nifedipine,[207–210] nimesulide,[211] naproxen,[192] nitrendipine,[212] oridonin,[213] oxaprozin,[204] phenobarbital,[207] rafoxanide,[214] sulfathiazole, sulfadimidine,[113] salbutamol sulfate,[215] valdecoxib[216]
Poly(vinylpyrrolidone-*co*-vinyl acetate) (PVP/VA)
Acetaminophen,[191] apremilast,[193] carvedilol,[199] celecoxib,[198] felodipine,[217] ibuprofen,[218] itraconazole,[219] irbesartan, oxaprozin,[204] nimesulide,[220] Kollidon®VA64: aripiprazole,[221] carbamazepine,[222] cannabidiol,[223] ezetimibe,[224] flutamide,[225] nisoldipine,[226] probucol,[227] triclabendazole[228]
Soluplus®
Aripiprazole,[221] celecoxib sodium salt,[229] carvedilol,[199] dronedarone,[230] ezetimibe,[231] erlotinib,[232] itraconazole,[219] lacidipine,[233] rivaroxaban,[234] siderol,[235] posaconazole[236]
Hydroxypropyl cellulose (HPC)
Cyclosporine A,[237] ezetimibe,[238] valdecoxib[216]
Hydroxypropyl methylcellulose (HPMC)
Celecoxib,[198,239] indomethacin,[202] itraconazole,[240,241] indapamide, metolazone[242]
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)
Ciprofloxacin,[243] celecoxib,[239] carvedilol-L-aspartic acid,[244] carbamazepine,[245] cinnarizine, clofoctol, clotrimazole,[246] fluconazole,[247] griseofulvin,[246,248,249] indomethacin,[202,203] itraconazole,[203,219,241,250,251] ibrutinib,[252] ketoconazole,[246] lumefantrine,[253] nifedipine,[208,254] piperine,[255] β-lapachone[256]
Cellulose
Cyclosporine A,[257] rifampicin,[258] sulfathiazole[108]
Poly(acrylic acid) (PAA)
Clofazimine,[259] ketoconazole,[205] lamotrigine, pyrimethamine, trimethoprim,[260] nifedipine[254]
Polyethylene glycol (PEG)
Esomeprazole zinc,[261] itraconazole,[241] ritonavir[262]
Other polymers
Chitosan: curcumin[263]
Dextran sulfate: itraconazole[240]
Pectin: thiamine chloride hydrochloride[265]
Eudragit L 100: lumefantrine[253]
Poloxamers: triclabendazole[264]
Gelucire: indomethacin[266,267]

above examples, Table 5 lists some of the reported examples of ASDs.

To optimize binary ASDs, a third component can be added to the system to create ternary ASDs, and the third component can be another polymer, surfactant, excipient, or small molecule. Urbanetz[268] prepared ASDs of nimodipine–PEG–povidone, in which povidone acted as a recrystallization inhibitor, and the solid dispersions were stored at 25 °C for 6 months without crystallization. Davis *et al.*[269] prepared a ternary amorphous solid dispersion of itraconazole (ITZ)–HPMCP-Soluplus by spray drying, and ITZ remained amorphous after one year of storage at 40 °C and 75% RH. In addition to the above examples, Table 6 lists some reported examples of ternary ASDs.

In addition to ASDs composed of polymers, co-amorphous systems consisting of drugs and organic small molecules, such as amino acids, organic acids, flavonoids, and carbohydrates, are receiving a lot of attention.[174,322,323] Numerous studies illustrate that co-amorphous systems possess superior physical stability compared to solitary amorphous drugs. Given that the glass transition temperature (T_g) of the co-amorphous system typically lies between the T_g of its individual constituents, the elevated physical stability cannot be solely attributed to T_g. In the majority of studies, the enhanced physical stability of co-amorphous systems is ascribed to intermolecular interactions, which include hydrogen bonding, π–π interactions, and even ionic interactions.[322,324] Kasten *et al.*[325] evaluated twenty different L-amino acids and six

Table 6 Some examples of ternary ASDs

Third component: polymer			
Drug and ref.	Polymer–polymer	Drug and ref.	Polymer–polymer
Aprepitant[270]	TPGS[a]–PVP[b]	BI 730357 (ref. 271)	HPMCAS[c]–TPGS
Carbamazepine[272]	PHEMA[d]–PVP	Cyclosporine A[273]	HPC[e]–HPMCAS
Celecoxib[274]	PVP–TPGS	Curcumin[275]	HPMC[f]–Eudragit®
Efavirenz[276]	HPC–Eudragit®	Fenofibrate[277]	Kollidon®–HPL[g]
Griseofulvin[278]	HPMCAS–PHPMA[h]	Griseofulvin[279]	Soluplus®–Kollidon
Griseofulvin[280]	PVP–PHPMA	Gefitinib[281]	Eudragit®–HPMC
Itraconazole[282]	HPMC–HPC	Itraconazole[283]	PVA–PVP/VA
Itraconazole[284]	HPMCP–Soluplus®	Itraconazole[285]	TPGS–PVP/VA
Indomethacin[286]	PVP/VA–PEO[i]	Indomethacin[272]	PHEMA–PVP
Indomethacin[287]	Eudragit®–HMPC	Indomethacin[288]	PAA[j]–PVA
Ibuprofen[289]	Kollidon®–HPMCP	Ketoconazole[290]	HPMC–PAA
Lopinavir[291]	Eudragit®–MCC[k]	LW6 (ref. 292)	PVP–poloxamer
Loratadine[293]	Shellac–HPMC	Lacidipine[294]	Soluplus®–Gelucire®
Niclosamide[295]	HEC[l]–Kolliphor	Olmesartan medoxomil[296]	HP-β-CD[m]–MG[n]
Progesterone[280]	PVP–PHPMA	Phenindione[280]	PVP–PHPMA
Probucol[297]	PVP–poloxamer	Regorafenib[298]	PVP–HPMCAS
Telmisartan[299]	PVP–Soluplus®	VR1 antagonist[188]	HPMCAS–HPMC
Third component: surfactant			
Drug and ref.	Polymer–surfactant	Drug and ref.	Polymer–surfactant
Atazanavir[300]	PVPVA–SDS[o]	Atorvastatin Calcium[301]	HPMC–SLS[p]
Curcumin[302]	PVP–Tween 80	Docetaxel[303]	PVP–SDS
Felodipine[304]	PVP/VA–SDS	Griseofulvin[305]	Soluplus®–SDS
Lacidipine[306]	Soluplus®–SDS	Probucol[307,308]	HPMC–SDS
Ritonavir[309]	HPMC–SLS	Ritonavir[310]	PVP/VA–Span
β-carotene[311]	HPMCAS–Span 20		
Third component: excipient			
Drug and ref.	Polymer–excipient	Drug and ref.	Polymer–excipient
Coenzyme Q[312]	Poloxamer–Aerosil 200	Indomethacin[313]	HPMC–silicon dioxide
Indomethacin[314]	PVP–kaolin	Naringenin[315]	Poloxamer–neusilin
Toltrazuril[316]	PEG–$Ca(OH)_2$	Telmisartan[317]	PEG–magnesium oxide
Third component: organic small molecule			
Drug and ref.	Polymer–molecule	Drug and ref.	Polymer–molecule
Indomethacin[318]	PVPVA–L-arginine	Indomethacin[319]	PVP–saccharin
Ketoconazole[320]	PVP–organic acids[q]	Tetrabenazine[321]	HPMC–citric acid

[a] D-α-Tocopherol polyethylene glycol 1000 succinate. [b] Polyvinyl pyrrolidone. [c] Hydroxypropyl methylcellulose acetate succinate. [d] Poly(2-hydroxyethyl methacrylate). [e] Hydroxypropyl cellulose. [f] Hydroxypropyl methylcellulose. [g] Hydrogenated phospholipid. [h] Poly[*N*-(2-hydroxypropyl)methacrylate]. [i] Polyethylene oxide. [j] Poly(acrylic acid). [k] Microcrystalline cellulose. [l] Hydroxyethyl cellulose. [m] Hydroxypropyl-β-cyclodextrin. [n] *N*-Methyl-D-glucamine. [o] Sodium dodecyl sulfate. [p] Sodium lauryl sulfate. [q] Tartaric acid, citric acid, succinic acid.

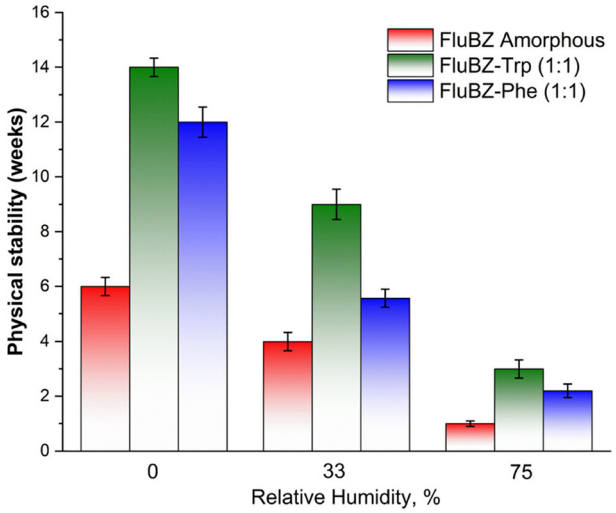

Fig. 11 Stability of amorphous and co-amorphous flubendazole (FluBZ). Phe: L-phenylalanine, Trp: L-tryptophan. Reproduced from ref. 326. Copyright 2023 American Chemical Society.

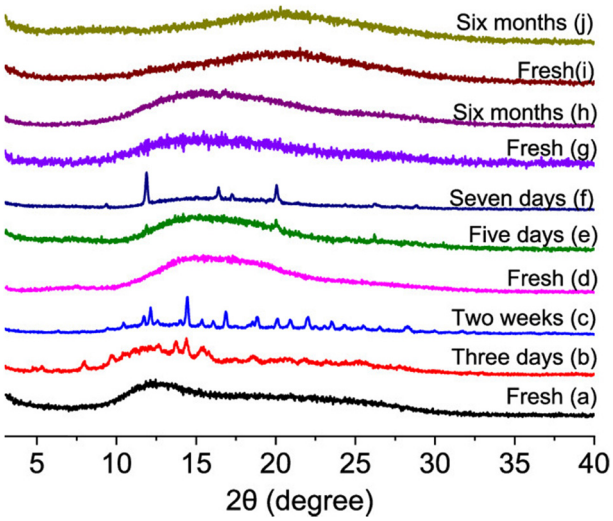

Fig. 12 PXRD patterns of amorphous sinomenine (a–c), amorphous platensimycin (d–f), co-amorphous sinomenine–platensimycin (g and h), and sinomenine–sulfasalazine (i and j) before and after storing at different periods under 25 °C and 75% RH. Reproduced from ref. 356. Copyright 2022 American Chemical Society.

different acidic and basic model drugs (carvedilol, mebendazole, carbamazepine, simvastatin, indomethacin, and furosemide) and the ability to form co-amorphous preparations. The results suggest that basic amino acids are potentially good conformers in the case of acidic drugs. Vasilev *et al.*[326] prepared co-amorphous systems of flubendazole (FluBZ) with L-phenylalanine (Phe) and L-tryptophan (Trp), respectively. The two co-amorphous systems containing Phe and Trp were stable for 3 months at 25 °C and 0% RH, twice as long as pure FluBZ. (Fig. 11). Some examples of drugs prepared as co-amorphous systems with organic small molecules are listed in Table 7.

In the co-amorphous system, two drug molecules that can either synergize each other's actions or can work in a tandem manner can also be selected, called drug–drug co-amorphous. Allesø *et al.*[355] prepared an amorphous binary system of naproxen–cimetidine by cryogenic milling. The amorphous form was maintained after storage at 40 °C for 186 days. The inherent

Table 7 Some examples of using small molecule additives to form co-amorphous systems to inhibit the crystallization of amorphous drugs

Drug and ref.	Additive	Drug and ref.	Additive
Additives: amino acids			
Carvedilol[327]	L-Aspartic acid	Carbamazepine[328]	Tryptophan
Ciprofloxacin[329]	L-Leucine	Carbamazepine[330]	L-Arginine
Flubendazole[326]	L-Phenylalanine, L-tryptophan	Glibenclamide[331]	Serine, threonine
Indomethacin[328]	Arginine	Indomethacin[332]	Arginine, histidine, lysine
Naproxen[333]	Arginine, tryptophan, proline	Ranolazine[334]	Tryptophan
Simvastatin[335]	Leucine, tryptophan, lysine	Simvastatin[331]	Lysine
Spironolactone[336]	L-Tryptophan		
Additives: organic acid			
Cenicriviroc mesylate[337]	Fumaric acid	Carbamazepine[330]	Citric acid
Carbamazepine[338]	Tannic acid	Indomethacin[338]	Tannic acid
Ketoconazole[339]	Oxalic, citric, tartaric, succinic acid	Lamotrigine[340]	Cholic acid
Paracetamol[341]	Citric acid	Pyrimethamine[340]	Cholic acid
Sulfathiazole[342]	Citric acids, L-artaric	Trimethoprim[340]	Cholic acid
Additives: carbohydrates			
Biclotymol[343]	pentaacetylglucose	Celecoxib[197,344]	Octaacetylmaltose
Carbamazepine[345]	Glycosyl rutin	Diphenhydramine hydrochloride[346]	Lactose
Ibuprofen[347]	Octaacetylmaltose	Indomethacin[348]	Octaacetylmaltose, octaacetylsucrose
Lurasidone hydrochloride[349]	Saccharin	Metronidazole[350]	Acetylated cyclodextrin
Nifedipine[351]	Acetylated maltose, acetylated sucrose	Olanzapine[352,353]	Saccharin
Repaglinide[354]	Saccharin		

Table 8 Examples of the preparation of a co-amorphous binary drug for stabilization of amorphous systems and combination therapy

Co-amorphous binary drug	Ref.	Co-amorphous binary drug	Ref.
Atorvastatin–glipizide	359	Atorvastatin–probucol	360
Atorvastatin–lisinopril	361	Atenolol–hydrochlorothiazide	362
Antipyrine–paracetamol	363	Artemisinin–curcumin	364
Ciprofloxacin–colistin	329	Cilnidipine–valsartan	365
Ezetimibe–indapamide	366	Glipizide–simvastatin	115
Lurasidone hydrochloride–repaglinide	367	Lurasidone hydrochloride–puerarin	368
Indomethacin–cimetidine	369	Indomethacin–ranitidine hydrochloride	370
Indomethacin–ritonavir	371	Indomethacin–paracetamol	372
Indomethacin–nicotinamide	372	Indapamide–ezetimib	366
Nifedipine–nimodipine	373	Naproxen–cimetidine	369, 374
Naproxen–aceclofenac	375, 376	Naproxen–indomethacin	375–377
Ritonavir–quercetin	378	Tranilast–matrine	379
Sulfamethoxazole–trimethoprim	380	Sinomenine–platensimycin, sinomenine–sulfasalazine	356

dissolution rates of both naproxen and cimetidine were observed to be four and two times higher respectively, in comparison to their crystalline counterparts. Chen *et al.*[356] developed two co-amorphous systems combining sinomenine (SIN) with two potent antibiotics, namely platensimycin (PTM) and sulfasalazine (SULF). Following an exposure period of one month at 25 °C and 75% RH, both of these co-amorphous systems effectively maintained their amorphous properties (Fig. 12g and h). In contrast, after a few days, the two amorphous forms of SIN and PTM began to recrystallize (Fig. 12b and f).

Regarding co-amorphous binary drug systems, Shelke *et al.*[357] and Wang *et al.*[358] have recently published relevant review articles. Some examples of drug–drug co-amorphous are listed in Table 8.

3.5 Spatial confinement techniques

Polymorph transformation can be suppressed by placing amorphous or crystalline forms in spatial confinement, including the application of coatings, loading in mesoporous materials, *etc.*

It has been reported that the rate of surface crystallization significantly surpasses that of bulk (interior) crystallization by multiple orders of magnitude.[381–385] For example, Huang *et al.*[386] reported very fast surface diffusion in amorphous griseofulvin, 108 times that of bulk diffusion at T_g, which is consistent with the rapid growth of crystals on its surface. Thus, surface-specific techniques that limit the mobility of surface molecules can be used to inhibit polymorph transformation. Two mechanisms have been reported for surface coatings to inhibit crystalline transformation or

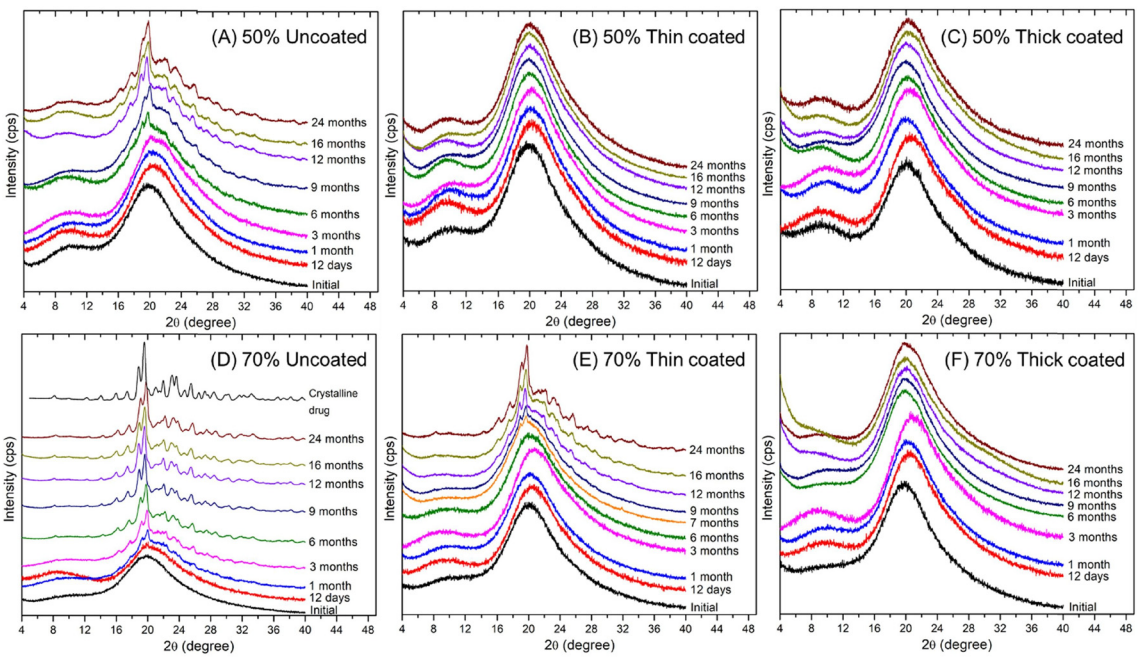

Fig. 13 X-ray diffractograms of ezetimibe ASDs samples at 50% and 70% loading with and without Al_2O_3 coating during two years of storage at 40 °C and 75% RH. Reproduced from ref. 388. Copyright 2022 Elsevier B.V.

amorphous recrystallization, the first mechanism being that the coating acts as a barrier to reduce water adsorption. The second mechanism is that the coating can directly inhibit surface mobility, effectively eliminating the surface-air interface of the particles.[387–389]

Duong *et al.*[388] developed ASDs of ezetimibe using HPMCAS with drug loadings at 50 and 70% w/w, and employed the atomic layer coating (ALC) process to apply a layer of aluminum oxide onto the surface of the ASD particles. As shown in Fig. 13, under accelerated storage conditions, crystallization was observed in the uncoated ASDs with 50% and 70% drug loadings, merely a few days into storage. In contrast, both thin and thick-coated samples at 50% loading showed no physical instability for two years. Ehmann *et al.*[390] reported stabilization of unstable crystalline form III of paracetamol by treating silica surfaces under ambient conditions. Moseson *et al.*[387] prepared ASDs of three drugs including erlotinib, naproxen, and lumefantrine with HMPCAS or PVPVA by spray drying (SD) and hot melt extrusion (HME) processes, respectively. Aluminum oxide (Al_2O_3) and zinc oxide (ZnO) were then coated on the ASDs particles by the ALC process. As shown in Fig. 14, crystallization of certain ASDs systems was effectively delayed or completely inhibited for up to 48 weeks. Some examples of cladding coatings to inhibit amorphous crystallization are listed in Table 9.

In recent years, the application of mesoporous carriers has been evolving in the pharmaceutical field for stabilizing the amorphous. Drug molecules adsorbed in the nanoscale pores or microchannels of the carriers can restrict molecular mobility and molecular diffusion due to spatial constraints, reducing the probability of nucleation. In addition, interactions such as hydrogen bonding between the drug molecules and the carriers may be formed, which also contributes to the stabilization of the amorphous.[177,389,404,405]

Wang *et al.*[406] reported surface-functionalized mesoporous silicon (pSi)-based formulations for the delivery of the insoluble drug indomethacin (IMC). Indomethacin was present in amorphous form in the mesoporous silica matrix, and IMC–pSi demonstrated superior solid-state stability for six months when subjected to accelerated stability test conditions (40 °C and 75% RH). Zhang *et al.*[407] reported that the extremely unstable crystalline form VIII of flufenamic acid was sufficiently stable under nanoscale confinement in controlled pore glass. Nielsen *et al.*[408] noted that the degree of crystallization in amorphous indomethacin was lessened when the amorphous drug was encapsulated inside micro-

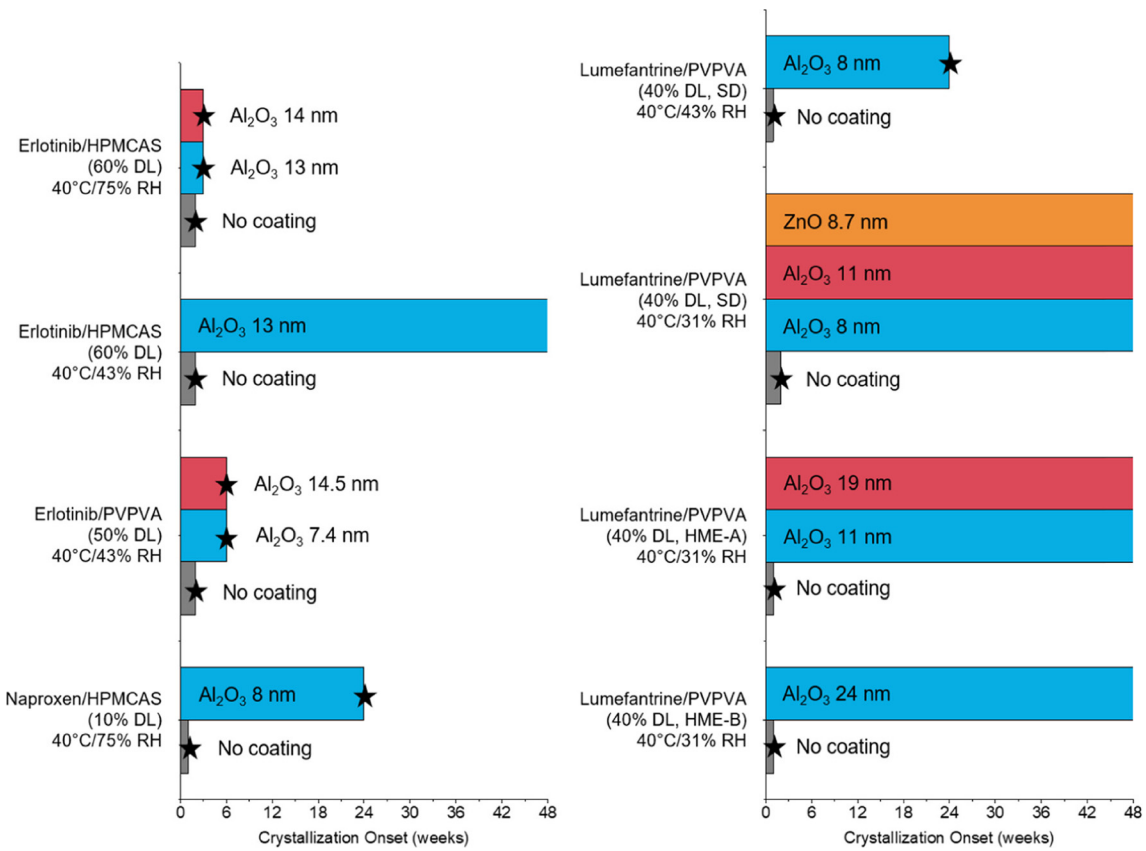

Fig. 14 Physical stability of ASD systems with and without coating. The star symbol (★) indicates that crystallization was detected. The open columns indicate that the sample did not crystallize after 48 weeks. DL: drug loading. The *xx* nm indicates the coating thickness. Reproduced from ref. 387. Copyright 2022 American Chemical Society.

Table 9 Examples of cladding coatings used to inhibit amorphous crystallization

Drug and ref.	Coating	Drug and ref.	Coating
Acetaminophen[391]	Carnauba wax	Celecoxib[392]	Ethyl cellulose
Carvedilol[393]	Tripalmitin, polysorbate	Clofazimine[394]	Alginate, PSS[a]
Delamanid[395]	Poly(methacrylic acid)	Felodipine[396]	Eudragit®
Ketoprofen[397]	Perfluorohexane	Indomethacin[398]	Gelatin, chitosan
Indomethacin[399]	Gelatin	Indomethacin[400]	Gold, PSS, PDDA[b]
Loratadine[401]	Dextran sulfate	Nifedipine[399]	Gelatin
Posaconazole[402]	Al_2O_3	Stavudine[403]	PMMA[c]

[a] Sodium poly(styrenesulfonate). [b] Poly(dimethyldiallyl ammonium chloride). [c] Poly(methyl methacrylate).

containers, compared to the amorphous indomethacin found in a bulk drug. A reduction in the micro-container size from 223 μm to 174 μm led to improved stability of the amorphous form. Speybroeck *et al.*[409] used a solvent impregnation method to load 10 model drugs with different physicochemical properties (carbamazepine, cinnarizine, danazol, diazepam, fenofibrate, griseofulvin, indomethacin, ketoconazole, nifedipine, and phenylbutazone) onto ordered

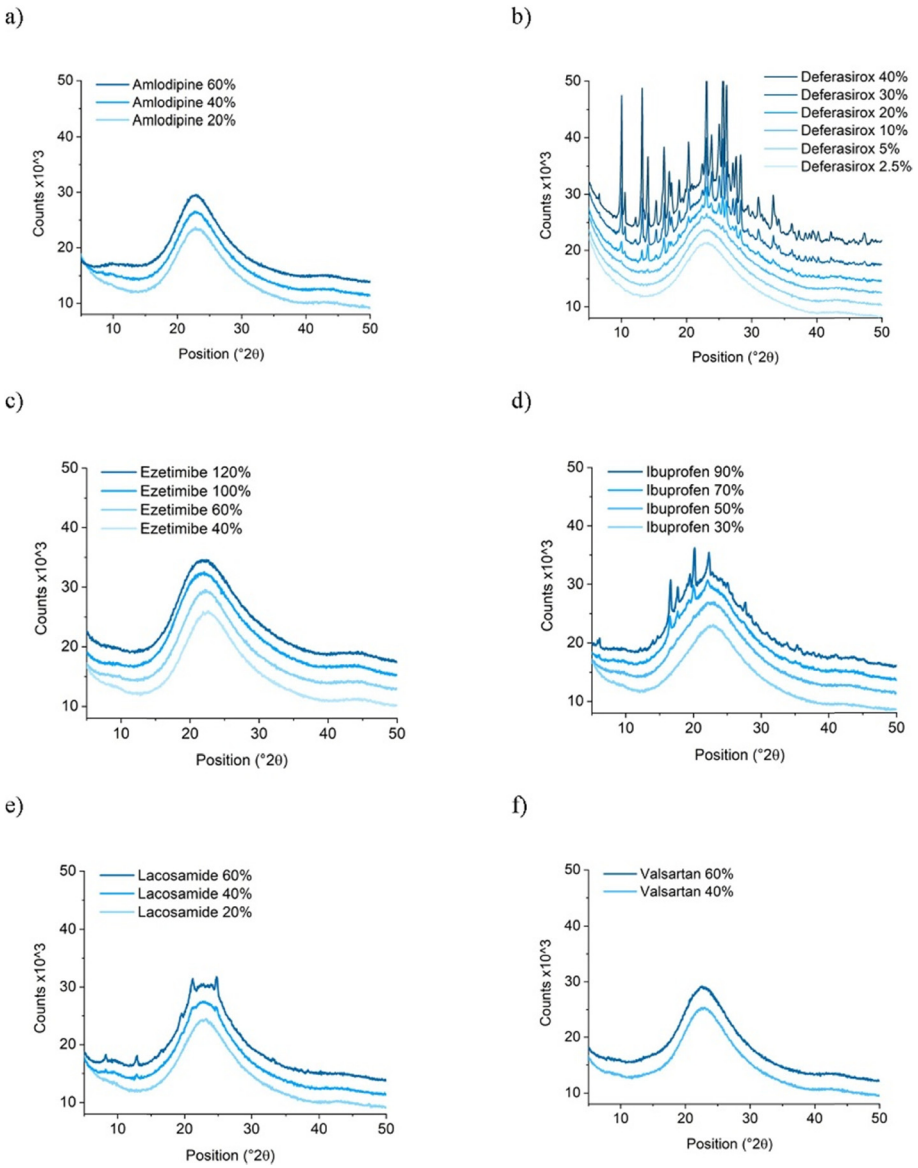

Fig. 15 PXRD patterns of different APIs loaded into the mesoporous silica. (a) Amlodipine, (b) deferasirox, (c) ezetimibe, (d) ibuprofen, (e) lacosamide, (f) valsartan. Reproduced from ref. 410. Copyright 2021 Elsevier B.V.

Table 10 Some examples of mesoporous materials used to inhibit amorphous crystallization

Drug and ref.	Mesoporous matrix	Drug and ref.	Mesoporous matrix
Aprepitant[411]	Silica	Aripiprazole[412,413]	Silica
Carvedilol[414]	Silica	Celecoxib[415]	Magnesium carbonate
Celecoxib[416–419]	Silica	Celecoxib[420]	$CaCO_3$
Celecoxib[421]	Terpolymeric nanoparticle	Darunavir[422]	Silica, magnesium aluminosilicate
Ezetimibe[423]	Neusilin US2	Fluconazole[424]	Silica
Fenofibrate[417,425,426]	Silica	Felodipine[427]	Silica
Gemfibrozil[428]	Silica	Ibuprofen[410,414,429,430]	Silica
Indomethacin[431,432]	Silica	Itraconazole[433]	Syloid XDP
Ivermectin[434]	Silica	K-832 (ref. 435)	Silica
Nifedipine[436]	Glass	Paclitaxel[437]	Hematite nanorods
Quercetin[438]	Silica	Ritonavir[439]	Silica
Riluzole[440]	Silica	Silymarin[441,442]	Silica
Simvastatin[443]	Silica	Vortioxetine[444]	Silica

mesoporous silicate SBA-15. In all cases, the loaded drugs were amorphous and no crystallization was observed after 6 months of storage at 25 °C and 52% RH. Šoltys *et al.*[410] systematically compared the performance of four different types of silica when loaded with different APIs. The silica materials used include two commercially procurable silica excipients, namely Parteck® SLC 500 and Syloid® 72FP, along with two silica particles prepared in the laboratory, one being highly porous sub-micron particles while the other hierarchically porous microparticles. These silica materials mainly differed in their particle size, pore size, and pore volume. The sub-micron particles exhibited the best performance of all the tests. As shown in Fig. 15(a, c, and f), using sub-micron particle loading, no crystalline form was detected for the three APIs at different loading levels. Some examples of mesoporous materials used to stabilize drug amorphous forms are listed in Table 10.

4. Conclusions and outlooks

Metastable crystal forms and amorphous are in a high-energy state and are prone to transition from metastable forms to stable forms and recrystallization of amorphous during manufacture and storage. Therefore, it is necessary to understand the various factors that cause the polymorph transformation of drugs, including solvents, temperature, humidity, pressure, impurities, defects, *etc.* The problem is that it is difficult to predict whether crystals can undergo phase transitions and the conditions and results under which they occur, usually only after extensive experimentation and the acquisition of polymorphs. In addition, the modeling of the polymorph transformation process is not yet complete and it is important to develop appropriate models to understand the factors affecting the kinetic process.

It is also important to understand the means of stabilizing metastable or amorphous form, including optimization of the preparation process, use of additives or excipients, spatial confinement, storage at suitable temperature and humidity conditions, *etc.* Changing the temperature and humidity is a common strategy to inhibit polymorph transformation, which requires the selection of appropriate storage temperature and humidity based on drug properties. Factors such as solvents, temperature, humidity, stress, *etc.* that may cause polymorph transformation in the preparation process also need to be noted and optimized. Additives are one important strategy to inhibit polymorphic transformation. Amorphous solid dispersions in particular have been widely studied as a strategy to inhibit amorphous crystallization. Adding a third component to the binary dispersion can also improve the physical stability of the amorphous form. Detailed knowledge of key drug and polymer properties is required when designing additive formulations to ensure safe drug use. However, for a wide variety of additives, the selection of ideal additives is still dominated by experimental screening and the precise selection of additives is still a difficult problem. Meanwhile, molecular simulation is becoming a common tool to understand the interaction between drugs and additives, which is important for additive design and needs to be further investigated. Surface coating as well as mesoporous materials can also be used to inhibit polymorph transformation due to their good stabilizing ability. In conclusion for specific drugs, the advantages and disadvantages of each crystalline inhibition method need to be fully explored to optimize the process parameters and overcome the challenges of polymorph transformation.

Data availability

Data sharing not applicable – no new data generated.

Author contributions

Yaoguang Feng: writing – original draft, investigation, data curation. Hui Wang: data curation. Di Wu: investigation. Kui Chen: formal analysis. Na Wang: funding acquisition, validation, writing – review & editing. Ting Wang: resources. Xin Huang: conceptualization, project administration. Lina Zhou: validation. Hongxun Hao: funding acquisition, validation, writing – review & editing. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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