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REVIEW ARTICLE

Effects of Additives on the Physical Stability and Dissolution of Polymeric Amorphous Solid Dispersions: a Review

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Abstract

Polymeric amorphous solid dispersion (ASD) is a popular approach for enhancing the solubility of poorly water-soluble drugs. However, achieving both physical stability and dissolution performance in an ASD prepared with a single polymer can be challenging. Therefore, a secondary excipient can be added. In this paper, we review three classes of additives that can be added internally to ASDs: (i) a second polymer, to form a ternary drug-polymer–polymer ASD, (ii) counterions, to facilitate *in situ* salt formation, and (iii) surfactants. In an ASD prepared with a combination of polymers, each polymer exerts a unique function, such as a stabilizer in the solid state and a crystallization inhibitor during dissolution. *In situ* salt formation in ASD usually leads to substantial increases in the glass transition temperature, contributing to improved physical stability. Surfactants can enhance the wettability of ASD particles, thereby promoting rapid drug release. However, their potential adverse effects on physical stability and dissolution, resulting from enhanced molecular mobility and competitive molecular interaction with the polymer, respectively, warrant careful consideration. Finally, we discuss the impact of magnesium stearate and inorganic salts, excipients added externally upon downstream processing, on the solid-state stability as well as the dissolution of ASD tablets.

Keywords amorphous solid dispersion · dissolution · physical stability · polymer · surfactants

Introduction

The development of poorly water-soluble active pharmaceutical ingredients (APIs) has been a major challenge in the pharmaceutical industry. Approximately 90% of newly developed chemical entities obtains low aqueous solubility, leading to low bioavailability and poor therapeutic efficacy [1]. Amorphous solid dispersion (ASD) has emerged as a popular strategy for enhancing the solubility of insoluble APIs. Compared to their crystalline counterparts, amorphous drugs exhibit higher free energy, which contributes to their enhanced solubility [2]. However, the high energy state of the amorphous form can lead to stability concerns, as recrystallization can occur during storage, compromising the solubility advantages of amorphous pharmaceuticals. To address these stability concerns, molecularly dispersing drugs in a polymer matrix to form ASDs has been regarded as an effective approach [2]. In addition to improving physical stability, polymers can also prolong supersaturation upon ASD dissolution [3, 4], which is desirable for *in vitro* dissolution, membrane transportation, and *in vivo* oral absorption [5–7].

Recent studies have shown that the congruent release of drug and polymer is critical to the rapid generation of supersaturation [4, 8]. However, this can only be achieved at a low drug/polymer ratio, potentially resulting in a "pill burden" for high-dose APIs [9, 10]. The limit of congruency (LoC) is the threshold for an ASD to achieve congruent release [8]. The strength of the drug-polymer interaction is also a critical factor during polymer selection. Drug-polymer interactions, such as ionic interactions, hydrogen bonding, and hydrophobic forces, can improve the physical stability of ASDs by reducing molecular mobility [11–13]. Strong molecular interactions can substantially decrease LoC, meaning that

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the ASD must be formulated at a high polymer concentration for excellent dissolution performance [14]. However, strong drug-polymer interactions can also inhibit drug recrystallization during dissolution [15–17]. Therefore, in many cases, ASDs cannot simultaneously achieve excellent physical stability and a desirable dissolution profile [14, 18, 19]. As a result, secondary additives can be added to ASDs to improve their performance, either internally or externally. By adding pharmaceutical excipients to the drug and amorphous polymer matrix, the microenvironment of the drug particles at the dissolution front can be modified, leading to increased solubility of the API [20]. The addition of polymer or surfactant could potentially inhibit drug recrystallization during shelf life and, at the same time, improve dissolution. For instance, the physical stability as well as dissolution of an ASD can be manipulated by polymer combinations each with different interactions with the drug [21]. Additionally, surfactants can be incorporated into ASDs to enhance the dissolution rate of poorly water-soluble drugs by promoting wettability [22]. However, the choice and quantity of functional additives are critical in formulating stable, multicomponent ASDs.

In this review paper, we first classified and reviewed five classes of amorphous polymers that are commonly used in ASDs, which are (i) polyvinylpyrrolidones (PVP) and poly(vinylpyrrolidone-co-vinyl-acetate) (PVPVA), (ii) hydroxypropyl methylcellulose (HPMC) and hypromellose acetate succinate (HPMCAS), (iii) polymethacrylate-based copolymers, Eudragit®, (iv) acidic polymers: polyacrylic acid (PAA) and hydroxypropyl methylcellulose phthalate (HPMCP) and (v) Soluplus®. Afterward, three classes of additives that can be added internally were introduced: (i) a second polymer, in other words, the use of a polymer combination, (ii) counterion to the drug, to enable *in situ* salt formation, and (iii) surfactant. Furthermore, we discuss the effects of magnesium stearate, a common lubricant in tablet formulations, on the physical stability and dissolution of ASDs. Finally, we review the role of inorganic salts in promoting the disintegration of ASD tablets, which can further improve ASD dissolution. In summary, this review paper discusses the effects of secondary additives on the physical stability and dissolution performance of ASDs. The knowledge gained from this review can aid in the formulation design of amorphous formulations, ultimately improving the therapeutic efficacy of poorly water-soluble APIs.

Review of Commonly Used Polymers in ASDs

In this work, we first review five groups of commonly used amorphous polymers in ASD preparation, which are classified based on their structures or chemical properties, to provide an improved understanding of their effects on the physical stabilization or dissolution of ASDs. Those polymers include (i) polyvinylpyrrolidones (PVP) and poly(vinylpyrrolidone-co-vinyl-acetate) (PVPVA), (ii) hydroxypropyl methylcellulose (HPMC) and hypromellose acetate succinate (HPMCAS), (iii) Eudragit®, (iv) acidic polymers, including polyacrylic acid (PAA) and hydroxypropyl methylcellulose phthalate (HPMCP), and (v) Soluplus®. Their chemical structures and some critical physicochemical parameters are summarized in Fig. 1 and Table I , respectively. Polymer selection is a critical step in ASD development. Therefore, a systematic discussion about the widely used polymers based on their physicochemical properties and potential interactions with the API can be useful guidance to ASD development. In addition, we want to point out that, although it is well-known that cyclodextrins, by forming inclusion complexes, have been used in solubility enhancement [23, 24], compared

Table I Glass Transition Temperatures, Molecular Weight and Aqueous Solubility of the Polymers Discussed in the Current Review Paper. The Data are Adapted from [13, 26–30]

Polymers	T_g (°C)	Molecular weight (kDa)	Aqueous solubility*
Polyvinylpyrrolidones	175 ~ 180	2.5 ~ 3000	Soluble
Poly(vinylpyrrolidone-co-vinyl-acetate)	70 ~ 110	45 ~ 70 (PVPVA 64)	Soluble
Hydroxypropyl methylcellulose	175 ~ 180	10 ~ 1500	Soluble Gelation followed by dissolution
Hypromellose acetate succinate	100 ~ 110	55 ~ 93	L grade: soluble at pH 5.5 ~ 6.0 and above M grade: soluble at pH 6.0 ~ 6.5 and above H grade: soluble at pH > 6.8
Eudragit®	> 150	135 ~ 250	Eudragit® S: soluble at pH > 6 Eudragit® L: soluble at pH > 7 Eudragit® E: soluble at pH < 5
Polyacrylic acid	106	2 ~ 4000	Soluble
Hydroxypropyl methylcellulose phthalate	133 ~ 137	80 ~ 130	Soluble at pH > 5
Soluplus®	~ 70	~ 118	Soluble

*Unless otherwise stated, based on the United States Pharmacopeia, "soluble" indicates aqueous solubility is > 10 mg/mL[31]

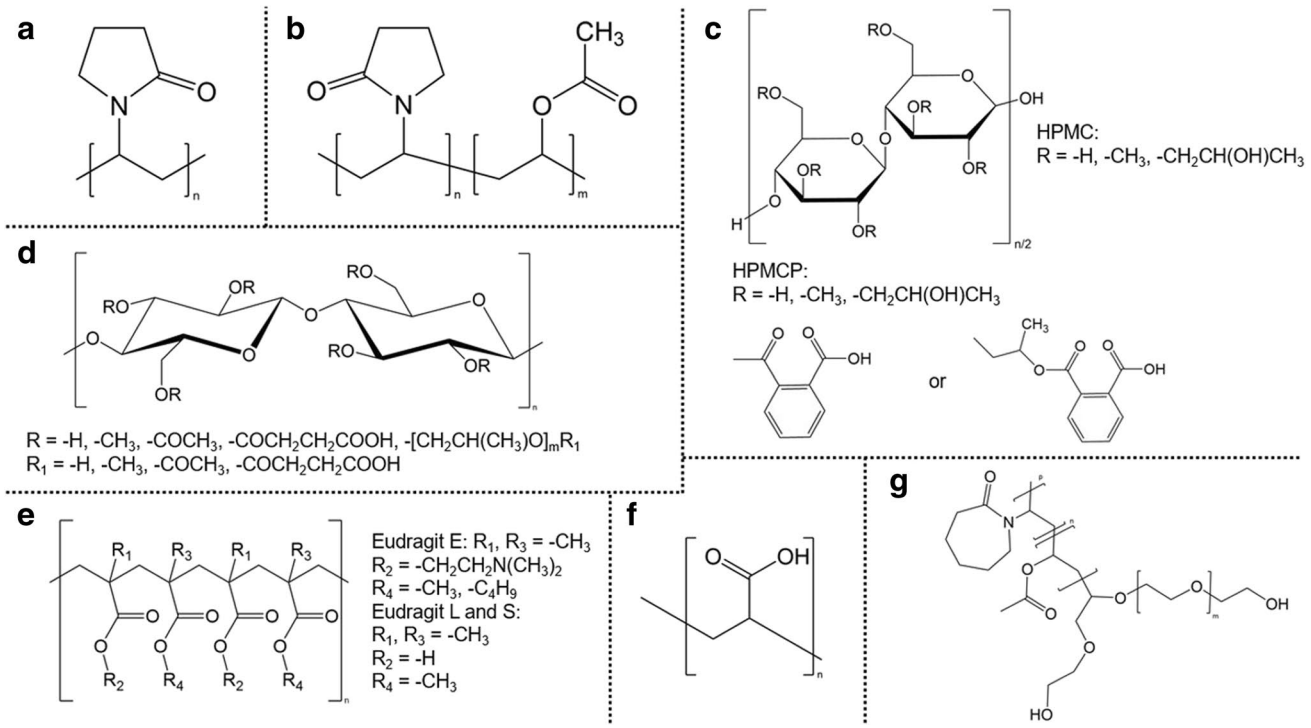

Fig. 1 Chemical structures of commonly used polymers in ASDs. **a** Polyvinylpyrrolidone (PVP). **b** Poly(vinylpyrrolidone-co-vinyl-acetate) (PVPVA). **c** Hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose phthalate (HPMCP). **d** Hypromellose acetate succinate (HPMCAS). **e** Eudragit® E, L, and S. **f** Polyacrylic acid (PAA). **g** Soluplus®

to polymers, they are not widely used because of economic and toxicity reasons [25, 26]. Therefore, we keep our focus on discussing the commonly used polymers in ASDs as well as performance improvement using secondary additives.

Polyvinylpyrrolidones and Poly(vinylpyrrolidone-co-vinyl-acetate)

Polyvinylpyrrolidones (PVP) (Fig. 1a), also known as polyvidone and povidone, are hydrophilic polymers composed of N-vinylpyrrolidone monomers. They are one of the most commonly used groups of polymers in ASDs. Based on the length of the polymer chain, the molecular weight of PVP ranges from ~ 2.5 to 3000 kDa as the "*K*" value increases from 12 to 120 [26]. In oral dosage forms, PVPs are widely used as binders, coating and suspending agents. In light of their role as a polymer matrix in ASDs, the carbonyl group acts as a proton acceptor, facilitating hydrogen bonding with APIs that have active proton donors, such as nifedipine and indomethacin [12, 32]. On the other hand, for drugs without any proton donors, such as ketoconazole and itraconazole (ITZ), weak drug-polymer interactions result in poor physical stability of the ASDs [11, 33]. The effect of such molecular interactions in the solid state continuously exsists in supersaturated drug solution [17]. Besides, higher PVP molecular weight also leads to increased viscosity of the ASDs, thereby reducing molecular mobility and improving physical stability [34]. Because of the highly hydrophilic nature of PVP, most reported ASDs exhibited a fast dissolution rate at an adequate polymer loading [35, 36]. However, upon storage at humid conditions, PVP can absorb a large amount of water. For example, PVP K30 takes up around 12% of water as the relative humidity (RH) increases from 3 to 33% [37]. As a strong plasticizer, the increased amount of water can lead to a substantial decrease in the T_g, increasing the crystallization propensity of the API. Besides, the presence of water, by perturbing the drug-polymer interaction, can lead to amorphous-amorphous phase separation, inducing the formation of drug-rich and polymer-rich domains [37]. Although such phase separation may not significantly impact the dissolution performance of ASDs (e.g., for APIs with low crystallization propensity) [38], the potential risks of high water uptake in PVP and its ASD need careful evaluation to avoid drug recrystallization upon storage and undesired dissolution performance [39]. In addition, gelation may occur upon dissolving PVP ASD in tablet forms, which retards tablet disintegration [40]. Therefore, additives should be added during the downstream processing of PVP ASDs to faciliate rapid tablet disintegration.

Poly(vinylpyrrolidone-co-vinyl-acetate) (PVPVA) (Fig. 1b), copolymers of vinylpyrrolidone (VP) and vinyl acetate (VA), is another group of widely used polymers in ASDs. The most commonly used grade is PVPVA 64, in which the molar ratio between VP and VA is 6:4. Although carbonyl groups persist in both VP and VA groups, in most reported cases, VP exhibits stronger intermolecular interactions with the APIs than VA [41]. This indicates that the two repeating subunits play different roles in ASD stabilization and dissolution. Upon dissolution, the hydrophilic VP is responsible for rapid ASD dissolution, while the hydrophobic VA can maintain drug supersaturation [42]. This is possibly due to the hydrophobic drug-VA interactions inhibited API crystallization and, thereby, improved *in vitro* dissolution as well as *in vivo* drug absorption. Such an interaction was not directly characterized by the paper, but indirectly revealed by different performances of ASDs prepared with PVPVA, at variable VP/VA ratios. Although PVPVA has a lower moisture sorption tendency than PVP, similar amorphous phase separation occurs during the storage of PVPVA ASDs [43]. However, the strength of drug-polymer interactions dominates such phase separation behavior. For instance, the strong hydrogen bonding between indomethacin and PVPVA is more water-resistant, preventing amorphous phase separation [38]. Another similarity between PVPVA and PVP is that they both exhibit gelation upon tablet dissolution, which can retard disintegration and impair the dissolution [44].

Hydroxypropyl Methylcellulose and Hypromellose Acetate Succinate

Hydroxypropyl methylcelluloses (HPMC) (Fig. 1c), also known as hypromelloses, are propylene glycol ether of methylcellulose, with different fractions of methoxy and hydroxypropyl substitutions. The polymers are used in oral solid dosage forms as a binder, coating agent, and matrix for extended-release tablets [26]. HPMC is less hydrophilic compared to PVP and PVPVA. Therefore, HPMC ASDs usually exhibit a relatively slow dissolution rate, in which the initial drug release mechanism is diffusion-controlled rather than the dissolution of the polymer matrix (or congruent drug-polymer release) [45, 46]. During ASD dissolution, the presence of HPMC can effectively inhibit drug recrystallization [47]. However, its slow dissolution rate retards the drug supersaturation, making it less popular than its derivative—hypromellose acetate succinate (HPMCAS) (Fig. 1d). HPMCAS is synthesized by reacting HPMC with acetic and succinic anhydrides [48]. HPMCAS has three grades, L, M, and H (LG, MG and HG), with increasing acetyl while decreasing succinoyl content [49]. Due to the presence of carboxylic acid groups, the solubility of HPMCAS at neutral pH is substantially higher than that in acidic conditions [50, 51]. However, rapid drug release at neutral pH was most pronounced in ASDs prepared with HPMCAS L grade. This is because of the more hydrophobic nature of HPMCAS MG and HG due to decreasing succinoyl content [49]. Therefore, the HPMCAS LG is considered more favorable due to its faster dissolution rate. In light of physical stability, HPMCAS stabilizes the ASDs via hydrophobic interactions (e.g., acetyl groups of HPMCAS with the hydrophobic moieties of the drug) or by disturbing the drug-drug interactions [16, 52, 53]. Despite the presence of the carboxylic group, few studies observed ionic interaction between basic APIs and HPMCAS. A molecular simulation study revealed that the carboxylic group in HPMCAS tends to form intramolecular interactions with adjacent proton acceptors (e.g., carbonyl group) instead of interacting with the API. [52].

Eudragit®

Eudragit® is a group of polymethacrylate-based copolymers with different substituted groups (Fig. 1e). They are commonly used as film-forming and coating agents [28]. Among all the grades, Eudragit® E, S, and L (EDE, EDS, and EDL) are commonly used in ASDs. EDS and EDL are common enteric coating agents for oral dosage forms, exhibiting high solubility at neutral or weakly basic conditions but are poorly soluble at acidic conditions [28]. In their ASDs, the carbonyl groups act as proton acceptors upon hydrogen bonding to the APIs [54]. EDE, one of the few basic polymers, attracts more attention in the design of ASDs. The basic tertiary nitrogen, with a pK_a of 9.0, acts as an active proton acceptor [55]. When amorphized with acidic APIs, such as ibuprofen, naproxen, and indomethacin, the carboxylic acid group of the API forms ionic interaction with the tertiary nitrogen of EDE, contributing to the improved physical stability of the ASDs [56, 57]. However, the dissolution of EDE ASDs is likely to be pH-dependent. During the dissolution of lacidipine-EDE ASD, fast dissolution followed by supersaturation was realized at pH 1.2, while it almost remained undissolved at pH 6.8 [58]. However, this compromised dissolution performance at neutral pH will not undermine the *in vivo* performance of an ASD prepared with a weakly acidic drug and EDE. If the acidic API completely dissolves in the stomach, the pH increases as the gastric fluid is transferred from stomach to small intestine will not result in drug precipitation [59].

Acidic Polymers: Polyacrylic Acid and Hydroxypropyl Methylcellulose Phthalate

As a large fraction of APIs and new chemical entities in the pipeline are weak bases, acidic polymers can be promising candidates for ASD development. Two typical

examples are polyacrylic acid (PAA) and hydroxypropyl methylcellulose phthalate (HPMCP) (Fig. 1c and f). PAA ($pK_a = 4.5$) is a polymer of acrylic acid. It can form ionic interactions with a variety of basic APIs, such as ketoconazole, trimethoprim, lamotrigine, lumefantrine, and clofazimine [11, 29, 60, 61]. The strong ionic drug-polymer interactions could stabilize the ASDs under "stressful" conditions (i.e., 40°C/75% RH). Besides, PAA is a hydrophilic polymer and therefore usually exhibits a fast dissolution rate. The strong ionic interaction also leads to substantially prolonged drug supersaturation during dissolution [60, 61]. However, the presence of PAA could also lead to a decrease in the microenvironmental pH [52], raising concerns about the chemical degradation of drugs in amorphous state upon storage, especially in humid conditions. Similarly, HPMCP ($pK_a \sim 3.0$), a phthalic acid ester of HPMC, could form ionic interactions with the basic moiety in the APIs [62, 63]. However, as a cellulosic polymer, it is comparatively less hydrophilic. Thus, its dissolution rate is dependent on the polymer loading, where desirable drug dissolution was realized at high polymer concentrations [64].

Soluplus®

Soluplus® is an amphiphilic copolymer comprised of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate [30]. It is specifically designed for hot melted extrusion, as it has low T_g (~70°C) and high stability against thermal stress (Fig. 1g) [65]. At high polymer concentrations, Soluplus® ASDs usually exhibit rapid drug release upon dissolution [66]. From a structural perspective, both the carbonyl groups in vinylcaprolactam and the acetate groups can act as proton acceptors. However, as with PVPVA, hydrogen bonding is more likely to form with the carbonyl group located in vinylcaprolactam rather than the acetate group [67]. The same study highlighted that the strength of such a hydrogen bonding, forming between vinylcaprolactam group and the proton donor, was even stronger than that involving the carbonyl group from VP [68].

Based on the above discussion, there are many cases where adequate physical stability and dissolution performance cannot be simultaneously achieved in an ASD prepared with a single polymer. For example, cellulosic polymers typically reveal a strong crystallization inhibition effect in supersaturated drug solutions while exhibiting a slow dissolution rate. Moreover, while contributing to improved physical stability, the strong intermolecular interactions with the API often compromise ASD dissolution. This phenomenon can be further exacerbated at high drug loading. Therefore, in the following section, the use of a secondary additive in ASD formulations will be discussed in the context of physical stability and dissolution performance.

Secondary Additives

A Second Polymer: Polymer Combination

The ideal polymer for an ASD is expected to physically stabilize the amorphous drug while improving dissolution, specifically facilitating rapid drug release as well as prolonging supersaturation. However, due to the different hydrophilicity of polymers and their molecular interactions with the API, the improvement in physical stability and dissolution may not be achieved simultaneously. Therefore, the use of a polymer combination, with each having a specific function in solid and dissolved states, can be an effective approach (Table II and Fig. 2).

For example, Tian *et al.* identified the role of several polymer combinations, such as PVP or PAA with HPMC or HPMCAS, in the stabilization and dissolution of celecoxib (CEX) ASDs [47, 69]. In the ternary PVP/cellulosic polymer ASDs, PVP formed strong drug-polymer interactions, acting as the stabilizer in the solid state, while the other component, especially cellulosic polymers (i.e., HPMC and HPMCAS), by inhibiting drug recrystallization in the dissolution medium, improved drug dissolution by maintaining drug supersaturation.

In the context of dissolution, the use of polymer combinations can influence both the dissolution rate and drug supersaturation. For example, while cellulosic polymers such as HPMC and HPMCAS contributed to prolonged supersaturation, their relatively less hydrophilic nature may compromise the dissolution rate. The addition of a more hydrophilic polymer, such as PAA, improved the dissolution rate (Fig. 3) [47, 69–71]. Structural modifications within the same class of polymers can also lead to different effects on the performance of an ASD. For instance, HPMCAS LG and HG, with their varying fractions of acetyl, succinoyl, methoxyl, and hydroxypropoxy groups, exhibit different degrees of hydrophilicity [72]. While the binary nifedipine-HPMCAS LG ASD showed greater supersaturation but rapid drug recrystallization, its combination with HPMCAS HG facilitated a fast dissolution rate as well as a higher level of supersaturation. However, the drug–polymer–polymer ratio needs to be carefully determined based on the physical stability and dissolution performance of the ASDs to balance the improvement in stability against the decline in drug supersaturation, and vice versa [47].

Counterions: *In Situ* Salt Formation

The glass transition temperature (T_g) is often considered a key indicator of amorphous solid dispersion (ASD) stability, with higher T_g indicating lower crystallization propensity due to decreased molecular mobility [73, 74]. This is particularly important for APIs with low T_g values,

Table II ASDs Prepared with Polymer Combinations

API	Polymer combinations	Role of different polymers
Celecoxib [47]	PVP/HPMC	• PVP: enabled rapid drug release and inhibited drug recrystallization
	PVP/HPMCAS	• HPMC or HPMCAS: prolonged drug supersaturation
Celecoxib [69]	PAA/HPMC	• PAA: enabled rapid drug release
		• HPMC or HPMCAS: prolonged drug
	PAA/HPMCAS	supersaturation
Indomethacin [70]	Eudragit® EPO/HPMC	• Eudragit® EPO: enabled rapid drug release
		• HPMC: prolonged drug supersaturation
		• The dissolution
Efavirenz [71]	Soluplus®/HPMCAS HG	• Soluplus®: favored rapid drug dissolution
		• HPMCAS HG: stabilizer in solid state
Nifedipine [72]	HPMCAS LG/HPMCAS HG	• HPMCAS LG: enabled a higher degree of supersaturation
		• HPMCAS HG: prolonged drug supersaturation

such as lumefantrine ($T_g = 19.7°C$) and sulfamethoxazole ($T_g = 30.4°C$) [55, 75].

One way to increase T_g and enhance ASD stability is to add counterions during ASD preparation to form salts in the amorphous matrix (Table III and Fig. 4). For example, Duong *et al*. demonstrated that the addition of sulfonate salts to form salts with delamanid effectively stabilized the ASDs under 40°C/75% RH [76]. The addition of organic acids can also improve ASD stability by reducing molecular mobility, as evidenced by increased T_g and α-relaxation time (a measure of molecular mobility) for ketoconazole-PVP ASDs [77]. However, the strong ionic interactions resulting from increased T_g can negatively impact drug-polymer congruent release, a desirable attribute for rapidly generating supersaturated drug solutions upon dissolution. In such cases, a high polymer content may be necessary to achieve a fast dissolution rate. For example, lumefantrine/sulfate/PVPVA ASDs required a drug loading of less than 5% to achieve rapid drug release [75]. Salt formation is a commonly used approach to improving the solubility of poorly water-soluble drugs [78], which can also be applied to amorphous systems. For instance, in celecoxib-Soluplus® ASDs, *in situ* formation of potassium and sodium drug salts substantially enhanced dissolution rate, *in vivo* pharmacokinetics (higher C_{max} and $AUC_{0\text{-}48}$), and physical stability compared to crystalline drugs and binary drug-polymer ASDs [79]. However, it should be noted that the crystallization propensity of the drug salt during dissolution may be even higher than that of the free form (in other words, the formation of an insoluble salt), leading to a rapid decline in the supersaturation level and compromised drug dissolution. For example, both the crystalline drug and salt form were detected in sulfamethoxazole-trimethoprim ASDs during storage and dissolution [55]. Therefore, achieving a balance between improved physical stability and potentially compromised drug dissolution requires careful consideration. Furthermore, to facilitate strong intermolecular interactions, the molar ratio between the drug and counterion must be determined at a specific stoichiometry, usually a 1:1 drug: counterion molar ratio. For example, the most physically stable naproxen-meglumine ASD was only achieved when the two drugs were added at a 1:1 molar ratio [80]. Similar observations have been made in many coamorphous systems, in which two small molecules are stabilized with each other via strong intermolecular interactions [81–83]. These systems are only physically stable when prepared at a specific molar ratio, while the "residual" component exhibits a high crystallization propensity. From a chemical stability perspective, *in situ* salt formation can form molecular interactions with reactive functional groups and prevent chemical decomposition (e.g., hydrolysis) during dissolution and storage [84]. However, the addition of counterions (e.g., acids) can also reduce the solid-state "pH". Under such a scenario, the evaluation of both chemical and physical stability is recommended [76].

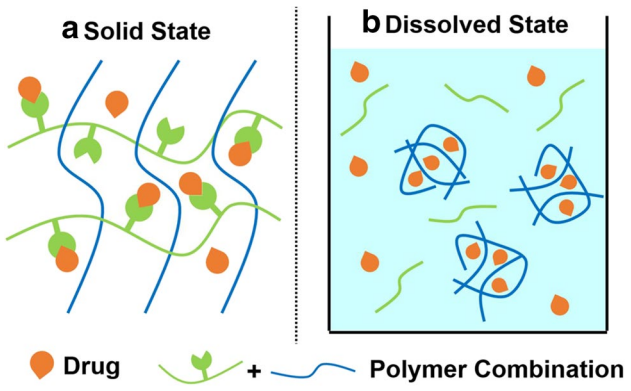

Fig. 2 Schematic of the use of polymer combination in improving ASD physical stability (**a**) and dissolution performance (**b**). In solid state, the polymer (green) stabilizes the drug (orange) by intermolecular interactions, while in the aqueous solution, the other polymer (blue) forms drug-polymer nanodroplets

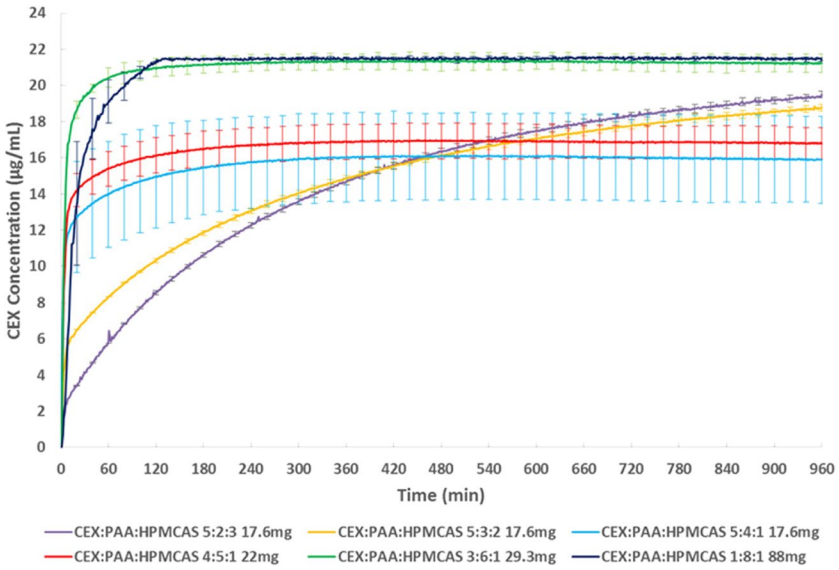

Fig. 3 Dissolution profiles of celecoxib/polyacrylic acid/hydroxypropylmethyl cellulose acetate succinate ternary ASDs. The total mass of dispersion added to the medium to achieve a theoretical CEX concentration of 22 µg/mL is indicated. Reprinted with permission from [69]. Copyright, 2016, ACS Publications

The counterions added to ASDs are typically small molecules. As a result, they can be another API with a synergistic pharmacological effect. This approach can be a promising strategy for simultaneously enhancing the solubility of poorly water-soluble drug combinations [55, 80, 84].

Surfactants

Surfactants are frequently incorporated into ASD formulations as plasticizers to enhance the rheological properties of drug-polymer mixtures during hot melt extrusion or as wetting agents (Table IV) [85, 86]. The addition of surfactants as plasticizers may lead to a decrease in the T_g due to increased molecular mobility. For example, in a study by Yao *et al*., the addition of 10% nonionic surfactants significantly improved the crystal nucleation and growth rate of amorphous nifedipine [87]. Interestingly, the study also showed that the surfactants' structures and hydrophilic-lipophilic balance (HLB) values did not affect drug nucleation and crystal growth, indicating that the surface adsorption of surfactants in the amorphous drug was not the primary cause of drug recrystallization. This adverse effect was also observed in the presence of polymers that the surfactants plasticized the ASDs, as revealed by decreased T_g and the higher crystallization propensity of the APIs [22, 88]. Besides, surfactants have varying effects on drug-polymer miscibility, depending on their physciochemical properties. Using Flory–Huggins model and relevant thermal analysis, Bhanderi *et al*. found that the addition of sodium dodecyl sulfate (SDS) and cationic dodecyl trimethylammonium bromide could reduce the free energy of mixing and enhance the miscibility between griseofulvin and HPMCAS up to two-fold compared to binary drug-polymer systems, which consequently mitigated the recrystallization propensity. However, Pluronic F127® (poloxamer 407) increased the recrystallization propensity as a function of surfactant

Table III ASDs with *In Situ* Salt Formation

API	Polymer	Additives	Advantage
Delamanid [76]	HPMCP	Tosylate, besylate, edisylate, or mesylate	• Reduced crystallization tendency • Almost complete drug release at 25% drug loading • Adequate chemical stability
Ketoconazole [77]	PVP	Oxalic, tartaric, citric, or succinic acid	• Improved physical stability • Rapid drug release and prolonged supersaturation
Celecoxib [79]	Soluplus®	NaOH or KOH	• Enhanced dissolution rate, *in vivo* pharmacokinetics and physical stability
Sulfamethoxazole [55]	Eudragit® EPO PAA	Trimethoprim	• Improved dissolution performance and physical stability
Naproxen [80]	PVP, PVPVA Soluplus®	Meglumine	• Enhanced dissolution rate and improved physical stability
Meloxicam [84]	PVPVA	Meglumine	• Improved physical and chemical stability • Enhanced dissolution rate and prolonged drug supersaturation

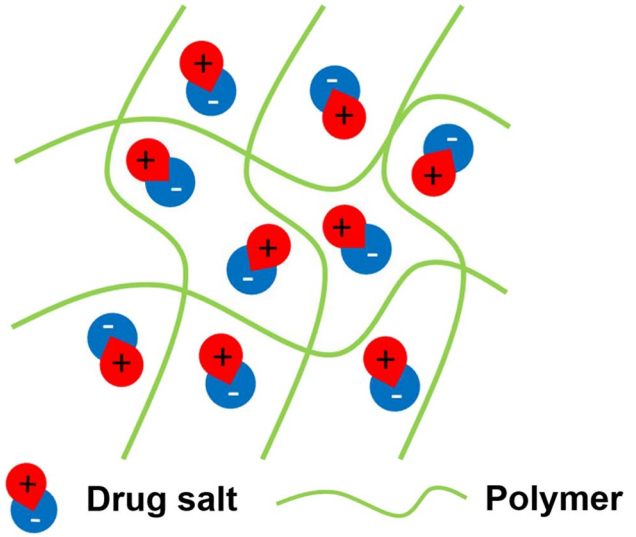

Fig. 4 Schematic of the *in situ* salt formation in ASD (solid-state), where the drug and counterions (either red or blue) form their salt, contributing to improved physical stability of the ASD

concentration and did not improve drug-polymer miscibility [89]. The results from ITZ-Soluplus® ASDs were consistent with those from other studies, wherein the addition of poloxamer 188 led to a decrease in drug-polymer miscibility from up to 40 to < 10%, whereas no such decrease in miscibility was observed in ITZ-HPMCAS ASDs [90]. The difference in results can be attributed to the strong hydrogen bonding between HPMCAS and other components, which not only retained the drug in an amorphous state but also inhibited surfactant crystallization. Since poloxamer has a high crystallization propensity, its crystallization may be the precursor to drug recrystallization, possibly due to the compromised drug-polymer interactions [90]. Therefore, the effect of surfactants on the physical stability of ASDs can result from numerous factors, including (i) the strength of the surfactant's plasticization effect, (ii) the strength of intermolecular interactions between the surfactant and polymer (or drug), and (iii) the relative concentrations of the three components.

The first step in dissolution is the wetting of solid surface [86]. As amphiphilic compounds, surfactants can preferentially absorb at interfaces. X-ray photoelectron spectroscopy has confirmed the surface enrichment of surfactants in ASDs [104]. The surface adsorption of surfactants can reduce surface tension and accelerate wetting upon dissolution [93], leading to a faster dissolution rate. A recent study observed that surfactants improved water ingress upon the hydration of ASD compacts [92]. Besides, at high polymer loading, in which drug-polymer congruent release was not observed during the dissolution of an ASD (tablet), the fast release of the polymer results in the surface enrichment of the hydrophobic drug [8]. The presence of surfactants disrupted the surface enrichment of the hydrophobic API, which promoted the dissolution of drug and polymer. However, in the same study, ASD recrystallization was induced by SDS. As solubility enhancers, surfactants can enhance the apparent drug solubility, resulting in a higher degree of supersaturation (Fig. 5a, illustrated by the formation of drug-surfactant micelles and drug-polymer nanodroplets) [93–95]. However, surfactants can exhibit a drastically different effect on drug supersaturation. For example, during the dissolution of posaconazole-HPMCAS ASD, SDS undermined the crystallization inhibition effect of HPMCAS by interacting with the polymer in the aqueous solution (Fig. 5b, shown by the polymer-surfactant hemimicellar aggregates) [96]. This surfactant-polymer interaction was likely due to hydrophobic interactions between the cellulose chain of HPMCAS and the hydrophobic tails of SDS, as revealed by two-dimensional nuclear magnetic resonance (NMR) including nuclear Overhauser effect spectroscopy (NOESY). In contrast, in nimodipine-PVP ASDs, the presence of sodium taurocholate (NaTC) resulted in improved dissolution by encapsulating the drug in the hydrophobic core of the micelle and, consequently, enhanced the apparent solubility of the drug [97]. In the same study, the authors also showed that the adverse effect of SDS on supersaturation was concentration dependent.

In addition to directly characterizing surfactant-polymer interactions using solution NMR, comparing surfactant critical micelle concentration (CMC) and critical aggregation concentration (CAC)—the surfactant concentration upon the formation of a micellar structure on the polymer chain—provides insight into the competition between drug-polymer and surfactant-polymer interactions in the dissolution medium. The CAC of the SDS-PVP solution was found to be lower than the CMC of SDS [97], indicating that the interaction between the surfactant and polymer overwhelms drug-polymer interactions in the supersaturated drug solution (Fig. 6a). Therefore, SDS can only benefit drug supersaturation above its CAC concentration. Conversely, in the presence of PVP, the CAC value was identical to the CMC of pure NaTC solution, indicating weak surfactant-polymer interaction (Fig. 6b). Similar conclusions were made in other studies that selected surfactant-polymer systems should exhibit a similar CAC value to the surfactant CMC to avoid such competitive interactions [98–100]. Additionally, when surfactants exist in their monomer or hemimicelle states, their long hydrophobic tails may facilitate drug nucleation and subsequent crystal growth by decreasing the interfacial energy at the solid/liquid interface (Fig. 5b, shown as diamond-shaped crystalline drug on the hydrophobic tails of the surfactant or in the solution) [101, 102]. Thus, surfactants with long

Table IV ASDs with the Addition of Surfactants

API	Polymer	Surfactants	Effect of surfactant
NA [22]	PVP-K30, plasdone-S630, HPMC-E5, HPMCAS	Tween 80, docusate sodium, Myrj-52, pluronic-F68, and SDS	• Reduction in T_g • Enhanced dissolution rate
NA [91]	PVP-K30, plasdone-S630, HPMC-E5	Tween 80, docusate sodium	• Surfactants undermined the physical stability of ASDs
Griseofulvin [89]	HPMCAS	SDS, cationic dodecyletrimethylammonium bromide (DTAB), Pluronic® F127	• Pluronic® F127 enhanced the ASD recrystallization propensity • SDS and DTAB increased the miscibility
Itraconazole [90]	Soluplus®, HPMCAS	Poloxamer 188	• The surfactant had poor miscibility with Soluplus®, leading to drug recrystallization upon storage
Ritonavir [92]	PVPVA	SDS, Tween 80, Span 20, or 85	• Improved wetting and drug release of ASD compacts • SDS and Tween 80 improved drug release at drug loading > 30% • SDS promoted recrystallization of the ASD compacts, while increasing miscibility of drug-polymer-water system • Upon hydration, disrupted the formation of interconnected drug-rich phase
Celecoxib [93]	PVPVA	d-α-tocopheryl polyethylene glycol 1000 succinate	• Improved powder wetting • Facilitated the formation of nanoaggregate spray dried particles • Enhanced ASD dissolution
Efavirenz [94]	HPMCP, Soluplus®, Kollicoat IR®	Sucrose palmitate and Tween 80	• Improved dissolution by forming drug-rich particles • Enhanced *in vivo* bioavailability
Felodipine [95]	PVPVA	d-α-tocopheryl polyethylene glycol 1000 succinate	• Facilitate drug-polymer congruent release at high drug loading
Posaconazole [96]	HPMCAS	SDS	• Undermined drug supersaturation and *in vivo* performance of ASD
Nimodipine [97]	PVP	SDS and NaTC	• SDS only improved drug supersaturation at concentration > CAC NaTC prolonged supersaturation independent of concentration
Itraconazole [98]	PVPVA, Soluplus®, HPMCAS HG, Eudragit® L100-55	SDS, d-α-tocopheryl polyethylene glycol 1000 succinate	• Excellent ASD dissolution performance when the polymer did not influence the surfactant CMC
Nifedipine [99]	HPMC, PVPVA	NaTC, Tween 20 and 80, d-α-tocopheryl polyethylene glycol 1000 succinate, SDS, dodecyl trimethyl ammonium bromide	• Reduced drug supersaturation with the presence of surfactant disturbed drug-polymer interaction
Sorafenib [100]	PVPVA	SDS	• SDS impaired drug supersaturation by interacting with the polymer
l-tetrahydropalmatine [101]	HPMCP	SDS, Tween 80, kolliphor RH40, poloxamer 188, and 407	• Drug supersaturation improved with the addition of surfactants with high HLB values • Poloxamer 188 decreased *in vivo* bioavailability, possibly due to promoted drug recrystallization
Celecoxib [102]	HPMCAS	SDS, sodium taurocholate, Triton X100, Tween 80, poloxamer 188	• SDS and Tween 80 promoted the recrystallization of ASD suspension Sodium taurocholate and Triton X100 inhibited ASD recrystallization
Atazanavir [103]	PVPVA	SDS, d-α-tocopheryl polyethylene glycol 1000 succinate, Tween 80, Span®80, Span®85, Span®20, cetrimonium bromide	By decreasing the T_g, surfactant facilitated congruent drug-polymer release at relatively high drug loading

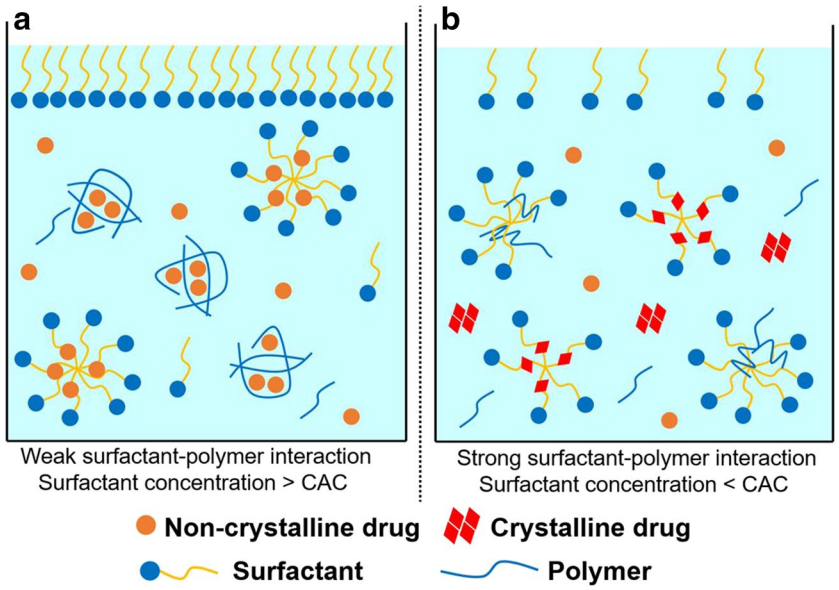

Fig. 5 Role of surfactants on drug supersaturation, when the surfactant has a weak interaction with polymer at its concentration > CAC (**a**), and in the presence of strong surfactant-polymer interaction at surfactant concentration < CAC (**b**)

hydrophobic tails, featured by low hydrophilic-lipophilic balance (HLB) value, can accelerate drug nucleation [101]. This effect can be exacerbated in a supersaturated drug solution, where the dissolved drug has a high recrystallization propensity. Ionic surfactants, such as SDS, may form insoluble drug-surfactant precipitates [105, 106]. For instance, during the dissolution of ritonavir tablets containing SDS, a poorly soluble amorphous precipitate was formed at a ritonavir (its conjugate acid)/dodecyl hydrogen sulfate molar ratio of 1:2 [107]. Therefore, the use of ionic surfactants in ASD, whether added internally or externally, requires extra attention.

As discussed in the previous section, a high T_g value of an ASD, especially those prepared at a high drug loading, is not a desirable attribute for drug release. Adding surfactants as plasticizers, which reduce T_g, can improve ASD dissolution by enhancing drug-polymer congruent release [93, 95, 103]. Due to the reduction in T_g, the limit of congruency (LoC), which is the drug loading threshold for this congruent release, increases in the presence of surfactants. This presents a potential ASD formulation approach for high-dose APIs.

To summarize, the impact of surfactants on ASD dissolution requires careful evaluation based on four factors: (i) the wettability of ASD particles, (ii) the effect of surfactant on the desupersaturation of drug solution, and (iii) the T_g value and its implication on the LoC. The role of surfactants in the physical stability and dissolution of ASDs is not always appreciated and requires extensive investigation both in solid and solution states.

Magnesium Stearate

Magnesium stearate (MgSt) is a commonly used lubricant to enhance the powder flowability [108]. For amorphous solid dispersions that are formulated as tablets, MgSt is often added to improve powder flow, especially for those prepared by spray drying [109]. Additionally, during the tableting of amorphous pharmaceuticals, lubrication of the die wall can significantly reduce compression-induced drug

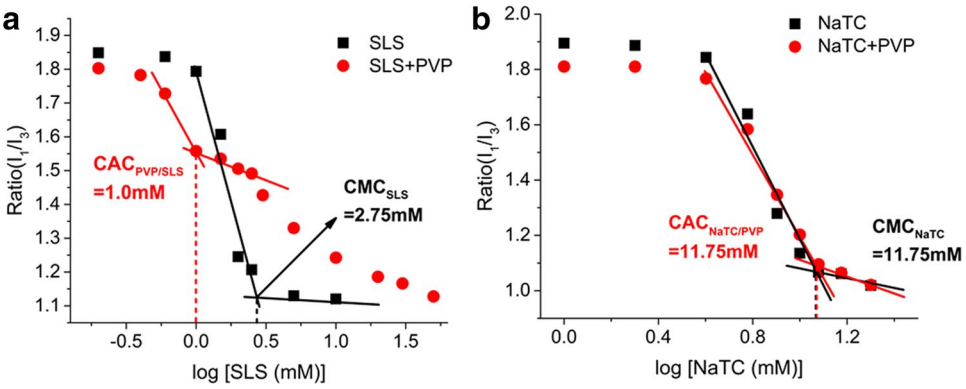

Fig. 6 CMC/CAC values of surfactant and surfactant/PVP (200 µg/mL): **a** Sodium dodecyl sulfate (labeled as SLS); **b** Sodium taurocholate. Reprinted with permission from [97]. Copyright, 2018, ACS Publications

recrystallization [110]. However, recent studies have revealed concerns with the use of MgSt in product stability and dissolution performance. Although MgSt is physically mixed with the powder, its basic nature can increase the solid-state "pH" of the blend [111]. This may cause salt disproportionation and cocrystal dissociation, where crystalline complexes can transform back to free forms through solid-state reactions in the presence of moisture and vigorous processing [112–115]. In this interaction, magnesium ions can interact with acid counterions (or coformers), leading to the formation of crystalline phases of stearic acid and API (free base). In a case study, MgSt was found to accelerate the recrystallization of ITZ-PVPVA ASD, with the hydrophobic environment of MgSt facilitating drug nucleation and crystal growth [116]. Considering the acidic nature of HPMCAS, it is possible that the presence of MgSt may also perturb the drug-polymer interaction, particularly during storage under highly humid conditions. Thus, caution should be exercised when using MgSt in the formulation of ASDs.

Moreover, MgSt can impede drug dissolution by forming insoluble drug-stearic acid precipitates. For instance, tablets of itraconazole-polyvinylpyrrolidone-vinyl-acetate ASD containing MgSt showed lower drug release compared to those without the lubricant [117]. Upon dissolution in 0.1 N HCl, the triazole moiety of itraconazole hydrogen bonded with stearic acid, resulting in the formation of a crystalline precipitate. However, by replacing the polymer with hydroxypropyl methylcellulose (HPMC), a polymer with a stronger crystallization inhibition effect, the precipitation of itraconazole-stearic acid complex was effectively prevented [118]. Therefore, the selection of external additives, especially ionizable excipients like MgSt, for downstream processing of ASDs should be carefully evaluated based on their potential to form molecular complexes with the APIs.

Inorganic Salt

Despite the hydrophilic nature of polymers used in ASDs, the dissolution of ASD tablets can be impeded by slow disintegration [49]. Hughey *et al*. discovered that salts with a kosmotropic effect, or "salting out" effect, on the polymer significantly improved tablet hydration, while salts with a chaotropic effect, or "salting in" effect, typically did not [119].

The kosmotropic effect of salt was assessed experimentally by measuring its ability to reduce the clouding point of a 1% HPMC solution in accordance with the Hofmeister series [120, 121]. For example, kosmotropic salts like KCl, KH_2PO_4, and $KHCO_3$ substantially lowered the clouding point of HPMC, promoting the dissolution of ITZ-HPMC ASD tablets, whereas the chaotropic salt KI did not improve tablet dissolution (Fig. 7). X-ray microcomputed tomography revealed that the addition of NaCl to the tablet facilitated

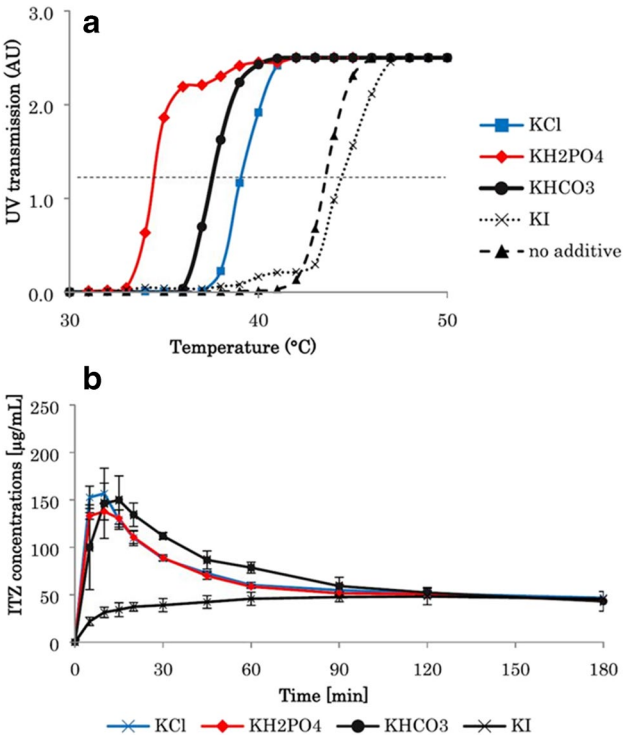

Fig. 7 **a** Cloud point determination of a 1% HPMC in simulated gastric fluid containing (▲) no additive (■) 0.2 M KCl, (◆) 0.2 M KH_2PO_4, and (●) 0.2 M $KHCO_3$ (×) 0.2 M KI. The mean UV transmission values are plotted as a function of temperature ($N=3$). Transmission value at 50% is marked by a dashed horizontal line. **b** Dissolution curves of tablets including 2% KCl, KH_2PO_4, $KHCO_3$, or KI. Amount of ITZ released from tablets (mean ± sd, $N=3$). Tablets were stored under 25°C/0% RH for 24 h before the test. Reprinted with permission from [120]. Copyright, 2020, ACS Publications

disintegration, while Na_2SO_4 did not have the same effect due to the formation of a highly concentrated salt solution inside the tablet that inhibited the dissolution and gelling of the polymer [44]. However, the efficacy of inorganic salts on ASD disintegration may not be a universal approach, as another study found that the addition of $KHCO_3$ and KCl only provided marginal improvement in the dissolution of PVP ASDs [40]. Additionally, this study found that salts did not improve tablet disintegration after moisture adsorption during storage. Therefore, the role of inorganic salts, particularly those with a kosmotropic effect on the polymer, in promoting the disintegration of ASD tablets and their effects on moisture absorption during storage, needs further investigation.

Conclusion

As an increasing number of new chemical entities obtain extremely low aqueous solubility, ASD has become a popular approach not only in enhancing the oral bioavailability of

the final dosage form but also facilitate preclinical research (e.g., pharmacokinetic/pharmacodynamic and toxicity study). However, there are many cases in that excellent ASD physical stability and dissolution cannot be realized using a single polymer. The current paper reviewed the role of polymer combination, *in situ* salt formation and surfactants on the physical stability and dissolution of polymeric ASDs. The use of polymer combinations shows promise in stabilizing amorphous drugs and improving drug release. *In situ* salt formation can effectively enhance the T_g, but its impact on dissolution performance needs to be evaluated in relation to drug loading. The effects of surfactants on the physical stability and dissolution of ASDs are complex and dependent on various factors. Furthermore, the review discusses the influence of externally added excipients, including MgSt and inorganic salts. MgSt can promote ASD crystallization and form insoluble precipitates during tablet dissolution. Kosmotropic inorganic salts have the potential to accelerate the disintegration of ASD tablets; however, the broad applicability of this approach requires further investigation.

Author Contribution The writing, reviewing, and editing of the review paper are assigned to the authors as follows:

Jinghan Li: introduction, sections of polymer combination, counterions, surfactants, and inorganic salts.

Yihan Wang: sections of the commonly used polymers in ASDs.

Dongyue Yu: writing of abstract, introduction and conclusion, sections of surfactants, MgSt, inorganic salts, and overall reviewing and editing of the paper.

Declarations

Conflict of Interest The authors declare no competing interests.

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