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REVIEW

Advances in coamorphous drug delivery systems ☆

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Abstract In recent years, the coamorphous drug delivery system has been established as a promising formulation approach for delivering poorly water-soluble drugs. The coamorphous solid is a single-phase system containing an active pharmaceutical ingredient (API) and other low molecular weight molecules that might be pharmacologically relevant APIs or excipients. These formulations exhibit considerable advantages over neat crystalline or amorphous material, including improved physical stability, dissolution profiles, and potentially enhanced therapeutic efficacy. This review provides a comprehensive overview of coamorphous drug delivery systems from the perspectives of preparation, physicochemical characteristics, physical stability, *in vitro* and *in vivo* performance. Furthermore, the challenges and strategies in developing robust coamorphous drug products of high quality and performance are briefly discussed.

Abbreviations: API, active pharmaceutical ingredient; T_g, glass transition temperature; RH, relative humidity; HME, hot melt extrusion; DSC, differential scanning calorimetry; PXRD, powder X-ray diffraction; D_c, relative degree of crystallization; LFRS, low-frequency Raman spectroscopy; NMR, nuclear magnetic resonance; FT-IR, fourier transform infrared spectroscopy; MTDSC, modulated temperature differential scanning calorimetry; LLPS, liquid–liquid phase separation; IDR, intrinsic dissolution rate; C_{max}, maximum plasma concentration; AUC, area under plasma concentrations-time curve; T_{max}, time of maximum plasma concentration; P-gp, P-glycoprotein; BCS, bio-pharmaceutics classification systems; C_{ss}, plasma concentration at steady state; HPLC, high performance liquid chromatography; UV, ultraviolet spectroscopy; DVS, dynamic vapor sorption; TGA, thermogravimetric analysis; SEM, scanning electron microscope

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1. Introduction

With the development of high-throughput screening technology, an increasing number of new active pharmaceutical ingredients (APIs) have been discovered[1,2]. Since there has been an increase in the structural complexity of drug candidates, 75% of new drug candidates have shown the problems of poor aqueous solubility and low bioavailability, seriously affecting their clinical efficacy[3]. The problems of delivering poorly water-soluble drugs have been addressed by several established and emerging strategies such as cyclodextrin inclusion, microemulsion, nanocrystals, cocrystals, amorphous dispersions, etc[4]. Among these strategies, the amorphization of poorly water-soluble drugs has become one of the most effective approaches to improve their solubility and dissolution, and thus enhance drug bioavailability[5]. Compared to their crystalline counterparts, amorphous solids lack the long-range order of molecular packing and have higher internal energy[6]. Therefore, from the thermodynamic perspective, amorphous pharmaceutical solids are unstable and tend to crystallize over time. Once amorphous drugs crystallize, their advantages will be negated. Therefore, it is crucial to maintain the physical stability of amorphous pharmaceutical solid during the manufacturing process and storage.

Polymer-based amorphous solid dispersions have been widely used to stabilize amorphous material and enhance oral bioavailability for poorly soluble compounds over crystalline APIs[7]. As described in several reviews, the polymer-based amorphous solid dispersion also has its limitations. Many polymeric carriers are hygroscopic which might absorb water to plasticize the system and thus increase the molecular mobility of APIs to crystalize[8,9]. In addition, the increased volume of final product may cause a problem for a high-dose drug formulation[10,11]. Furthermore, some polymers with low glass transition temperatures might accelerate rather than inhibit crystallizations of amorphous solids dispersions[12–15].

In the past decade, instead of using macromolecules such as polymers, mixing specific low molecular weight co-formers with APIs at the molecular level has been developed as an alternative approach to stabilize the amorphous form and enhance the dissolution profiles of poorly water-soluble drugs. This coamorphous system is characterized as a single phase amorphous solid system composed of binary or multi-components[16,17]. Based on the selection of co-formers, coamorphous systems can be categorized into drug-excipient and drug-drug coamorphous systems (Fig. 1). In drug-excipient coamorphous systems, the excipients can be urea, sugars, nicotinamide, amino acids and carboxylic acid, etc. In particular, amino acids have been extensively used as co-formers in coamorphous system to enhance physical stability and dissolutions. For instance, the use of arginine as a co-former can effectively stabilize amorphous indomethacin, leading to a 200-fold increase in the intrinsic dissolution rate in comparison with the pure crystalline form[18]. In the drug-drug coamorphous systems, two drug components can often effectively stabilize each other in the amorphous state, which could provide desired physical stability and dissolution profiles at very high drug loadings. More importantly, the use of two pharmacologically relevant drugs has potential benefits to achieve the synergistic effect of combined therapy[19].

In this review, we will focus on recent developments in the preparation and physicochemical properties of coamorphous systems. Conventional and newly emerging techniques for manufacturing and characterizing coamorphous solids will be systemically described. Then, the following parts of this review will discuss the different aspects in the development of co-amorphous formulations, including physical stability, *in vivo* and *in vitro* performance.

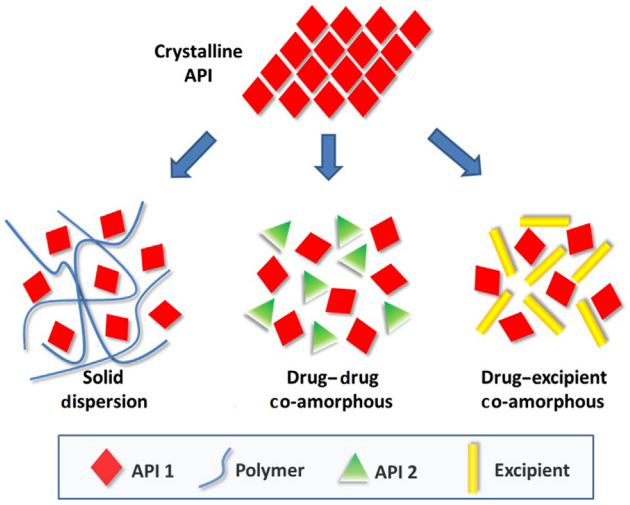

Figure 1 Classification of amorphous mixtures based on the co-formers.

2. Preparation of coamorphous formulations

Selecting an appropriate approach to prepare coamorphous formulations is crucial to achieve a satisfactory performance of the final products. Typically, properties of drug substances and excipients both influence the selection of preparation methods. Furthermore, coamorphous formulations prepared by different approaches could exhibit significant differences in their physical stability and dissolution performance. According to the formation mechanisms, the coamorphous materials can be generally produced *via* mechanical milling, solvent evaporation and melt quenching (Table 1)[11].

2.1. *Milling*

Milling is a well-known technique to produce the disordered pharmaceutical material as a consequence of the mechanical activation. From the molecular packing perspective, crystalline materials could lose their long-range crystallographic periodicity by introducing mechanical stress that is sufficient to create crystal defects[20,21]. The kinetics of transition from crystalline to amorphous state strongly depends on the milling conditions. During the milling process, there is a kinetic competition between mechanically induced amorphization and thermodynamically driven re-crystallization. Sometimes conventional ball milling is not efficient enough to produce amorphous materials due to an increase temperature during the milling process, which may potentially enhance re-crystallization. Given the importance of milling temperature, conducting milling at low temperatures promotes the formation of amorphous materials while avoiding fast re-crystallization.

Löbmann et al.[18] carried out a milling study at the cold room temperature (6 °C) to produce the stable coamorphous systems composed of indomethacin or carbamazepine with amino acids. Recently, using liquid nitrogen as a coolant, cryo-milling has received considerable interest in producing coamorphous formulations[16,22–24]. At the cryogenic temperature which is far below the

Table 1 Dissolution performance of coamorphous systems.

Coamorphous system	Preparation method	Dissolution method	Formation mechanism	Dissolution behaviors	Ref
Naproxen (NAP)–cimetidine (CIM)	Ball milling	IDR	π–π interaction	• 4 and 2-fold increase compared with the crystalline NAP and CIM • Synchronized release	75
Indomethacin (IMC)–naproxen (NAP)	Melt quenching	IDR	Hydrogen bonding interaction	• 7.62 and 1.16-fold increase compared with the crystalline and amorphous IMC • 1.37-fold increase compared with the crystalline NAP • Synchronized release	84
Simvastatin (SIM)–glipizide (GPZ)	Cryogenic milling Ball milling	Powder dissolution	Intimate mixing	• No improvement for SIM in amorphous/coamorphous/amorphous physical mixture compared with the crystalline form • Improved dissolution in coamorphous mixtures/amorphous physical mixture compared with the crystalline GPZ	22
Carbamazepine (CBZ)–amino acids	Ball milling	IDR	Hydrogen bonding interaction π–π interaction	• CBZ-tryptophan (1:1), CBZ-phenylalanine-tryptophan (1:1:1), CBZ-arginine-tryptophan (1:1:1) coamorphous mixtures show 1.08-, 1.20-, and 1.38- fold increase compared with the crystalline CBZ • Slightly increase of coamorphous mixtures in intrinsic dissolution rates	18
Indomethacin (IMC)–amino acids	Ball milling	IDR	Hydrogen bonding interaction π–π interaction	• IMC- arginine (1:1) and IMC-arginine-phenylalanine (1:1:1) coamorphous mixtures show approximately 200-fold increase compared with the crystalline IMC • IMC- phenylalanine(1:1) and IMC- tryptophan(1:1) coamorphous mixtures show 3 and 1.5-fold increase compared with the amorphous IMC • 2-fold increase in IMC-tryptophan-phenylalanine (1:1:1) coamorphous mixture compared with the amorphous IMC	18
Repaglinide (REP)–saccharine	Solvent evaporation	Powder dissolution	Hydrogen bonding interaction	• Faster dissolution profile of REP in coamorphous mixtures compared with the physical mixtures and the crystalline REP	97
Ritonavir (RIT)–indomethacin (IMC)	Solvent evaporation	Powder dissolution	Intimate mixing	• 4.30, 5.23, and 7.69-fold increase in coamorphous mixtures at the molar ratios of 1:1, 1:2 and 2:1 compared with the crystalline RIT(for the first 30 min in powder dissolution)	79
Lurasidone HCl (LH)–saccharine	Solvent evaporation	IDR	Hydrogen bonding interaction	• 5.6-fold increase in coamorphous mixture compared with the crystalline LH • Initial fast dissolution behavior of amorphous drug followed by a significant reduction	64
Indomethacin (IMC)–arginine	Spray drying	Tablet and powder dissolution	Hydrogen bonding interaction	• Immediate release of the tablet by erosion method • Same dissolution result is observed after 12-months storage sample at 40°C in a desiccator over silica gel	39
Clozapine (CLZ)–carboxylic acid	Solvent evaporation.	Tablet dissolution	Hydrogen bonding interaction	• Improved dissolution in coamorphous mixture (95% in 20 minutes) compared with the crystalline CLZ (56%) • CLZ-tartaric acid coamorphous system shows the highest dissolution rate, followed by CLZ-oxalic acid and CLZ-citric acid amorphous systems	104
Glipizide (GPZ)–atorvastatin (ATV)	Cryomilling	Tablet dissolution	Intimate mixing	• GPZ-ATV coamorphous mixtures at 1:1, 1:2, and 2:1 molar ratios show 2.63, 3.53 and 2.42-fold increase compared with the crystalline ATV(for the first 90 min in tablet dissolution) • GPZ-ATV coamorphous mixtures with 1:1, 1:2, and 2:1 molar ratios show 1.57, 2.11, and 1.45-fold increase compared with the amorphous ATV	23
Glipizide (GPZ)–atorvastatin (ATV)	Cryomilling	Powder dissolution	Intimate mixing	• Coamorphous mixtures in the molar ratios of 1:1, 1:2, and 2:1 show 3.18, 1.99, 5.50-fold increase compared with the crystalline GPZ(for the first 90 min in powder dissolution) • Coamorphous mixtures with 1:1, 1:2, and 2:1 molar ratios show 1.53, 1.02, and 2.83-fold increase compared with the amorphous GPZ	23

Table 1 (*continued*)

Coamorphous system	Preparation method	Dissolution method	Formation mechanism	Dissolution behaviors	Ref
Lurasidone HCl–repaglinide (REP)	Solvent evaporation	IDR	Intimate mixing	• No dissolution improvement	105
β-Azelnidipine (AZE)–maleic acid (MA)	Solvent assisted/ neat grinding	Powder dissolution	Hydrogen bonding interaction	• Coamorphous with 1:2 molar ratio shows faster dissolution compared with the crystalline AZE and physical mixture	94
Olanzapine (OLZ)–carboxylic acids	Solvent evaporation	Film dissolution	Hydrogen bonding interaction	• Almost complete dissolution of the coamorphous film within 10 min, whereas the pure crystalline OLZ film dissolves 55.34 % at 35 min	106
Sulfamerazine (SMZ)–deoxycholic acid (DA)/citric acid (CA)/sodium taurocholate (NaTC)	Cryomilling	Disk and powder dissolution	Hydrogen bonding interaction (SMZ-NaTC/DA) No molecular interaction (SMZ-CA)	• SMZ-DA coamorphous shows the worse dissolution compared with the crystalline SMZ • SMZ-CA coamorphous mixture shows improved disk dissolution compared with the physical mixture and crystalline SMZ • SMZ-NaTC coamorphous shows improved disk and powder dissolution compared with the physical mixture and crystalline SMZ	24
Nateglinide (NAG)–metformin HCl (MH)	Ball milling	Powder dissolution	Hydrogen bonding interaction	• Physical mixture shows a higher release profile(49.65% over 60 min) than crystalline and ball milled NAG, while coamorphous mixture exhibits superior release profile than physical mixture • 95% drug release is observed in both crystalline and coamorphous MH	107
Indomethacin (IMC)–arginine (ARG)	Ball milling	IDR	Hydrogen bonding interaction	• 200-fold dissolution enhancement compared with the crystalline IMC	83
Valsartan (VAL)–amino acid	Vibrational ball milling	IDR	Hydrogen bonding interaction	• Improved dissolution in coamorphous mixture compared with the crystalline VAL in different pH media • An approximately 1000-fold increase in both the solubility and IDR is observed in the ternary mixtures in pure water.(VAL- histidine -arginine, VAL-arginine-lysine, VAL- histidine-lysine ternary mixtures at the molar ratios 1:1:1)	108
Irbesartan (IRB)–atenolol (ATE)	Hand grinding	IDR	Hydrogen bonding interaction	• 35-fold increase compared with the crystalline IRB and the physical mixture	109
Curcumin (CUR)–piperazine	Liquid assisted grinding	Powder dissolution	Hydrogen bonding interaction	• Coamorphous mixtures show a faster dissolution rate compared with the pure drugs	26
Loratadine (LOR)–citric acid (CA)	Solvent Evaporation	Powder dissolution	Hydrogen bonding interaction	• Improved dissolution in coamorphous mixture compared with the crystalline and amorphous LOR	110
Ibuprofen (IBU)–nicotinamide (NIC)	Solvent evaporation	Powder dissolution	Hydrogen bonding interaction	• Improved dissolution in coamorphous mixture compared with the co-crystal and crystalline IBU • Coamorphous mixture shows a similar dissolution profile as amorphous IBU	111
Chloramphenicol–amino acid	Freeze drying	Powder dissolution	No molecular interaction	• Improved dissolution in all coamorphous mixtures compared with the crystalline drug	112
Indomethacin (IMC)–arginine (ARG)	Spray drying	Powder dissolution	Ionic interaction	• Improved dissolution at different pH compared with both the crystalline IMC and the physical mixture • Coamorphous mixture with 1:2 molar ratio has higher release profile than 1:1 molar ratio	38
Atenolol (ATE)–hydrochlorothiazide (HCT)	Cryogenic milling	IDR	Hydrogen bonding interaction	• 12.5 and 2.2-fold increase compared with the crystalline HCT and physical mixture	16
Indomethacin (IMC)–lysine	Ball milling	IDR and powder dissolution	Ionic interaction	• 90 and 38.6-fold increase compared with the crystalline and amorphous IMC • 2.8-fold increase compared with the crystalline salt	113
Curcumin (CUR)–folic acid dehydrate (FAD)	Liquid assistant grinding	Powder dissolution	Hydrogen bonding interaction	• After 1 h, 4.38-fold increase compared to crystalline CUR form I (for the first 60 min in powder dissolution)	25

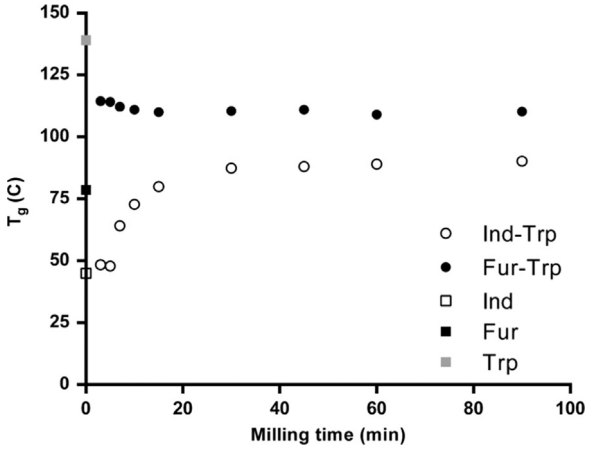

Figure 2 Evolution of the glass transition temperature (T_g) of indomethacin (Ind)-tryptophan (Trp) and furosemide (Fur)-tryptophan (Trp) ball milled for 3, 5, 7, 10, 15, 30, 45, 60, and 90 min, respectively. (Adapted from the Ref. 27 with the permission. Copyright © 2015 American Chemical Society).

glass transition temperature (T_g) of most pharmaceuticals, materials become quite brittle and the formation of disordered form is thus favored upon mechanical activation. In addition, the risks of heat induced degradation and recrystallization can be avoided during the process of cryo-milling[16,21]. In the study of coamorphous simvastatin-glipizide, either cryogenic milling or ball milling could convert the crystalline mixture into the coamorphous form, while ball milling was not able to produce the individual amorphous drug substance[22]. Furthermore, some studies demonstrated that the formation of coamorphous can be facilitated by introducing a small amount of solvent into the milling process[25,26]. For instance, Pang et al.[26] found that curcumin-piperazine coamorphous system can be produced *via* ethanol-assisted grinding but not by neat grinding. The addition of small amount of ethanol partially dissolved API and excipient, thus increasing the mixing interfaces and promoting the formation of coamorphous materials[26].

Co-milling of two or more component has been demonstrated to be more efficient to produce the amorphous material than the milling of individual components[27]. For instance, in the study of milling drugs–tryptophan mixtures, Jensen et al.[27] observed that the binary crystalline mixture was easier to convert to amorphous than the pure drug or tryptophan, indicating that milling of two components simultaneously facilitates the amorphization process. They also proposed that the change of T_g position of drug-amino acid mixtures during the milling could be used to identify the formation mechanism of coamorphous system[27]. As shown in Fig. 2, the T_g of indomethacin–tryptophan system increases upon milling, indicating that indomethacin became amorphous first and the crystalline tryptophan was gradually dissolved in the amorphous indomethacin upon milling. However, in the case of the furosemide-tryptophan mixture, coamorphous was formed by furosemide being dissolved into amorphous tryptophan, as suggested by the decline of T_g during the milling process[27].

It is important to note that the milling method can sometimes produce the highly defective crystals rather than the real amorphous solids[28]. Crystal defects could promote the nucleation and the crystal growth in amorphous solids[29]. Amorphous solids prepared *via* the milling method is often less physically stable compared to those prepared by spray drying or melt quenching, which can be attributed to the heterogeneous relaxation of the milled amorphous solids and the presence of a high proportion of nuclei[30–32].

2.2. *Solvent evaporation*

The approach of solvent evaporation has also been extensively studied for preparing coamorphous formulations[33–35]. In this approach, crystalline drugs or excipients are primarily dissolved into a solvent, followed by the rapid evaporation of the solvent and precipitation of the remaining solids to form the coamorphous formulations. The solubility of drug substances and excipients in the selected solvent is of great importance to the particle sizes, physical stability and dissolution behavior of coamorphous solids prepared by solvent evaporation. The solvent removal rate and the temperature during evaporation process are also critical for yielding coamorphous formulations with a desirable pharmaceutical performance[36,37].

A spray drying process can be generally separated into two steps, *i.e.* atomization step and drying step. The former step mainly involves with the spraying of a suitable solution of APIs into a heated chamber under control of droplet size and spray rate. The latter step refers to an outward movement of the solvent from droplets to yield dry particles. For the spray drying process, desired particle size distributions and morphologies can be often achieved by controlling the spray solution composition, droplet formation, and drying rates[36]. Spray drying has the additional advantages for easily scaling up and continuous manufacturing[38–40]. However, the preparation of coamorphous formulations by spray drying is commonly limited by the difficulty in selecting a suitable solvent for all components (drugs or excipients). In addition, residue solvent is likely to induce the recrystallization of coamorphous formulations. Considering the use of organic solvents may pose safety concerns during the production, Ojarinta et al.[38] prepared ibuprofen-arginine and indomethacin-arginine coamorphous formulations *via* spray drying by using water as the solvent. Recently, Chen et al.[41] reported the significant surface enrichment and depletion of the drugs in spray dried amorphous solid dispersion. It is conceivable that the surface compositions of spray dried coamorphous particles could also be different from the bulk compositions if the solubility or relative diffusion rates of the components are significantly different.

Lyophilization, also known as freeze drying, can be also used to prepare coamorphous solids with low-density and porous nature. Zhu et al.[42] successfully prepared high-dose zwitterionic compound ofloxacin-amino acid coamorphous solids through lyophilization. In particular, due to the strong drug–excipient ionic interactions and π–π stacking, ofloxacin lyophilizated with tryptophan at a 1:1 molar ratio in coamorphous form exhibited over 10-times solubility increase compared to its crystalline counterpart[42]. The ofloxacin-tryptophan coamorphous solids were physically and chemically stable for more than 2 months at 40 °C/75% RH[42].

2.3. *Melt quenching*

Apart from milling and solvent evaporation methods, the melt quenching technique is also one of the commonly used methods for converting crystalline physical mixtures to coamorphous solids[43–46]. In this method, APIs and/or excipients are first heated to a molten liquid state in which the components undergo intensive mixing. The resulting liquid is then rapidly cooled to well below the melting temperatures of the compounds to avoid

crystallization. The rapid cooling rate prevents the nucleation and crystal growth, thus facilitating the formation of amorphous solids. Hoppu et al.[47] reported that the 50/50 (*w/w*, %) citric acid-paracetamol coamorphous solids prepared by melt quenching remained the amorphous form at least two years in dry ambient conditions. It has been demonstrated that amorphous solids prepared *via* melt quenching might exhibit a better physical stability than those prepared *via* milling[48]. One interpretation is that the milling may not be able to completely remove trace amount of residual crystals which can serve as seeds to promote the crystallization[49]. The additional relaxation process observed in the milled sample is probably connected with it recrystallization behavior in comparison with the melt quenched products[32].

Hot melt extrusion (HME), initially adopted from the plastic industry, is a single continuous process that melts or softens materials at elevated temperatures followed by downstream cooling to produce solidified phase[50,51]. Consisting of a temperature-controlled barrel and rotating screws to mix and feed materials through a die, a hot melt extruder is particularly useful for developing amorphous solid dispersions from the laboratory scale to future scale-up or commercialization. Compared to the large-scale spray drying process, there is no solvent involved in the process of HME, resulting in a low level of residual solvent in the amorphous extrudates and low risk of solvent-induced recrystallization. For the first time, Lenz et al.[52] prepared the indomethacin-arginine coamorphous solids by using a twin-screw extruder. They found that the coamorphous formulations containing indomethacin in combination with arginine and copovidone showed enhanced dissolution behavior over the formulations with only copovidone or arginine[52]. It is important to note that the physical attributes and pharmaceutical performance of extruded solids can be greatly affected by the HME process conditions including feeding, melting, plasticizing, conveying, mixing, stripping and cooling[50]. Attentions should be paid during the HME process due to the risk of thermal degradation of compounds at high operating temperatures, which are often required to melt drugs and reduce the viscosity of liquid for extrusion. Arnfast et al.[53] reported that the addition of small amounts of polyethylene oxide can effectively reduce the melt viscosity and prevent the phase separation of indomethacin-cimetidine coamorphous formulations, proving the advantages of additives in manufacturing the desired coamorphous formulations.

3. Physicochemical characteristics of coamorphous systems

For understanding the amorphous nature of coamorphous systems, a variety of conventional and emerging techniques have been used to qualitatively and quantitatively characterize their physicochemical properties. In this part, we will mainly focus on some of key physicochemical characteristics of coamorphous systems, including crystallinity, miscibility, molecular interactions and molecular mobility.

3.1. *Crystallinity*

Coamorphous pharmaceutical solids have the tendency to crystallize during the processing or storage. Once the crystallization occurs, the performance of coamorphous formulations can be significantly altered. Therefore, how to determine the degree of crystallinity in a coamorphous formulation has attracted considerable attention in this field. A number of techniques have been utilized to determine the crystallinity of coamorphous formulations[6]. For example, differential scanning calorimetry (DSC) is widely used to analyze the thermal events associated with the transitions between amorphous and crystalline materials[54]. One important parameter used to quantify crystallinity is the change in heat capacity at T_g. However, amorphous formulations prepared by milling methods sometimes lack the clear signals of glass transition[55]. Powder X-ray diffraction (PXRD) is also the one of the well-established techniques to quantify the crystallinity of coamorphous formulations during processing and storage. As shown in Fig. 3, the relative degree of crystallization (D_c) is determined on the basis of the obtained x-ray diffraction

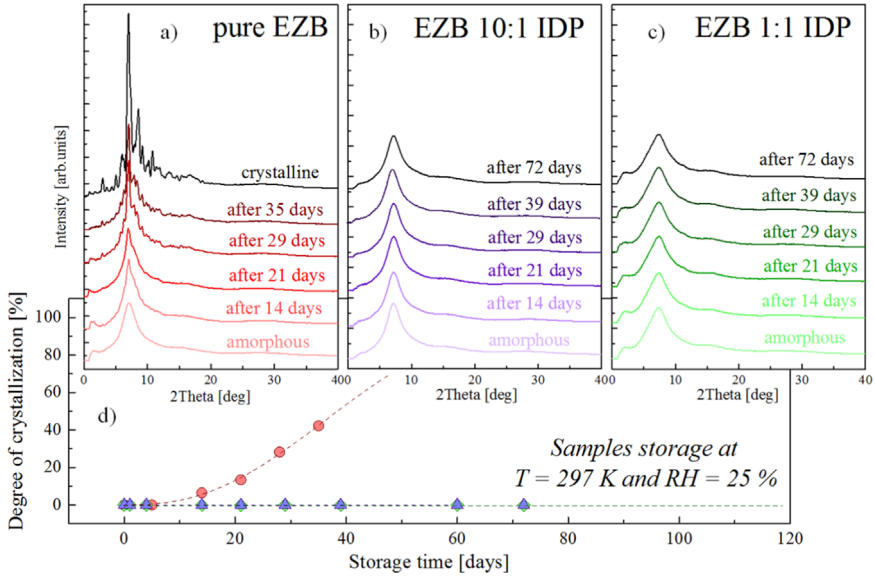

Figure 3 (a) – (c) The representative X-ray diffraction patterns for pure ezetimib (EZB), ezetimib 10:1 indapamide (IDP), and ezetimib 1:1 indapamide measured after specified time period. (d) The relative degree of crystallization D_c of amorphous EZB, EZB 10:1 IDP, and EZB 1:1 IDP as a function of storage time at $T = 297$ K and RH = 25%. (Adapted from the Ref. 45 with the permission. Copyright © 2015 American Chemical Society).

patterns[45]. Here, the value of D_c is calculated as a ratio between the areas under the sharp diffraction peaks of the partially crystallized sample and the crystalline reference sample.

A reliable indicator of amorphous nature of materials is the halo feature in PXRD patterns. Nevertheless, the relatively low sensitivity of conventional PXRD is a major limitation in detecting crystallization of coamorphous formulation at the early stage. With the aid of synchrotron radiation and a two-dimensional area detector, the estimated limit of detection of crystals in their amorphous counterpart matrix has shown a considerable improvement[56,57]. In addition, the low-frequency Raman spectroscopy (LFRS) technique was also reported to be a sensitive approach to determine crystallization of amorphous solids at the very early stages[58]. Recently, the change of real parts of the complex dielectric permittivity obtained from broadband dielectric spectroscopy can be used to characterize the crystallization of amorphous formulations to a certain extent[59,60]. For instance, in the study of physical stability of amorphous probucol in the presence and absence of atorvastatin, the progress of isothermal crystallization is monitored and analyzed in terms of the normalized real permittivity[61].

3.2. *Miscibility*

Miscibility of multi-components in coamorphous formulation is one of the important aspects related to the physical stability. If components in coamorphous formulations are miscible with each other, the effects of stabilizers can be fully exploited and a good physical stability can be achieved[19,62,63]. In general, a clear single T_g of a coamorphous formulation indicates the miscibility of the components in the mixture[64]. In addition, solubility parameters, considered as estimates of molecular similarities, can also be measured for evaluating the miscibility of components in coamorphous formulations. Hildebrand first put forward the concept of solubility parameter and defined it in the term of total cohesive energy[65]. The major limitation of Hildebrand solubility parameter is its insufficient description of solubility behaviors in those systems with polar or specific interactions between components[66]. Subsequently, Hansen proposed a modified approach to determine the total solubility parameter of polar compounds[67]. In this approach, the total solubility parameter consists of the squares of contributions form dispersion, polar, hydrogen-bonding forces[67]. Compared to Hildebrand solubility parameters, Hansen solubility parameters are more appropriate and widely applicable. Another alternative approach to investigate the miscibility of components in amorphous formulations is based on the Flory-Huggins theory combined with calculated solubility parameters from the melting point depression method[68], annealing method[69] or *in silico* method[70]. The Flory-Huggins interaction parameters (χ), which essentially determine the miscibility, can be used to characterize the interactions of components within the blend. A negative or slightly positive value of χ indicates a good miscibility, while a large positive value points to immiscibility[71]. In recent years, several emerging techniques such as fluorescence-based techniques[72], Raman mapping[73] and solid-state nuclear magnetic resonance (NMR) techniques[74] have been introduced to investigate the miscibility of the various components in the amorphous formulations.

3.3. *Molecular interactions*

Characterizing molecular interactions between drugs and co-formers are beneficial for understanding the physical stability of coamorphous systems at the molecular level. Molecular interactions in coamorphous formulations have been extensively investigated by several distinct techniques such as Fourier transform infrared spectroscopy (FT-IR)[16], Raman spectroscopy[23,75] and nuclear magnetic resonance (NMR)[26,27]. With the aid of Raman spectroscopy, Allesø et al.[75] demonstrated the solid-state interaction between the carboxylic acid moiety of naproxen and the imidazole ring of cimetidine, which probably connected to the synchronized release of the two drugs in the binary coamorphous formulation. In the study of the ketoconazole-organic acid coamorphous system, the FT-IR technique has been demonstrated as a sensitive probe to characterize specific interactions between drugs and excipients. For instance, the FT-IR spectrum of ketoconazole–oxalic acid coamorphous exhibits a new absorption band at 1635 cm^{-1}, suggesting the formation of amorphous ketoconazole oxalate (Fig. 4). Very recently, Pang et al.[26] systematically investigated the molecular interaction of curcumin-piperazine coamorphous systems by means of FT-IR, solid-state NMR spectroscopy and modulated temperature differential scanning calorimetry (MTDSC). In this case, piperazine can effectively stabilized the diketo structure of curcumin through the formations of hydrogen bonding interactions between amino group of piperazine and carbonyl group of curcumin[26]. Solid-state NMR spectroscopy is also a very useful tool to study the molecular interactions in coamorphous systems. Yuan et al.[76] have detected and quantified hydrogen bonded species in amorphous indomethacin and indomethacin-based solid dispersion by using the ^{13}C solid-state NMR spectroscopy.

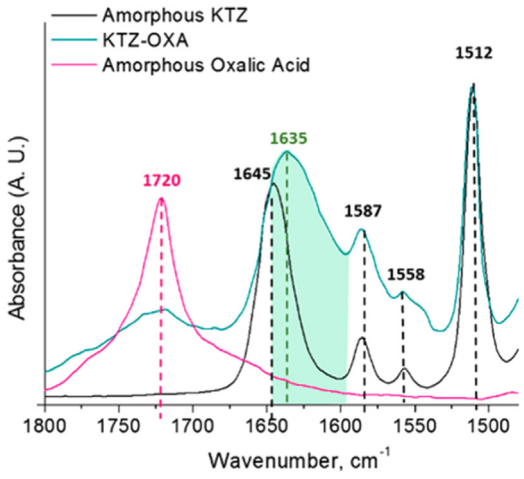

Figure 4 IR spectra of amorphous ketoconazole (KTZ), coamorphous ketoconazole (KTZ) – oxalic acid (OXA) and amorphous oxalic acid (OXA). (Adapted from the Ref. 77 with the permission. Copyright © 2018 American Chemical Society).

3.4. *Molecular mobility*

Molecular mobility is one of the most fundamental factors affecting the physical stability (crystallization) of amorphous systems[78]. The Molecular mobility of amorphous API is mainly investigated by modulated DSC[54] or dielectric spectroscopy[45,77]. In the study of the ezetimib-indapamide coamorphous mixture, the addition of a small amount of indapamid (8.8%, *w/w*) significantly stabilized the amorphous form of ezetimid, which had a strong tendency to crystallize[45]. This is evident from the dielectric

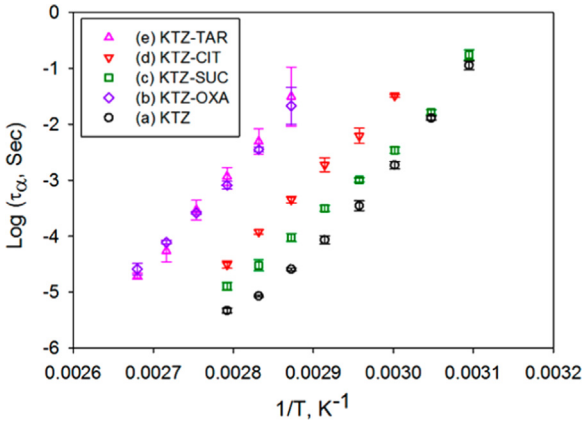

Figure 5 Temperature dependence of α-relaxation times of (a) amorphous ketoconazole (KTZ), (b) coamorphous KTZ-oxalic acid(OXA), (c) KTZ-succinic acid (SUC), (d) KTZ-citric acid (CIT), and (e) KTZ-tartaric acid (TAR). (Adapted from the Ref. 77 with the permission. Copyright © 2018 American Chemical Society).

spectra, where the molecular mobility of this binary system is gradually slowed down with an increase of indapamid contents[45]. In addition, the excellent physical stability of the binary system is also related to its decreasing fragility parameters[45].

Very recently, Fung et al.[77] reported that there are stronger interactions between weakly basic ketoconazole with several organic acids, as translated to the longer structural relaxation times (Fig. 5) and the higher physical stability against crystallization. Molecular mobility and structural factors of the ketoconazole-organic acids binary coamorphous systems have both been demonstrated to contribute to the stabilization effects. Furthermore, the enthalpy relaxation rate of amorphous drugs in a glassy state also reflects the molecular mobility. As shown in Fig. 6, the formation of tranilast (TRL) and diphenhydramine hydrochloride (DPH) coamorphous system can significantly reduce the enthalpy relaxation rates and decrease the molecular mobility compared to the two individual amorphous drugs[46].

4. Physical stability

The essential prerequisite to achieve the desirable physical stability of coamorphous solids is that the two or more components are miscible at the molecular level. Coamorphous systems can be stabilized by several mechanisms including salt formation[38], hydrogen bonding interactions[16], π–π interactions[18], intimate mixing[79] and anti-plasticizing effect[45,77] (Table 1). Generally, the chemical structure of compounds can affect molecular interactions and hence physical stability of coamorphous systems. For instance, naproxen can form a coamorphous system with arginine *via* balling milling while a blend of naproxen and tryptophan could not be fully converted to the amorphous state under the same condition[80]. It was found that a salt formation between the acidic drug naproxen and the basic amino acid arginine, but a lack of interactions in the naproxen–tryptophan system[80]. However, it is worth noting that the existence of intermolecular interactions between the components of coamorphous system is not always necessary for obtaining a desired physical stability. The coamorphous solid of ritonavir and indomethacin prepared by solvent evaporation exhibited a better physical stability compared to the

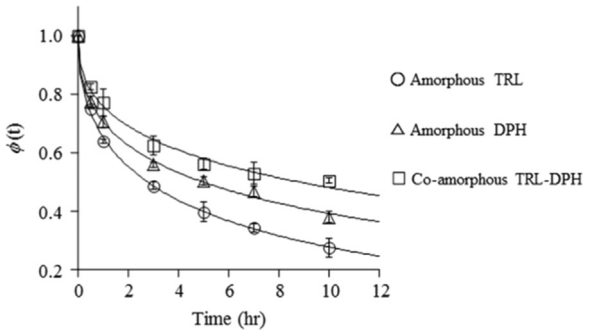

Figure 6 Enthalpy relaxation profiles of amorphous tranilast (TRL) and diphenhydramine hydrochloride (DPH), and coamorphous TRL-DPH (1:1) at $T_g - 20$ °C. (Adapted from the Ref. 46 with the permission. Copyright 2017 © Elsevier)

amorphous drug alone despite the fact that no intermolecular interaction was observed in the FT-IR spectroscopy[79].

The glass transition temperature (T_g) is defined as the critical temperature at which a supercooled liquid falls out of equilibrium and a glass is formed[81]. The T_g of a coamorphous system is usually observed in the temperature range between the T_g of the two individual components. However, it has been reported that a salt could be formed if there are strong ionic interactions present in amorphous mixtures between the drug and the co-formers, and the T_g of the resulting salt could be higher than that of individual components[18,82]. In most cases, an elevated T_g of coamorphous system could correlate with an enhanced physical stability[18,82,83]. But, T_g is not always a reliable indicator of physical stability of coamorphous solids. For instance, the naproxen–indomethacin coamorphous system in 1:1 molar ratio exhibits the highest physical stability under different storage conditions, even though it does not have the highest T_g among the coamorphous mixtures of varying ratios[84]. The higher stability of the coamorphous naproxen–indomethacin at the 1:1 molar ratio compared to the mixtures with other molar ratios can be attributed to the formation of the heterodimer between naproxen and indomethacin, resulting in the enhanced intermolecular interaction[43,84].

The amorphous–amorphous phase separation between two small molecules may occur prior to or during the crystallization process[85,86]. It is important to detect the potential phase separation and inhomogeneity in coamorphous systems which could induce crystallization over time. In the case of indomethacin-citric acid coamorphous system, a clear separation of a single T_g into two T_g values is observed when the weight fraction of citric acid increases above 0.2, an evident indicator of phase separation[87]. However, even a distinctive single T_g is observed for a binary amorphous system, it may not be sufficiently strong evidence of homogeneity[88]. Pajula et al.[89] reported that Fourier transform infrared imaging could be used as an effective tool to investigate the amorphous-amorphous phase separation of coamorphous systems (Fig. 7), whereas the conventional differential scanning calorimetry failed to appropriately detect due to the slow kinetics of phase separation. Very recently, Gniado et al.[90] reported that the natural bile acid surfactant sodium taurocholate can be a promising co-former in coamorphous formulations due to its ability to effectively prevent phase separation as well as recrystallization. Moreover, the addition of small amounts of polymer has also been demonstrated to have the potentials to effectively hinder amorphous-amorphous phase separation in the extrudates of coamorphous materials[53].

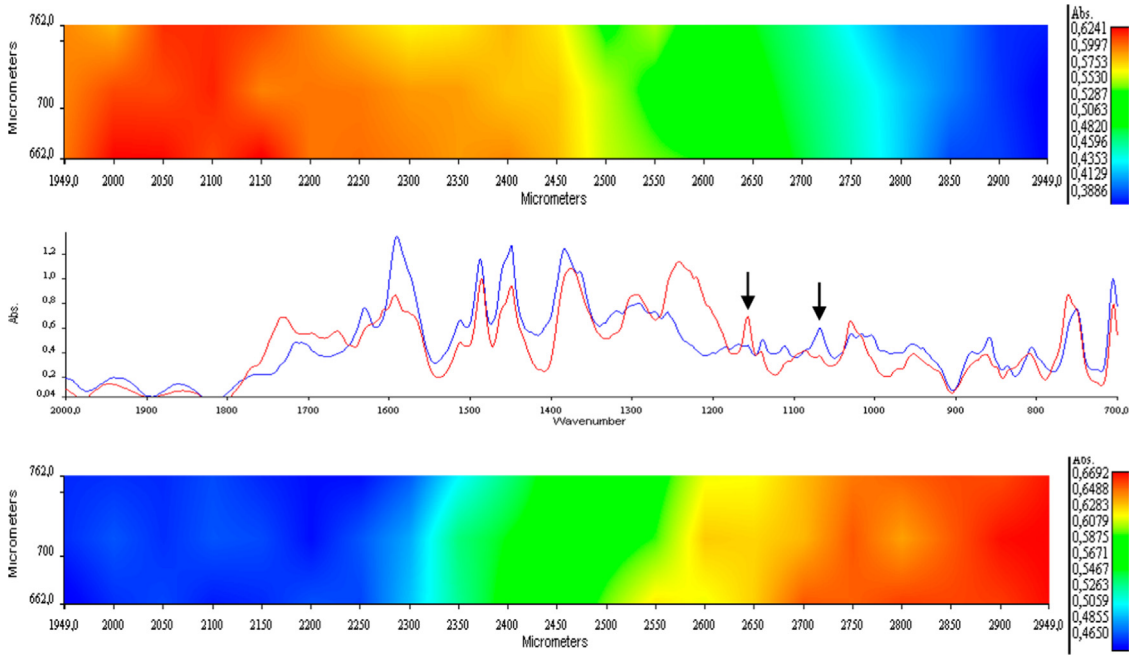

Figure 7 Phase separation for the terfenadine-acetylsalicylic acid coamorphous mixture detected by Fourier transform infrared imaging after 11 days of storage. The upper image illustrates the intensity of the characteristic peak of terfenadine while the lower illustrates the intensity of the characteristic peak of acetylsalicylic acid. The middle image represents the IR images of terfenadine (blue line) and acetylsalicylic acid (red line), the black arrow indicate the characteristic peaks for individual components. (Adapted from the Ref. 89 with the permission. Copyright © 2014 American Chemical Society).

It has been reported in many studies that molar ratio of components in the binary coamorphous systems can significantly affect their physical stability[43,75,91–93]. Typically, the coamorphous systems with stoichiometric ratios of API and co-former are preferred for maintaining the physical stability because the excess component would crystallize over time[43,75,91]. For instance, naproxen-cimetidine coamorphous solids prepared at the 1:1 molar ratio exhibit superior physical stability than that those at a 1:2 or 2:1 molar ratios[75]. When stored for 33 days at 40 °C under dry condition, a halo feature can still be observed in the PXRD pattern for the coamorphous solids in 1:1 molar ratio while trace crystalline naproxen or cimetidine was found in the systems in 2:1 or 1:2 molar ratios[75]. This phenomenon was attributed to the formation of a heterodimer structure *via* the hydrogen bonding interaction between the two drug molecules[75]. Interestingly, hetero-trimer structure has also been reported in several coamorphous systems, resulting in a stable coamorphous system in a molar ratio of 1:2[94,95]. Recently, Bayer et al.[92] systemically investigated the role of naproxen/indomethacin molar ratio in coamorphous physical stability[92]. They found that the naproxen/indomethacin coamorphous solid in a molar ratio of 3:2 (the eutectic composition) showed the highest physical stability, rather than the 1:1 molar ratio for most of coamorphous systems.

Water sorption has been known to decrease the physical stability of polymer-based solid dispersions. Water can act as a plasticizer to decrease the T_g of amorphous solid dispersions and thus increase molecular mobility to accelerate crystallization of amorphous drugs. In addition, sometimes water molecules can disrupt the molecular interactions between a drug and a polymer in an amorphous solid dispersion causing phase separation and eventual crystallization of the drug[9,96]. Several studies have been conducted to evaluate the physical stability of coamorphous solids after exposure to high humidity[35,64,97]. A more systematic work is required to compare the physical stability of coamorphous systems and polymer-based solid dispersions upon water sorption. In some cases, water can be introduced to transform physical mixtures to coamorphous solids. For instance, when the physical mixture of indomethacin and arginine was stored at 75% RH condition, an unexpected formation of coamorphous solid was observed[98]. Since some small-molecule co-formers may have strong tendency to adsorb water[99,100], the impact of moisture absorption on physical stability of those coamorphous systems should be carefully evaluated during the product development process.

Some small-molecules analogues of known polymeric crystallization inhibitors have been used as co-formers to stabilize a variety of amorphous drugs creating coamorphous materials[101]. Nevertheless, the mechanism of crystallization inhibition by small-molecules polymer analogues could be different from those of the polymer based solid dispersions. Compared to the coamorphous systems, in addition to molecular interactions, the segmental mobility of polymer chains relative to host-molecule dynamics is suggested to control its effect on crystal growth in polymer-based amorphous solid dispersions[13]. Despite the additional cost and complexity by introducing a third component into binary systems, the ternary coamorphous systems sometimes show advantages over the binary systems in terms of physical stability[52,80,102,103]. Recently, Ueda et al.[102] prepared a stable ternary coamorphous system composed of carbamazepine, citric acid, and L-arginine. The addition of citric acid and L-arginine as co-formers enabled a formation of salt, which dramatically enhanced the T_g of the coamorphous systems and thus improved their physical stability[102]. Finally, it has been reported that the physical stability of coamorphous solids can be effectively enhanced by mixing with low concentrations of anti-plasticizers due to their excellent glass forming ability[22,45].

5. *In vitro* and *in vivo* performance

5.1. *In vitro performance*

Due to the higher internal energy, the amorphous form of a poorly water-soluble API exhibits higher solubility and a faster dissolution rate than that of its crystalline counterpart. As shown in Table 1, it has been reported in many studies that the dissolution of coamorphous systems show an improvement when compared with the crystalline or amorphous form of individual drugs alone. In coamorphous systems, the enhancement of dissolution can be generally attributed to the so-called "spring and parachute effect"[86]. The "spring" is the higher energy amorphous API that facilitates dissolution and supersaturation of drugs when dissolves along with the other drugs or excipients. Here, supersaturation can be affected by multiple factors such as the exact nature of the dissolution media, the free energy difference between the crystalline and amorphous phases, and release rates of different components, etc[114]. The "parachute" is the co-former that delays nucleation and crystal growth of amorphous API to maintain or prolong the supersaturation over the desirable time period. Therefore, in order to achieve improved dissolution profiles, it is essential to select appropriate co-formers which can effectively inhibit the solution-mediated re-crystallization. It has been reported in many studies that small molecule co-formers which form strong specific interactions with the APIs can maintain supersaturation and help prevent crystallization from solution[25,64]. For instance, the charge-assisted hydrogen bonding interactions between lurasidone hydrochloride and saccharin effectively maintained a desirable level of supersaturation in two dissolution media over 24 h[64]. In contrast, the supersaturation of the neat amorphous lurasidone only was only maintained for 1 h, followed by a rapid decrease in dissolved lurasidone due to the solvent-mediated re-crystallization[64].

Nevertheless, the role of co-former to effectively maintain the amorphous state of API in aqueous environment is not always a prerequisite for the dissolution improvement of co-amorphous systems. For instance, the spray dried ketoconazole-organic acid coamorphous solids has been reported to exhibit higher dissolution rates than the crystalline counterpart, amorphous ketoconazole and their physical mixtures[40]. However, ketoconazole-succinic acid and ketoconazole-oxalic acid coamorphous systems crystallized more readily than pure amorphous ketoconazole did upon contact with water vapor or aqueous phosphate buffer[40]. The dissolution enhancement of the ketoconazole-organic acid coamorphous systems may be explained by an increase in particle surface areas upon particle size reduction and improved solubility of ketoconazole in the diffusion layer due to the decrease in pH[40]. It is noteworthy that a higher strength of acid yields a more pronounced dissolution enhancement[40]. In the study of amino acids-based coamorphous systems, a nearly 200-fold increase of intrinsic dissolution rate has been observed in the indomethacin-arginine binary system and indomethacin-arginine-phenylalanine ternary system in comparison with the crystalline indomethacin[18]. The significantly enhanced dissolution profiles are attributed to the ionization of the indomethacin in the coamorphous salt[18].

Strong intermolecular interactions in the drug-drug coamorphous systems can sometimes lead to a pairwise or synchronized release behavior of the individual components[75,84]. Allesø et al.[75] first reported the synchronized release behavior of two drugs in the naproxen-cimetidine coamorphous system. In this system, the intrinsic dissolution rate of individual drugs exhibited no significant difference, which was believed to be the pair-wise solvation of naproxen and cimetidine molecule during the dissolution. As shown in Fig. 8, a similar synchronized release of naproxen and indomethacin was also observed in their respective coamorphous formulation[84]. As identified by the FT-IR spectroscopy, a heterodimer structure between naproxen and indomethacin was formed *via* the hydrogen bonding interactions between the carboxylic acid groups of both drugs[84]. Lobmann et al.[84] proposed that the formation of heterodimer is responsible for the synchronized intrinsic dissolution of the naproxen-indomethacin coamorphous system at 1:1 molar ratio. In addition, solubility of the co-former also plays an important role in affecting the dissolution rate of API in coamorphous mixtures[18]. The use of a highly soluble co-former in a coamorphous system is suggested to be effective strategy to facilitate the dissolution of poorly water-soluble API. However, excessively high solubility of the co-former might show the negative effect for dissolution of coamorphous systems, where the rapid dissolution of the co-former would result in a lack of stabilizer for amorphous drugs[83].

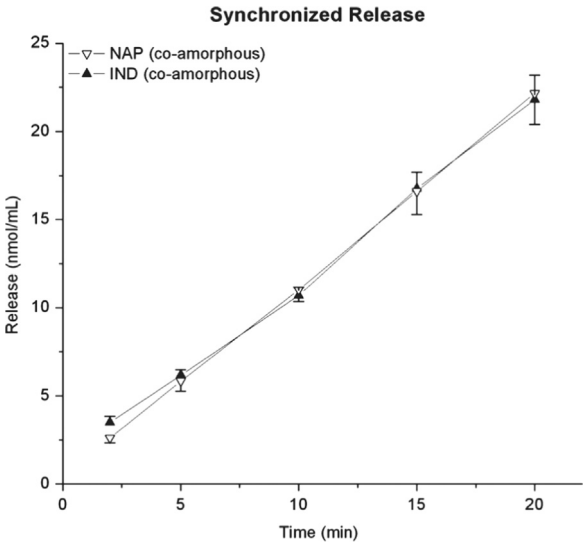

Figure 8 Intrinsic dissolution rate of the coamorphous naproxen (NAP)-indomethacin (IND) binary mixture demonstrates a synchronized drug release[84]. (Adapted from the Ref. 84 with the permission. Copyright © 2011 American Chemical Society).

An elevated and sustained level of drug supersaturation maintained in the fluids of the gastrointestinal tract may have a significant impact on drug absorption[115]. There are a number of literatures describes how the supersaturation of one component is affected by the presence of the other component(s) in a coamorphous system. Unlike dissolution study, the test for investigating supersaturation condition is typically conducted in a non-sink condition. In the study of ciprofloxacin–succinic acid coamorphous system, Paluch et al.[116] found the supersaturation of ciprofloxacin in co-amorphous solids exhibited an approximately 1000-fold increase in comparison with that of crystalline drug. They attributed the tremendous increase in supersaturation to the formation of amorphous salt between drug and succinic acid. While for the co-amorphous systems of atorvastatin calcium and carvedilol or glibenclamide, the impact of co-formers on the supersaturation of atorvastatin calcium was less pronounced[34]. Furthermore, it has been reported that the maximum achievable concentration of a drug can be

Table 2 *In vivo* performance of coamorphous systems.

Coamorphous System	Component (s) Studied	Experiment and Animal Model	Improvement	Ref.
Atorvastatin calcium (ATC)–nicotinamide	ATC	Pharmacokinetic study Rats model Female Wistar rats	2.2-Fold increase in C_{max} and 1.7-fold increase in $AUC_{0–24h}$ compared with the crystalline ATC	122
Curcumin (CUR)–artemisinin	CUR	Pharmacokinetic study Rats model Sprague–Dawley male rats	Oral administration of the co-amorphous formulation provides a high C_{max} value of 1μg/ml at short T_{max} of 30 min and $AUC_{0-\infty} = 24.7$ mg.h/mL for CUR, while no detectable levels in plasma after oral administration of the crystalline CUR	35
Ritonavir (RIT)–quercetin	RIT	Pharmacokinetic study Rats model Wistar strain rats	1.15-Fold increase in AUC, 1.26-fold increase in C_{max}, and 1.46-fold increase in C_{ss} compared with the crystalline RIT	95
Talinolol (TAL)–naringin	TAL	Pharmacokinetic study Rats model Wistar strain rats	1. 1.7-Fold increase in $AUC_{0–24h}$ and 8.6-fold increase in C_{max} compared with the crystalline TAL 2. Permeability of TAL in coamorphous mixture shows 1.27-fold increase compared with the control value	123
Olanzapine (OLZ)–carboxylic acids	OLZ	Pharmacokinetic study Human Model Healthy man	1. 1.31-Fold in $AUC_{0–24h}$ and 1.27-fold in C_{max} compared with the marketed drug OLZ tablet. 2. 1.26-Fold in $AUC_{0–24h}$ and 1.15-fold in C_{max} compared with the marketed drug Zyprexa® velotab	106
Irbesartan (IRB)–atenolol(ATE)	IRB-ATE	Pharmacodynamic study Rats model Female Wistar rats	The percent decrease in systolic blood pressure of coamorphous and physical mixture is $32.1 \pm 0.4\%$ and $23.6 \pm 0.4\%$	109
Loratadine (LOR)–citric acid	LOR	Pharmacokinetic study Rats model Male Sprague–Dawley rats	1. 2.6-Fold increase in C_{max} compared to the crystalline LOR. 2. 2.45-Fold increase in AUC_{0-t} compared to the crystalline LOR	110
Atenolol–hydrochlorothiazide (HCT)	HCT	Pharmacokinetic study Rats model Sprague–Dawley male rats	1. 3.4, 2.6, and 1.4-Fold increase in $AUC_{0–24h}$ compared with the crystalline HCT, amorphous HCT and its physical mixture 2. 7.3, 2.8, and 1.7-Fold increase in C_{max} compared with the crystalline HCT, amorphous HCT, and its physical mixture	16
Curcumin (CUR)–artemisinin	CUR	Pharmacokinetic and antitumor effect study Rats model female athymic nude mice, Sprague–Dawley male and female rats	1. Coamorphous solid shows 2-fold higher bioavailability than CUR-pyrogallol co-crystal (at 200 mg/kg oral dose) 2. Coamorphous mixture shows higher therapeutic effect and inhibits approximately 62% of tumor growth at 100 mg/kg oral dosage of CUR in xenograft models	124

significantly reduced by the addition of a second component dissolving into the medium[117–119]. For instance, Alhalaweh et al.[118] reported that the maximum concentration of each drug in the dispersion containing a 1:1 molar ratio of ritonavir and atazanavir was achieved only 50% of the supersaturation of the single drug dispersion. They also investigated the dispersion containing a 1:1:1 molar ratio of ritonavir, atazanavir and lopinavir. Interestingly, the maximum concentration of each drug decreased to only one third of that achieved for the formulation with the single drug[118]. These observations of the reduction on supersaturation can be attributed to the presence of other miscible drugs that contributed to the decrease in the concentration at which the drugs underwent liquid–liquid phase separation (LLPS). In addition, the transport study of the combinations of these drugs with Caco-2 cells also showed a reduction in the rate of membrane transport rate compared with that of the individual drugs[118]. Similarly, Arca et al.[120] investigated multidrug amorphous solid dispersions of three model anti-HIV drugs in cellulosic polymer matrices and found that the use of multi-drug formulations reduced rather than increased the amorphous solubility of the drugs in certain cases. Here, the partitioning of the drugs to form a solution into the immiscible phase of nanodroplet is suggested to play an important role in the reduction of amorphous solubility. Furthermore, the supersaturation of coamorphous formulations in biorelevant media could depend on the properties of the media as well as the interactions between components[39,121].

5.2. *In vivo performance*

In-vivo study is of great importance to evaluate the bioperformance of pharmaceutical formulations. So far, compared with the *in-vitro* study, limited work has been done on the *in vivo* performance of coamorphous formulations (Table 2). Based on the reported results, the maximum plasma concentration (C_{max}) and area under plasma concentrations-time curve (AUC) of poorly water-soluble drugs showed significant increase in coamorphous systems. For example, Moinuddin et al.[16] systematically investigated the *in vivo* performance of the poorly water-soluble drug hydrochlorothiazide (HCT) in the coamorphous formulation with atenolol (ATE). The C_{max} value of HCT in the coamorphous form was increased by 7.3, 2.8 and 1.7-fold compared to that of crystalline HCT, amorphous HCT and the respective physical mixture, respectively. The $AUC_{0–24h}$ value of HCT was found to be 194 μg · min/mL, which was significantly higher than that of the crystalline form (3.4-fold), amorphous form (2.6-fold) and physical mixture (1.4-fold)[16] (Fig. 9). In addition, a significant reduction in T_{max} of coamorphous formulations was observed[16]. The enhanced bioavailability of HCT in the coamorphous formulation has been attributed to the synergistic effect of amorphized HCT and the water-soluble co-former ATE[16]. In this study, the *in vivo* results are consistent with the observations of the *in vitro* study (intrinsic dissolution experiments). However, it is noteworthy that the advantages of coamorphous formulations observed in the *in vitro* study may not always correlate well with an improved *in vivo* performance[95].

In order to obtain an improved *in vivo* bioavailability, maintaining the supersaturation of coamorphous formulations in the gastrointestinal tract has been suggested to be an effective strategy, particularly for the drugs as glycoprotein (P-gp) substrates. Higher solubility of coamorphous formulations is propitious to form

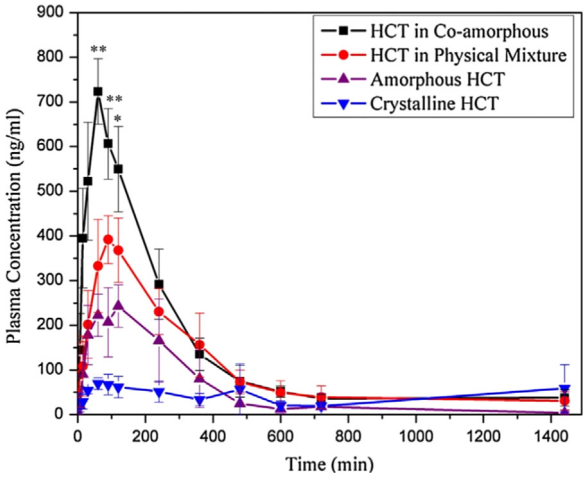

Figure 9 Mean plasma concentration of hydrochlorothiazide (HCT) *vs*. time profile of pure crystalline HCT, pure amorphous HCT, coamorphous of HCT and respective physical mixtures. (Adapted from the Ref. 16 with the permission. Copyright 2017 © Elsevier)

higher luminal concentrations of the drug, probably leading to the saturation phenomenon of efflux transporters of P-gp. Subsequently, the concentration of drug penetrating into the enterocyte is increased, and thus *in vivo* bioavailability is ultimately enhanced. For example, the presence of quercetin along with ritonavir in binary coamorphous systems is suggested to play an important role in the saturation of P-gp transporters and facilitate the permeation of ritonavir and thus increase the absorption[95]. Furthermore, the enhancement *in vivo* bioavailability of a coamorphous system can be reinforced by the use of a P-gp efflux pump inhibitor as a co-former. For instance, with the co-administration of a P-gp efflux pump inhibitor naringin in a coamorphous system, the bioavailability of efflux pump substrate talinolol showed a significant increase. The permeability measurement of talinolol in coamorphous systems has shown a slight increase when compared to that of the pure drug system, indicating that enhanced solubility and permeability are jointly responsible for the *in vivo* bioavailability enhancement[123]. The use of an efflux pump inhibitor as a co-former can also be applied to the class IV drugs in the biopharmaceutics classification system (BCS) which exhibit both poor solubility and permeability. The poor permeability of these drugs is mainly a result of them being the substrates of efflux pumps rather than the properties of size and polarity[125]. Besides the *in vivo* pharmacokinetic performance, the *in vivo* pharmacodynamic activity of coamorphous formulations is of equal importance. Haneef and Chadha first investigated the *in vivo* antihypertensive activity of irbesartan-atenolol coamorphous formulations in the Wistar strain rat model[109]. Following dose treatment at 3 h intervals, the percent decrease in systolic blood pressure detected in the irbesartan–atenolol coamorphous formulations was 32.1 ± 0.4%, while for its physical mixture, it was 23.6 ± 0.4%, indicating the enhanced biological activity of the coamorphous formulations[109].

6. Concluding remarks and future perspectives

In the past decade, coamorphous technology has become a promising approach to physically stabilize amorphous pharmaceuticals, significantly improve their dissolution and thus potentially

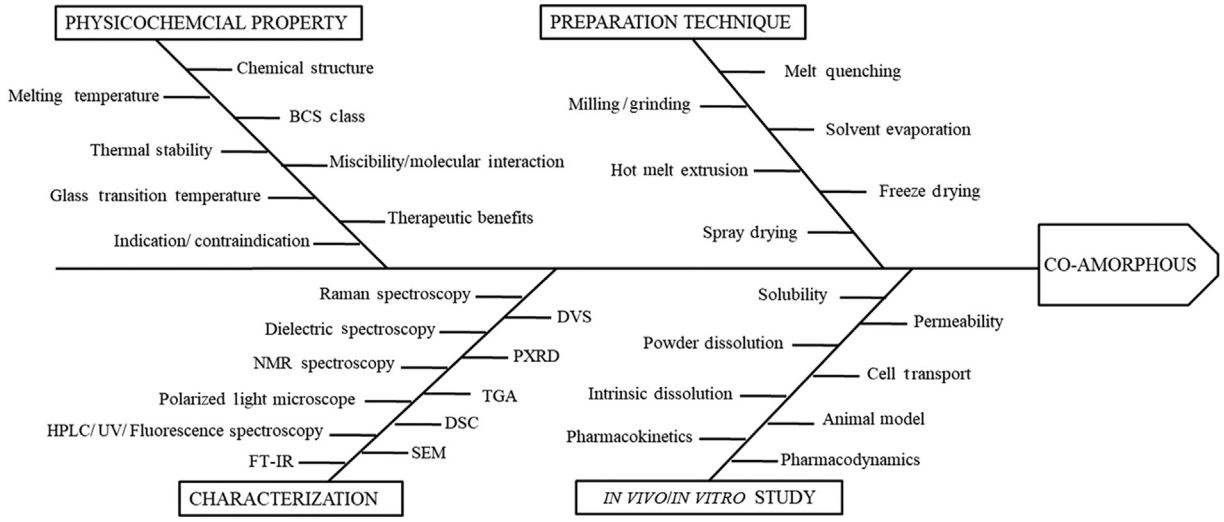

Figure 10 Fishbone diagram of coamorphous formulation development.

enhance their bioavailability. Generally, the successful development of coamorphous formulations can be mainly divided into the following four parts: (i) a comprehensive preformulation study with rational selections of components, (ii) a suitable preparative technique, (iii) a detailed characterization of physicochemical properties, (iv) desirable *in vitro* and *in vivo* performance with the potential benefits to achieve the synergistic effect (Fig. 10). However, considerable challenges in developing coamorphous formulations remain to be addressed; a deeper understanding of the mechanism of stabilization, their dissolution behaviors, pharmacokinetics and pharmacodynamics is required.

It appears that the selection of suitable co-formers is the key in obtaining a robust coamorphous formulation with desired pharmaceutical performances. A rational and systematic approach based on a thorough understanding of the physicochemical properties of a drug and its co-former should be employed in the co-former selection for coamorphous systems. Since it is still very difficult to predict the physical stability of coamorphous formulations, detailed research to elucidate the underlying stabilization mechanisms of coamorphous systems is required. For instance, the effect of a co-former on the nucleation and crystal growth of amorphous drugs *in vitro* should be investigated for designing stable coamorphous formulations at the early stage. Special attention to the surface properties of coamorphous formulations is required due to their important role in physical/chemical stability as well as dissolution performance. In consideration of the higher molecular mobility on the free surface, phase separation or crystallization of components may occur during the preparation of coamorphous solids.

It is worth mentioning that a drug–drug coamorphous formulation has the potential to achieve combination therapy. However, the dose requirement of the drug candidates for combination therapy is quite distinct from that of maintaining physical stability. From a pharmaceutical perspective, a fixed stoichiometric ratio of drug components in the coamorphous formulation poses a certain set of challenges. Simultaneous realization of physical stability and combination therapy should be taken into deep consideration to design a commercially feasible coamorphous formulation. A large number of *in vivo* studies are also required for intensively studying the pharmacological activities and the potential role of coformers in biological environments. Generally, the most common administration of coamorphous solids is oral route. It is also promising to deliver the coamorphous formulation *via* the buccal or pulmonary route depends on the physicochemical characteristics of API and coformers.

Furthermore, the scale-up preparation and downstream processing of the coamorphous formulations into final dose forms remain a challenging issue. The technologies utilized for producing polymer-based amorphous solid dispersions at industrial scale may not suitable for some coamorphous systems. The design space could be significantly limited by the requirement that the API and co-former both be sufficiently soluble in the same solvent or stable at elevated temperatures. The incorporation of additional excipients into the coamorphous formulations may help to improve the physicochemical properties of coamorphous solids and the downstream processing condition for conversion into final dosage forms.

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