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Review article

Development, recent advances, and updates in binary, ternary co-amorphous systems, and ternary solid dispersions

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ABSTRACT

Binary co-amorphous systems (CAMS) are a type of solid dispersion containing an active pharmaceutical ingredient (API) and small molecule excipients. The properties of these substances make them novel and a very demanding aspect of pharmaceutical research because they improve solubility, physical stability, and bioavailability in poorly soluble drugs in comparison to their pure crystal or amorphous counterparts. Binary CAMS may however not satisfy all criteria related to dissolution, solubility, recrystallization prevention, and stability. As a result, ternary systems incorporating a third ingredient in CAMS offer several advantages in terms of stability and drug solubility. Similarly, ternary systems in the context of amorphous solid dispersion (ASD) improve the drug's stability and solubility over binary solid dispersions. During this review, we summarize recent findings regarding ternary CAMS, ternary solid dispersion (TSD) and binary CAMS. Recent advances in the preparation, mechanism of stabilization, and in-vitro and in-vivo performances of binary and ternary systems are also discussed along with their final dosage forms.

1. Introduction

Low aqueous solubility is a major concern for drug formulations that results in low dissolution, poor bioavailability, and therefore unacceptable therapeutic efficacy [1,2]. Approximately 40% of commercially available drugs and 90% of new drug candidates demonstrate poor aqueous solubility. This makes it challenging for the new drug candidates to be commercialized as oral dosage forms [3,4]. It is well documented that the majority of active pharmaceutical ingredients (APIs) are included in the Biopharmaceutics Classification System (BCS) class II or IV drug substances which both classes represent poor aqueous solubility [5,6].

Several strategies are being used by pharmaceutical companies to enhance the oral bioavailability of poorly water-soluble drugs. These include physical, chemical, and solid dispersion strategies [7]. Regarding the physical strategy like micronization, the basic principle is that increasing the surface area improves the solubility profile [8]. In some cases, this simple method is appropriate and possible. Nevertheless, this technique may lead to particulate agglomeration, poor flow, and instability final product [9,10]. The chemical strategy can be achieved by molecular modifications of the drug structure, such as salt formation [11,12] and co-crystallization [13,14]. The salt formation can be used for basic or weak acid drugs but not feasible for neutral drugs. The utilization of this method is, however relatively limited as they tend to precipitate *in-vivo* [15]. Co-crystal pharmaceuticals can need sophisticated methods for preparation and stabilization via hydrogen bonding interactions [16,17]. There is also a possibility that co-crystals may not increase *in-vivo* drug solubility enough due to the formation of polymorphs and hydrates. Consequently, co-crystals and salts are prone to precipitate *in-vivo* [15,16]. Recently, Lam et al., have developed a

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technique known as liquid-pellet where the solubilized API in a co-solvent mixed with some excipients (e.g., carrier, coating material, and disintegrant) can be extruded and spheronised to overcome the poor dissolution and poor flowability [18–20].

Another strategy that has achieved considerable interest both in academia and industry is the preparation of solid dispersions. Solid dispersions are described as molecular mixtures of poorly water-soluble drugs that are dispersed in a hydrophilic carrier (polymer matrix) to increase surface area and improve solubility and stability [7]. Amorphous solid dispersion (ASD) containing APIs dissolved within amorphous carriers. The idea is that crystalline drugs are transformed into their amorphous state by combining them with amorphous polymers.

Although this approach offers obvious benefits, it is also often accompanied by challenges, such as difficulties with the manufacturing and processing of solid dispersions [21–23], the hygroscopicity of many polymers [23] and often the limited miscibility of the APIs with the polymers [7].

The use of co-amorphous systems (CAMS) has become increasingly popular in recent decades as a potential solution to the limitations of the solid dispersion approach. CAMS are defined as incorporating drugs with small molecules instead of using macromolecules such as polymers [24]. CAMS are, therefore a single-phase amorphous solid system made up of two or three components. Mostly, the term CAMS refers to binary CAMS which is the same concept used in this review article [25,26]. In such systems, molecular interactions between the involved components play a crucial role [27,28]. Considering the choice of co-formers, binary CAMS may also be described as drug-excipient and drug-drug CAMS. However, in some circumstances, the efficacy of binary CAMS solubilization and stabilization is poor, resulting in limited bioavailability improvement [29] and therefore has necessitated using another ingredient.

To improve the drug dissolution profile, numerous researchers have included a third ingredient in drug formulations to improve physical stability and drug solubility [30–35]. To optimize the binary CAMS, the third ingredient often used may be a surfactant, polymer, or small molecule [36]. This may be incorporated into the binary CAMS after the binary CAMS is formed (external third ingredient), or may be included in the CAMS alongside the other ingredients (internal third ingredient) [5].

A third ingredient can also be used in ASD research to enhance solubility and stability in binary ASDs (API/polymer). As a result, ASD research has also expanded beyond binary systems and more towards ternary solid dispersion (TSD). At a solid state, the dispersion of an active ingredient in two separate components is defined as a TSD [36]. Hence, by incorporating a third component, the TSD provides superior solubility and bioavailability than binary solid dispersions alone. The objective of this review is, therefore, to present an insight into the preparation and physicochemical properties of binary CAMS, ternary CAMS, and TSD. A particular focus of the review is on *in vitro-in vivo* performance correlations of newly designed formulations.

2. Solid dispersion

It is believed that solid dispersion was the first method of improving solubility/dissolution, and is widely investigated in pharmaceutical research. In the early 1970s, Chiou and Riegelman defined solid dispersions as "one or more active ingredients dispersed in an inert carrier at a solid state prepared by melting" [37]. They can also be categorized based on their physical state and number of phases (Table 1). A more in-depth description of different kinds of solid dispersions is presented by Laitine and Chiou and Riegelman et al. [37,38].

Glass solutions are the subtype of solid dispersions that form single amorphous phase systems, stabilize the amorphous drug and are sometimes referred to as ASDs [24]. Glass solutions can also be categorized by the type of excipient used to stabilize the amorphous drug. In this regard, Vaka and co-workers separated them into polymeric and non-polymeric excipients [39]. Polymeric-based glass solutions are formed by using hydrophilic polymers and non-polymeric excipients as auxiliary excipients, and they are classified as co-amorphous mixtures and mesoporous silica-based glass solutions (Fig. 1). Additionally, polymer-based glass solutions can be classified into binary solid dispersions and TSD. The co-amorphous mixture may also be classified into binary CAMS and ternary CAMS.

Table 1
Classification of solid dispersions based on solid phase. A: amorphous, C: crystalline. Reproduced from [224].

Solid dispersion	Number of phases	Physical state of phases
Eutectic mixture	2	C/C
Solid solution	1	C
Glass solution	1	A
Glass suspension	2	A/A or A/C

2.1. Polymer-based glass solution

In this review, the ASD that contains polymeric excipients is referred to as polymer-based glass solutions. Furthermore, the term binary solid dispersion commonly refers to polymer-based glass solutions.

In polymer-based glass solutions, an amorphous polymer can be utilized to stabilize drugs and therefore enhance their dissolution property (Fig. 2a). This usually involves the incorporation of a higher concentration of the polymer (approximately 50% by weight or higher) [40]. Many polymers have high glass transition temperature (T_g) that results in increasing the T_g of the drug in the glass solution whilst at the same time decreasing the molecular mobility of the drug through the polymer chains. This subsequently, inhibits the drug's phase transformation and crystallization tendency. Besides, intermolecular interactions among the functional groups of the polymer and the drug are also important factors in inhibiting recrystallization behaviour [29].

There are, however many challenges attributed to binary solid dispersions, for instance, limited miscibility drugs with polymer, and hygroscopicity [41]. To mitigate against the limited miscibility issues, large quantities of polymer are often used. This often leads to oversized dose units and does not necessarily make the formulation stable versus recrystallization behaviour [41,42]. Another challenge of this approach is the hygroscopicity inherent properties of numerous polymeric vehicles. This leads to the absorption of moisture, reduces the T_g (while increasing mobility), promotes phase separation, and accelerates recrystallization [24,43]. Table 2 displays some of the binary solid dispersions that are available on the global market.

2.1.1. Ternary solid dispersion(TSD)

The binary solid dispersion technique is based on converting APIs into an amorphous form by combining it with a polymeric carrier. Typically, the term ASD refers to binary solid dispersion or polymer-based glass solution. There are, however some challenges, such as physical stability, processability, and precipitation in the dissolution media [29]. Several researchers are utilizing TSD to address these issues. Along with the drug and polymeric carrier, the TSD also contains another ingredient that helps prevent precipitation and improve stability, enhance solubility, and processability [36]. TSDs have been reported to improve drug solubility much better than ASDs [44]. This third ingredient can either be another polymer, surfactant, pH modulator, or an adsorbent capable of improving solubility and formulation stability [34]. The type or choice of the third ingredient depends on the formulation strategies needed to make the TSD formulation more effective. Below, we will explain more in detail.

Regarding surfactants, when combined with a carrier reduce surface tension, inhibit recrystallization, maintain supersaturation, and increase the physical stability of the drug. In this regard, Guan et al. found that combining a polymer with a surfactant enhanced lacidipine's

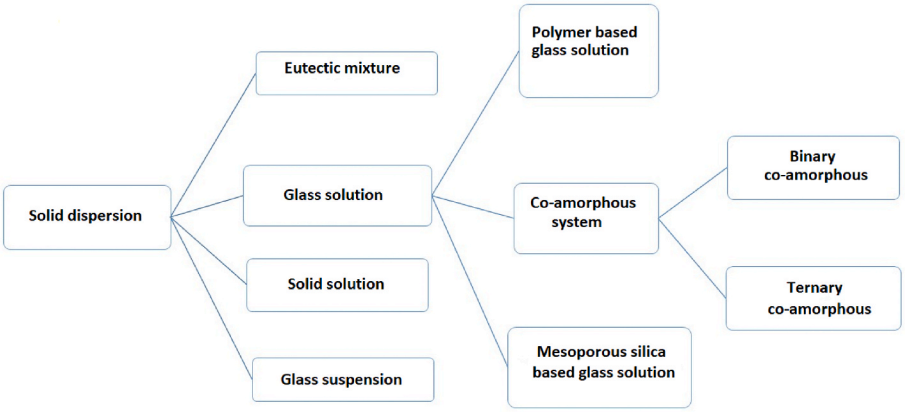

Fig. 1. Classification chart of solid dispersions.

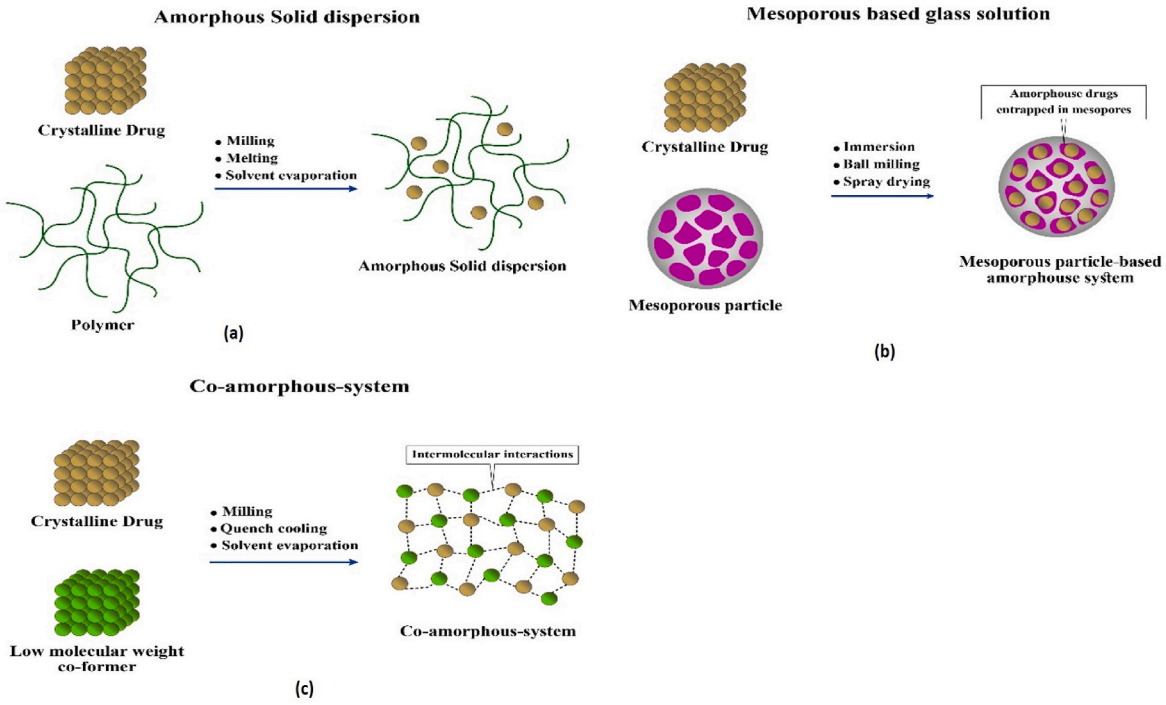

Fig. 2. Schematic illustration of (a) Amorphous solid dispersion, (b) mesoporous based glass solution, (c) Co-amorphous systems.

bioavailability. As an additional benefit, the surfactant maintained supersaturation better. As a result, the TSD had a high solubility, dissolution rate, and bioavailability when compared with binary solid dispersions [45]. In another study, Indulkar et al. investigated the effect of several surfactants sodium dodecyl sulfate (SDS), Polyoxyethylene stearate (Tween 80), Sorbitan monolaurate (Span 20), D-α-Tocopheryl polyethylene glycol (TPGS), and Sorbitan Trioleate (span 85) on the release, phase behaviour and stability of binary ASDs of ritonavir and copovidone. The results demonstrated that the inclusion of all the surfactants enhanced the release performance when compared to the binary ASD. Ionic surfactants, like SDS, can interact with the polymer and therefore influence ASD dissolution. Non-ionic surfactants, on the other hand, are capable of altering the polymer-drug phase separation. Surfactant type can also affect nanodroplet size. The authors observed nanodroplet size retention with the hydrophobic type surfactants (span), whereas size enhancement was found with the tween 80 and TPGS surfactants. The influence of spans might be attributed to the prevention of Ostwald ripening while the effect of tween 80 and TPGS may be attributed to a reduction in the T_g of ritonavir particles, hence promoting coalescence. The Span 85 demonstrated the greatest outcome (complete release, without crystallization/amorphous phase separation, and minimal droplet size) and there was no correlation found between physicochemical parameters and surfactant performance [46].

pH modulators are suitable excipients for drugs where solubility is pH-dependent [47]. Through hydrogen bonding between the drug molecules, pH-modifying agents reduce the crystallinity of drugs and increase their release by altering the pH. In weakly acidic or weakly basic drugs, alkalizers or acidifiers can improve their solubility and dissolution by modulating the microenvironment's pH [48,49]. They also work by creating an intermolecular bond with the drug, which aids in the process of supersaturation. According to a study, an alkalizer combined with kollidon® VA64 and glycyrrhetinic acid enhanced its dissolution through the formation of ionic complexes via electrostatic attraction [50]. ASD technology along with citric acid (an acidifier) significantly improved the carvedilol drug absorption even at high gastric pH levels [51].

Adsorbents play a crucial role in TSD as a third ingredient. These adsorption carriers are typically inert materials with favourable flow

Table 2
A list of commercially available amorphous solid dispersion medicines. HME: Hot melt extrusion.

Product name	Drug	Preparation method	Dosage form	Year of approval by FDA
Cesamet (US)/ Canemes (Austria)	Nabilone	Solvent evaporation	capsule	1985
Sporanox	Itraconazole	Spray drying	tablet	1992
Isoptin SR	Verapamil HCl	HME	tablet	1997
Crestor®	Rosuvastatin	Spray drying	tablet	2002
Intelence	Etravirine	HME	tablet	2008
Onmel	Itraconazole	HME	tablet	2010
Incivek	Telaprevir	Spray drying	tablet	2011
Lozanoc	Itraconazole	Spray drying	capsule	2012
Advagraf/ Astagraf XL	Tacrolimus	Wet granulation	capsule	2013
Viekira™ (US)/ Viekirax® (EU)	Ombitasvir/ Ritonavir/ Paritaprevir	Melt extrusion	tablet	2014
Epclusa	Sofosbuvir/ Velpatasvir	Spray drying	tablet	2016
Venclexta	Venetoclax	Melt extrusion	tablet	2016
Mavyret™	Glecaprevir/ Pibrentasvir	Melt extrusion	tablet	2017
Erleada	Apalutamide	Spray drying	tablet	2018
Lynparza	Olaparib	Melt extrusion	tablet	2018
Symdeko	Tezacaftor/ Ivacaftor	Spray drying	tablet	2019
Oriahnn™	Elagolix/estradiol/ norethindrone acetate	Melt extrusion	capsule	2020
Braftovi	Encorafenib	Melt extrusion	capsule	2020

and compressibility properties. They serve two important functions in TSD. Firstly, they prevent drug crystallization within the pores of the carriers by providing a protective environment. Secondly, they stabilize the drug in the TSD through chemical interactions. These interactions can contribute to the overall stability of the formulation by preventing drug degradation or recrystallization. It is important to understand the characteristics and properties of adsorbents to effectively utilize their benefits in TSD formulations [52]. According to Sriamornsak et al., they are able to significantly improve nifedipine's dissolution in the presence of Aerosil® 200. A gelatinous mass resulted in the absence of an adsorbent, while a free-flowing powder and improved dissolution were produced by an adsorbent in TSD [53].

In the case of polymers, the addition of a polymer to an ASD maintains supersaturation, inhibits the formation of crystals, and enhances the stability of TSD. Polymers prevent crystalline growth by raising the T_g and lowering the molecular mobility of amorphous drugs [54]. It was demonstrated that the TSD of itraconazole combined with polymeric carriers, including hydroxypropyl methylcellulose phthalate (HPMCP) and soluplus, increased bioavailability and solubility substantially and preserved the formulation's physical stability [55]. It is important to consider the advantages and disadvantages of each third component prior to its selection for research. Table 3 describes some recent research employed on TSD since 2016.

There is still however much to learn about the mechanism of binary solid dispersion, and TSDs are much more complicated systems. As a result, it may occasionally be challenging to fully characterize TSDs. Researchers are therefore attempting to develop novel methodologies or new perspectives on previously utilized techniques in order to comprehend the mechanism of these TSD [36].

2.2. Mesoporous silica-based glass solution

In past decades an alternative approach to stabilize the amorphous component is to utilize mesoporous silica materials as the carrier in mesoporous silica-based glass solutions [24]. Mesoporous silicon and silica refer to porous materials with pores between micropores and macropores [56] (Fig. 2b). There are different types of mesoporous silica utilized as pharmaceutical materials such as magnesium aluminometasilicate (Neusilin®) and calcium silicate (Florite®) [57]. Neusilin® and Florite® are manufactured via spray drying. Neusilin® has also been applied as an adsorption carrier to improve dissolution profiles and bioavailability of several poorly water-soluble compounds [58,59]. In studies involving the APIs BAY 12-9566 and naproxen, it was observed that these drugs exhibited significant improvements in stability and dissolution rates when they formed hydrogen bonds with an adsorbate [60]. Additionally, the formation of stable amorphous solid dispersion of drugs such as indomethacin, ketoprofen, progesterone, and naproxen with the use of Neusilin® was demonstrated via the ball milling process. The Fourier-Transform Infrared spectroscopy (FTIR) results provided significant evidence supporting the physical stability of the amorphous three carboxylic acid-group compounds (ketoprofen, indomethacin, naproxen) during a storage period of 4 weeks. The FTIR analysis revealed an acid-base interaction between Neusilin® and the carboxylic acid compounds when milled together. On the other hand, it was observed that progesterone interacts with Neusilin® through hydrogen bonding. These findings suggest that Neusilin® has the potential to stabilize the amorphous form of the carboxylic acid-group compounds and contribute to their physical stability during storage [61]. It should be noted, however, that the main disadvantage of this system is the use of organic solvents, as well as their limited loading capacity of around 20–30% [24,56]. No pharmaceutical product has yet been released to the market [62].

Drug stabilization mechanisms in mesoporous silica-based glass solutions have just recently been studied. It has also been demonstrated that merely the monomolecular drug layer is completely stable when directly in contact with the silanol functional groups within the mesoporous silica [63–65]. Depending on the pore diameter, higher drug loadings within the mesoporous could recrystallize [66,67]. More research is needed to comprehend the possibilities of mesoporous silica-based glass solutions [62,67].

2.3. Co-amorphous systems (CAMS)

Recently, this strategy has been shown to have some potential benefits over ASD since the percentage of drug loading may be raised from 20 to 30% to around 50% or greater in several circumstances [7,68]. In 2009, Chieng et al. developed the word "co-amorphous" [69] (Fig. 2c). Afterward, the number of published research articles on CAMS was expanded. Fig. 3 illustrates the relevant research examined for CAMS from 1998 to the year 2022 [70]. Fig. 3 shows that research interest in CAMS has risen in recent years. CAMS are an alternative to polymer-based glass solutions that can be classified as a binary or ternary system.

3. Binary CAMS

The earliest CAMS were described as binary CAMS preceding the year 2000 and are typically disregarded since these studies only focused on the thermal evaluation of binary CAMS [71–74]. In these mixtures, a low molecular co-former is used to stabilize the amorphous drug via strong intermolecular interactions. As considerable research is being conducted to make co-amorphous mixtures efficient, reliable, and adaptable to large-scale processing, new types of excipients are being explored. These include amino acids, organic acids, sugars and pharmacologically relevant second drugs. The type of co-former used means binary CAMS may be grouped into two main categories: drug-excipient

Table 3
Recent studies on ternary solid dispersion (TSD) since 2016. TPGS: tocopheryl polyethylene glycol 1000 succinate, SDS: Sodium dodecyl sulfate, SLS: Sodium lauryl sulfate, HPMCP: hydroxypropyl methylcellulose phthalate, HPMC: hydroxypropyl methylcellulose, PEG: polyethylene glycol, HP-b-CD: 2-Hydroxypropyl-beta-cyclodextrin, PVP: poly vinyl pyrrolidone, HPMCAS: hypromellose acetate succinate, HME: hot melt extrusion.

Binary solid dispersion	Third ingredient	The additional ingredient's type	outcomes	method	Ref.
LW6 (3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid methyl ester)-Povidone K30	Poloxamer 407	Polymer	Increase solubility	Solvent evaporation	[225]
Lurasidone -Poloxamer 188	Florite	Adsorbent	Inhibited transition from an amorphous to the crystalline form and enhanced stability of amorphous form.	Fusion method	[226]
Carbamazepine-Kollidon® VA64	Neusilin UFL2	Adsorbent	Enhanced the dissolution and carbamazepine flowability.	Rotary evaporation	[227]
Celecoxib -Phosphatidylcholine (PC)	Neusilin US2	Adsorbent	Improved flowability	Solvent evaporation	[228]
Itraconazole- HPMCP	Soluplus	Polymer	Increase solubility, stability and processability,	Hot melt extrusion/Spray drying	[55, 229]
Nateglinide-Poloxamer 188	Na2CO3	pH modulator	Boosting nateglinide's bioavailability by up to four times	melt dispersion	[230]
Abiraterone- HP-b-CD	HPMCAS	Polymer	Increase Precipitation inhibition	KinetiSol® technology	[163]
Tectorigenin- PVP	PEG4000	Polymer	Increase solubility	Rotary evaporation	[231]
Dipyridamole -Eudragit® S100	Tartaric acid	pH modulator	Rapid dissolution of dipyridamole	Freeze-drying	[232]
Glycyrrhetinic acid- PVP	l-arginine/ meglumine	pH modulator	enhance ionization, thereby increasing solubility	HME	[50]
Cinnarizine- Soluplus	HPMC/PVP	Polymer	Increase Solubility and stability	HME	[233]
Nifedipine- HPMC	Eudragit®-S	Polymer	Increase Solubility	Spray drying	[234]
Bedaquiline fumarate-Poloxamer 188	TPGS	Surfactant	Increase solubility, dissolution rate and permeability	Solvent evaporation	[235]
Ritonavir- HPMCAS	SLS	Surfactant	Inhibit recrystallization	Solvent evaporation	[236]
Loratadine-shellac	HPMC	Polymer	Increase solubility and supersaturation of loratadine	HME	[237]
Chlorthalidone -Soluplus	SLS	Surfactant	5.5 times more solubility compared with the pure drug	Spray dried	[238]
Felodipine -Soluplus	SDS	Surfactant	Increased dissolution	HME	[239]
Ezetimibe- PVP K30	Poloxamer 188	Surfactant	Improved solubility and supersaturation in the bio-relevant media.	Melt quenching	[240]

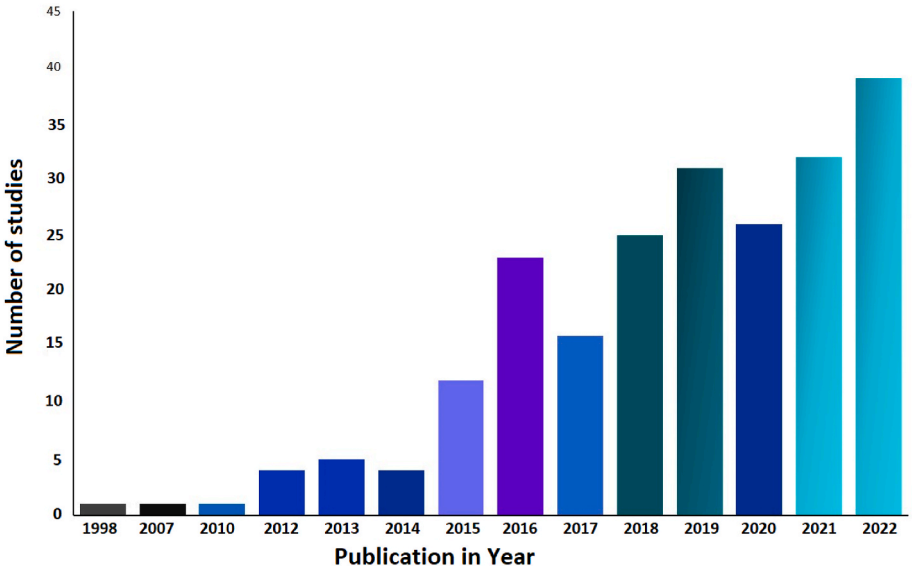

Fig. 3. An overview of the number of studies for Co-amorphous systems from 1998 to 2022 as represented in a column diagram [276].

CAMS and drug-drug CAMS. It is critical to investigate the physicochemical, thermodynamic and pharmacokinetic features of co-formers to optimize the possibilities of creating single-phase, reproducible and efficient CAMS [75].

3.1. Drug-excipient CAMS

3.1.1. Drug-amino acids

Currently, amino acid (AA) is the most frequently utilized co-formers in CAMS due to them being safe to use, lower cost, and the fact that they are zwitterions and simply create intermolecular interactions at the

receptor's biological binding sites [76,77]. Recent studies have found that receptor binding sites containing AA or significant molecular interactions such as ionic interactions are not required for the effective creation of drug–AA CAMS [78–80]. Generally, even in the absence of particular interactions, CAMS can contribute to physical stability improvement through molecular mixing [24,79,81–83]. Table 4 summarizes drug-AA CAMS from 2016 to date.

Choosing a specific (or optimal) AA as a co-former can be challenging. This is because different AAs might create co-amorphous formulations with varying physicochemical properties. Hirano et al. used the ball milling process to prepare several CAMS with different AA such as arginine (ARG), glycine, tryptophan, and aspartic acid, at varying molar ratios. Based on solubility studies, the co-amorphous mixture of ARG: quercetin at a molar ratio of 1:2 demonstrated the maximum solubility when compared to the pure drug and other co-amorphous mixtures. The "arginine-assisted solubilization system" approach was responsible for the increased solubility of quercetin when combined with ARG [84]. This formulation was then formulated into pellets by the extrusion-spheronization method. After a three-month stability study, the pellets were found to be stable with improved solubility and bioavailability [85].

Other studies have also been conducted on the application of 5 AA

Table 4
Overview of drug-AA binary CAMS since 2016. HME: hot melt extrusion, IDR: intrinsic dissolution rate, DBM: Dry ball milling.

co-amorphous mixture	Preparation Method	Molar ratio	Formation mechanism	Observation	Ref.
Quercetin-arginine	Ball milling	1:2	Hydrogen bonds	Enhanced the solubility of quercetin-arginine mixture. The loaded pellets indicated 95% *in-vitro* dissolution and 3 month stability	[85]
Telmisartan-arginine	Freeze-drying	1:2	Hydrogen bonding interaction	Showed about a 57-fold increase in solubility of telmisartan and the greatest dissolution percentage (100%) in phosphate buffer (pH7.5), while the 1:0.5 w/w ratio stable at least 90 days (40 °C/75% RH)	[92]
Griseofulvin-tryptophan	Ball milling	1:1	Hydrogen bonds	Tryptophan hindered griseofulvin recrystallization for 12 months, whereas Griseofulvin developed by Quench Cooling recrystallized in 1 week. At the greater dose, this CAMS enhanced the Area Under the Curve (AUC) in fasted state simulated gastric fluid; (88.6%) and fasted state simulated intestinal fluid (58.2%) media when compared to griseofulvin developed by quench cooling.	[86]
Budesonide(BUD)- arginine	Spray drying	1:1	Hydrogen bonds	Co-amorphization of BUD using ARG increases the physical stability of BUD by forming hydrogen bonds and reducing molecular mobility for 7 month. Furthermore, the presence of arginine as a co-former improved aerosolization and lung deposition performance of BUD.	[152]
Carvedilol(CVD) -aspartic acid (ASP)	*In situ* co-amorphization	1:1	Salt formation	FTIR spectroscopy solid state of immersed coated-tablet contains crystalline form of CVD and ASP in 0.1 HCl showed an *in-situ* co-amorphization while formulation containing CVD alone remained in the crystalline form. However due to insufficient disintegration of the coated tablet, drug release from the *in-situ* co-amorphous formulation was lower than the non-immersed tablet	[219]
Glibenclamide (GBC)- serine (SER), and arginine (ARG).	Cryomilling	1:1	Salt formation, hydrogen bonds	CAMS showed superior dissolution and higher AUC (11 times higher) compared to GBC amorphous alone. Also, co-amorphous GBC-ARG was stable for 18 months while drug alone was stable for 5 months	[122]
Ibuprofen-arginine and indomethacin-arginine (IBU-ARG and IND-ARG)	Spray drying	1:1	Salt formation	CAMS of IND-ARG and IBU-ARG showed higher cumulative dissolution amounts compared to its physical mixture or crystalline drug. Also, CAMS during tablet compaction were stable physically.	[87, 130]
Indomethacin (IND) - arginine, histidine, and lysine	Ball milling/spray drying	1:1	Salt formation	In both methods (ball milling/spray drying) CAMS showed a higher dissolution rate than the crystalline and amorphous drugs and were stable for up to eight months.	[136]
Indomethacin-lysine (IND-LYS)	DBM	1:1	Salt formation	DBM formed co-amorphous salt while liquid-assisted grinding (LAG) formed crystalline salt of IND-LYS. Co-amorphous salt presented the fastest dissolution rate compared to crystalline salt and amorphous IND (2.6 and 38.6-folds) and co-amorphous salt was able to reach and maintain supersaturation up to 6 h. Stability results showed 36-week stability for co-amorphous salt compared to <7 days stability for pure amorphous.in a dry condition at 25 and 40 °C.	[241]
Indomethacin (IND) -Arginine, phenylalanine, and tryptophan	Cryomilling	1:1	Salt formation	CAMS showed stabilization of IND solution in the super saturation state and prevented the drug from precipitation.	[142]
Indomethacin(IND)-arginine (ARG)	HME	1:1	Salt formation	Result show ARG is a suitable AA for stabilization of amorphous IND and increase super saturation potential.	[159]
Lurasidone hydrochloride-l-cysteine hydrochloride (LH-CYS)	Solvent evaporation	1:1	Hydrogen bonds	Compared between crystalline and amorphous LH, CAMS showed enhanced solubility (50- folds) and dissolution (1200- folds) without recrystallization during the supersaturated dissolution process. Also presented long term stability in storage conditions. (at least 180 days) compared to 10 days for amorphous LH.	[242]
Naproxen-arginine	Dry ball milling (DBM)	1:1	Salt formation	Co-amorphous state showed higher IDR and solubility compared to the pure crystalline drug (74.1 and 29.8-folds). Furthermore, pharmacokinetic data showed a 1.5-fold increase in AUC_{0-t} and a 2.15-fold increase in C_{max} compared to the pure crystalline drug.	[243]
Ofloxacin-tryptophan	Lyophilisation	1:1	Hydrogen bonds	CAMS improved ofloxacin solubility >10 times. Also show chemical and physical stability for 2 months at 40 °C.	[153]
Valsartan-l-histidine, l-arginine, and l-lysine	Vibrational ball milling	1:1	Hydrogen bonds	Co-amorphous mixtures showed stability for three months in dry conditions. Results showed co-amorphous systems increase solubility and IDR significantly compared to VAL in pH 4.6 and 6.8 buffers as well as pure water.	[244]
Simvastatin- tryptophan,lysine, and leucine	Spray drying	1:1	There is no interaction between molecules	The CAMS demonstrated stability for eight months. It exhibited a high fine particle fraction suitable for inhalation	[245]

(tryptophan, lysine, methionine, aspartic acid and valine) at 1:1 M ratio (as hydrophilic carriers) in the development of griseofulvin (GSF) CAMS to increase drug kinetic solubilization and stabilize GSF at solid state. Ball milling and quench cooling methods were used to develop the CAMS. The characterization of samples indicated that tryptophan had the greatest outcomes in terms of drug precipitation inhibition, drug amorphization, and solid-state stability of the GSF systems. Although tryptophan is a hydrophilic substance, it has a higher octanol/water partition value and making it the most suitable AA for interaction with the GSF lipophilic drug. In addition, tryptophan's ability to suppress GSF precipitation was dose-dependent and may be optimized [86].

The physical stability of these co-amorphous blends is based on diverse intermolecular interactions, including salt formation [87], intimate mixing [81], hydrogen bonding [25], and π–π interactions [79].

It was assumed that salt formation was a key molecular interaction responsible for amorphous stability and increased solubility. Wenqi et al. investigated the important role of salt formation between four model drugs and co-formers (ARG, citrulline) and the structural similarity of co-formers. It was found that salt-forming mixtures depicted considerably higher T_g, greater solubility, physical stability and faster dissolution rates compared to similar non-salt-forming mixtures. Structural similarity of the co-formers appears to play only a minor effect on CAMS performance [88]. However, although salt formation is not required for the development of CAMS, the formation of a co-amorphous salt system results in a better dissolution rate and physical stability.

The molar ratio between the drug and co-former is an important formulation parameter since it influences the interaction behaviours of the two components as well as the physical stability of CAMS. The molar ratio 1:1 is usually considered the "optimal ratio" in CAMS for achieving the highest physical stability and the highest T_g, assuming strong interactions are achievable between the molecules [80,89,90]. However, some recent studies have suggested that the ideal molar ratio may not always be 1:1. For example, Liu et al. prepared carvedilol-AA co-amorphous formulation at different molar ratios. Carvedilol and AA interact with each other due to their chemical structures in a 1:1 M ratio. On the other hand, physical stability measurements revealed that a molar ratio of 1:1.5 provided a homogeneous system and the highest stability [91].

Khanfar et al. prepared telmisartan (TLM) with various kinds and ratios of AAs by freeze-drying method. The 1:2 w/w ratio of TLM with ARG co-amorphous mixture indicated the highest solubility and dissolution profile owing to the basicity of the ARG is the most favourable co-former for the weakly acidic TLM drug. Furthermore, the 1:0.5 w/w ratio of TLM- ARG demonstrated the greatest stability [92].

Generally, three principles are outlined based on the likelihood of co-amorphous mixture formation and their physicochemical features, particularly dissolution rate and physical stability: (1) For acidic and basic pharmaceuticals, salt formation should be the initial option. (2) In general, nonpolar aromatic amino acids (AA) are useful co-formers. (3) Amino acids with nonpolar aliphatic groups, such as valine and leucine, are poor co-formers and should be eliminated as first options. [76,93].

3.1.2. Drug-organic acids

The study of organic acids has become increasingly widespread and extensive as efficient co-formers for the development of CAMS [94–97]. In CAMS, organic acids are used as co-formers, to produce significant interactions with basic drugs. Various molar ratios of basic drugs and organic acids are thought to promote salt formation. In this regard, 3 organic acids (citric acid, benzoic acid, malic acid) were assessed as co-formers for carvedilol with the CAMS manufactured through spray drying at molar ratios between 1:4 and 4:1. The findings indicated that the organic acids, due to their mono-, di-, and triprotic properties, may have formed CAMS with carvedilol via salt formation. In addition, CAMS at molar ratios of 2:1, 3:1, or even 4:1 demonstrated remarkable physical stability during 6 months, suggesting the potential of even higher 'drug loading' [94]. Sutar et al. investigated the potential of different organic acids to produce BX795 salts/CAMS/cocrystals in order to facilitate BX795 pharmaceutical development. The authors reported BX795 to form CAMS with citric and tartaric acid with the combination of BX795 with these organic acids increasing its thermodynamic stability. The BX795-citric acid CAMS, in particular, offers the potential for future pharmaceutical development because of its improved in-vitro cytocompatibility and unchanged antiviral effectiveness [98]. In another investigation, a co-amorphous formulation containing piroxicam and citric acid (PIR-CA) was prepared, and the skin permeability from the co-amorphous formulation was evaluated. This co-amorphous formulation had greater skin permeation and remained amorphous for at least 60 days at 40 °C with silica gel. Furthermore, the PIR-CA co-amorphous formulation increased piroxicam's solubility in polyethylene glycol 400 compared to the pure drug, and the physical mixture of piroxicam and citric acid, thereby demonstrating a supersaturated condition in the formulation [99]. Table 5 summarizes the drug-organic acid co-amorphous mixture from 2016 to date.

3.1.3. Drug-other excipients

Apart from the co-formers as mentioned above, other types of small molecules such as urea [100–102], nicotinamide [95,102–104], aspartame [105] and saccharin have been involved in the preparation of CAMS. The most popular among them is saccharin. Qian and co-workers combined lurasidone and saccharin to increase the dissolution profile with pH-independent solubility behaviour [106]. Gao et al. used a co-amorphization approach with saccharin to improve the solubility of repaglinide in phosphate buffer media with pH [107]. Additionally, sodium taurocholate, a natural bile acid surfactant, has been reported to prevent phase separation as well as recrystallization in co-amorphous formulations. In this regard, Gniado et al. investigated co-amorphization studies using sodium taurocholate (NaTC) with 18 different drugs. According to their findings, the co-former was ideal for co-amorphization because of its low crystallinity, combined with a high hydrogen bonding capacity, which allows it to be used in a wide range of applications instead of forming specific interactions with APIs [97].

Epigallocatechin-3-gallate (EGCG), another co-former, has shown promise due to its unique structure that consists of phenolic hydroxyl groups and a phenyl ring. A study by Chen et al. showed that simvastatin and nifedipine can be co-amorphized with EGCG due to its polyphenolic hydroxyl and polycyclic structure, which stabilize the hydrophobic drugs' amorphous state and improve their dissolution and bioavailability [108].

In another study, active metabolites were employed as co-formers in binary co-amorphous mixtures (CAMS). When the drug's own metabolite is used as a co-former, the pharmacological effects are the same or even greater than when the parent drug is used. Furthermore, choosing a combination of the drug and these metabolites could result in maximum therapeutic benefits due to the absence of any inactive co-formers. Li et al. prepared the CAMS of toltrazuril (Tol)-ponazuril (Pon) by solvent evaporation. The drug Tol is a type of triazine used mainly for treating coccidial infections. According to the reported data, the solubility and dissolution of co-amorphous Tol-Pon were remarkably improved over their crystalline drug counterparts. Moreover, the co-amorphous Tol-Pon was stable for at least one month at 40 °C. This could be attributed to the hydrogen bonds between Tol and Pon and the molecular miscibility, as well as to Pon's inhibition of crystallizing Tol from a supersaturated state [109].

3.2. Drug-drug CAMS

In drug-drug formulations, two drugs are often effectively stabilized with improvements in their dissolution profiles and physical stability. Aside from the benefits of improved stability and solubility, drug-drug CAMS provides the platform for prospective combination treatments [69]. For example, a binary CAMS containing glimepiride and irbesartan was developed by Cruz-Angeles et al. for a combination therapy application. Metabolism syndrome is commonly treated with two BCS class II

Table 5
An overview of drug-organic acids binary CAMS from 2016 to date.

CAMS	Preparation Method	Molar ratio	Formation mechanism	Observation	Ref.
Sulfamerazine-deoxycholic acid, citric acid, and sodium taurocholate	Cryomilling	1:1	Hydrogen bonds	A major enhancement in the cumulative dissolution rate of sulfamerazine	[246]
Desloratadine-benzoic acid	Quench cooling	1:1	Formation of salt	Improvement physical stability and increased cumulative dissolution rate of desloratadine in water and 0.1 N HCl	[247]
Loratadine-citric acid	Solvent evaporation	1:1	Hydrogen bonds	Exhibiting physical stability for 3 months and increased bioavailability of loratadine.	[247]
Olanzapine-ascorbic acid	Solvent evaporation	1:2	Hydrogen bonds	Improvement in the bioavailability of olanzapine, three months of physical and chemical stability, complete dissolution in 10 min as opposed to the dissolution of the crystalline olanzapine of 55.3% in 30 min.	[211]
Itraconazole- l-tartaric acid, fumaric acid	Ball milling	2:1	There was no interaction between molecules	Both CAMS kept their stability for two months.	[248]
Mirabegron- citric acid, and fumaric acid	Solvent evaporation	1:1	Formation of salt	Maintaining supersaturated dissolution, increase in equilibrium solubility of mirabegron in water for both of CAMS.	[96]
Azelnidipine-oxalic acid	Liquid assisted grinding and ball milling	2:1, 1:1, 1:2	Hydrogen bonding	Improved solubility in different media and the dissolution rate compared to the crystalline drugs	[249]
Palbociclib- (succinic, tartaric, citric, and malic acid)	Co-milling	1:1	Ionic bond interaction	Compared to crystalline and amorphous palbociclib, the four CAMS showed better stability and dissolution.	[250]

Table 6
Summary of drug-drug binary CAMS mixture.

CAM mixture	Preparation Method	Molar ratio	Formation mechanism	Observation	Ref.
Cimetidine- naproxen	Ball milling	1:1	Molecular interactions	Augmentation of stability and also IDR	[73]
Atorvastatin-irbesartan	Quench cooling	1:1	Molecular interactions	Boosted the physical stability and also dissolution of irbesartan, whereas co-amorphization had a negative effect on the dissolution profile of atorvastatin.	[251]
Tadalafil- repaglinide	Solvent-evaporation	1: 1	Intimate mixing	The intrinsic dissolution rate increased by 1.5–3 -fold, and the supersaturation level was maintained for at least 4 h in a non-sink condition. Also, improved stability compared to the pure amorphous forms under long-term stability and accelerated storage conditions	[200]
Profen analogs-nimesulide	Cryogenic milling	NA	NA	Three profen analogs had different effects on the crystallization kinetics of the amorphous nimesulide	[252]
Indomethacin- Nimesulide	Quench cooling	1:2	Hydrogen bonds	As compared to pure nimesulide, this CAMS has a six-fold improvement in dissolution rate.	[253]
Lurasidone hydrochloride-puerarin	Solvent-evaporation	1:1	Molecular interactions	Improved dissolution with synchronized lurasidone and puerarin release. Enhanced physical stability under accelerated and long-term storage conditions.	[254]
Raloxifene(RLX) - Quercetin	Solvent evaporation	1:1	Hydrogen bond	In CAMS, RLX solubility was reduced to half of the crystalline RLX, but it was stable for up to two months under 0-10%RH/25 °C.	[255]
Docetaxel- bicalutamide	Ball milling	1:1	NA	Exhibited physical stability under drying conditions during 18 months, maintaining supersaturated dissolution and higher bioavailability for both drugs	[209]
Irbesartan- atenolol	Ball milling	1:1	NA	Increase intrinsic dissolution rate of Irbesartan in Phosphate buffer	[256]
Telisartan-hydrochlorothiazide	Solvent evaporation	1:3	Molecular interaction	Apparent solubility and the dissolution of telmisartan was increased and binary CAMS remained stable in 60 °C for 30 days	[257]
Ketoprofen- ethenzamide	Quench cooling	1:2, 1:1, 2:1	Hydrogen bonds	Kept stability for one month and increased the skin permeation for ketoprofen	[258]
Sinomenine-different NSAID	Vacuum evaporation	NA	Salt formation	In all three co-amorphous samples, sinomenine displayed sustained release rates and there was no recrystallization observed in all three CAMS after four months at 25 °C and 75% relative humidity (RH).	[259]
Simvastatine - nifedipine	Melt-quenching	1:1	Hydrogen bonding	Enhanced solubility, 3.7 and 1.7 times for simvastatine and nifedipine	[260]
Budesonide- theophylline	Spray drying	1:1	NA	A significant increase dissolution both of drugs in phosphate buffer	[261]
Cimetidine- indomethacin	Hot melt extrusion	1:1	NA	Improvement in solubility, maintaining physical stability for one month.	[129]
Ciprofloxacin-quercetin	Spray-dried	1:1	Molecular interaction	Enhanced stability and improved aerosol performance	[262]
Cimetidine-diflunisal	Solvent evaporation	NA	Molecular interaction	Enhancements to both drug's solubility and dissolution	[263]
Talinolol-naringin	Quench cooling	1:1,2:1	Molecular interactions	Talinolol's bioavailability and solubility have improved	[263]
Curcumin-artemisinin	Solvent evaporation	1:1	Molecular interactions	Curcumin and artemisinin's pharmacokinetic profile was improved, as well as their solubility.	[264]
Curcumin-piperazine	Liquid assisted grinding	1:2	Hydrogen bonds	Cumulative dissolution rate enhancement of curcumin.	[145]
Glipizide-atorvastatin	Cryo- milling	1:1	NA	Dissolution enhancement and improved physical stability	[201]
Naproxen–indomethacin	Spray drying	NA	Molecular interactions	Formation of drug–drug heterodimers in the co-amorphous phase as a result of the simultaneous recrystallization of both drugs after being spray dried.	[265]

NA: not available, IDR: intrinsic dissolution rate.

drugs, glimepiride and irbesartan. Results showed that the prepared binary CAMS increased the dissolution of glimepiride and irbesartan 35 and 12-fold compared to their crystalline counterparts [110].

Cimetidine and naproxen were prepared as the first co-amorphous blend with improvement in solubility and dissolution behaviour by Yamamura et al. [72]. Following these results, the authors studied the development of drug-drug CAMS by mixing cimetidine and naproxen [73]. Likewise, the co-amorphous drug-drug approach resulted in increased bioavailability [81]. Nevertheless, it might not always be pharmaceutically feasible to combine pharmacologically related drugs in the required doses. Until now, there have been a few publications that address issues about the drug-drug CAMS (Table 6).

4. Ternary CAMS

There has been a recent interest in the creation of ternary CAMS by adding a third ingredient to a binary CAMS. Various ternary systems in addition to binary CAMS have been described in the literature [5]. In order to optimize these binary CAMS, a third ingredient, which might be a surfactant, polymer, or small molecule, is included in the system. The addition of the third ingredient in this approach aids in the prevention of precipitation and stability concerns. By using a melt-quench method, D'Angelo et al. obtained a more stable CAMS of three ingredients. The authors found that the ternary system was more stable over 4 weeks than its binary counterpart [111].

It has been reported that Liu et al. formulated carvedilol-aspartic acid (CAR-ASP) CAMS with a concentration of 10 %w/w of hydroxyl propyl methylcellulose (HPMC) to improve its dissolution profile. The authors reported that HPMC reduced the dissolution rate of CAR-ASP systems and extended supersaturation for longer periods when HPMC was added. Molecular interaction between HPMC and CAR-ASP systems is suspected to contribute to the dissolution process. The HPMC addition had no detrimental effect on the physical stability at 25 °C and 40 °C for 7 months [112].

Another stable ternary CAMS was developed by Ueda et al. from carbamazepine, ARG, and citric acid. The co-amorphous formulation had enhanced physical stability when ARG and citric acid were combined as co-formers, resulting in salt formation, which significantly increased their T_g [113]. The third ingredient can thus be classified into three classes including surfactants, polymers and small molecules which are discussed in more depth in the following sections.

4.1. Binary CAMS + surfactant

Surfactants that are routinely utilized in the preparation of ternary CAMS are, Tween 20, Tween 40, TPGS, and sodium lauryl sulfate (SLS). Surfactants can enhance wettability [114–116], dissolution improvement (with and without solubilization) [115,117] and prevent crystallization [118,119].

The effects of various surfactants on ARG-naproxen and lysine-naproxen CAMS were also evaluated. According to the results, the type of surfactant affected the formulation of binary CAMS [120].

To improve drug permeability, SLS was added to glibenclamide -AA binary CAMS. Ternary CAMS (Glibenclamide-ARG -SLS) showed higher dissolution and permeation rates than their binary counterparts, but not for ternary CAMS (glibenclamide-serine-SLS) [121,122]. It is clear that more research on various permeation enhancers and CAMS is needed to develop comprehensive guidelines for designing ternary systems to improve permeability. Based on the binary CAMS, care and consideration must be taken regarding the choice of the third ingredient. Table 7 relates to some of the ternary CAMS based on surfactants reported to date.

Table 7
Recent studies on ternary CAMS based on surfactants. SDS: Sodium dodecyl sulfate, SLS: Sodium lauryl sulfate, Tween 40: Polyoxyethylene (40) stearate, TPGS: tocopheryl polyethylene glycol 1000 succinate.

Binary CAMS	Surfactant	Preparation method	Outcomes	Ref.
Naproxen–Arginine	SDS	Freeze-drying	Increasing physical stability of samples at a certain concentration. Creation of a heterogeneous system.	[120]
Naproxen–Arginine	Pluronic® F127	Freeze-drying	Creation of a homogeneous system.	[120]
Naproxen– Lysine	TPGS 1000	Freeze-drying	Enhancement of the sample's physical Stability and creation of a heterogeneous system	[120]
Naproxen– Lysine	Tween 20	Freeze-drying	Increased physical Stability and creation of a heterogeneous system.	[120]
Naproxen–Arginine	Tween 40	Freeze-drying	Increased sample physical stability. Formation of a homogeneous system.	[120]
Glibenclamide–Arginine	SLS	Cryo-milling	Enhancement of permeability and dissolution of the drug.	[121, 122]
Naproxen–Arginine	Tween 20	Freeze-drying	Enhancement of sample physical stability at a certain concentration. Formation of a heterogeneous system.	[120]
Naproxen–Arginine	TPGS 1000	Freeze-drying	Enhancement of sample physical stability at a certain concentration. Formation of a heterogeneous system.	[120]
Naproxen–Lysine	SDS	Freeze-drying	Formation of a homogeneous system.	[120]

4.2. Binary CAMS + polymer

It has been found that ternary CAMS based on polymers perform better than binary CAMS, as well as provides an enhanced "parachute" and a lighter "spring" effect [2]. CAMS typically produces supersaturated dissolution followed by crystal formation and growth that is known as a "spring and parachute" effect [2]. The greater energy amorphous API, known as the "spring," promotes drug supersaturation and dissolution when dissolved with other drugs or excipients. The "parachute" is the co-former that delays amorphous API crystal growth and nucleation to preserve or extend the supersaturation over time [123,124].

Moreover, the dissolution behaviour is explained by the impact of small molecules (act as co-former) on accelerating the initial dissolution rate, while larger molecules (act as a polymer) function as precipitation

inhibitors or modulate the release rate [5]. In this regard, Petry et al. coated indomethacin-ARG CAMS with polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat® protect). According to their research, the coating inhibited the recrystallization of indomethacin-ARG CAMS during drug release and enhanced the drug release profile [125].

Ruponen et al. tested the dissolution and passive membrane permeability of a combination of hydrochlorothiazide (HCT)- ARG -polyvinylpyrrolidone (PVP) using a parallel artificial membrane permeability assay (PAMPA) as the permeation barrier. The PAMPA setup was a useful screening tool for selecting the most promising co-amorphous formulation candidates. It was observed that the intermolecular interactions that prevented the recrystallization of HCT in solution resulted in improved drug dissolution and drug permeation [126]. As compared to drug-co-formers, incorporating polymers into drug-drug CAMS enhances stability through phase separation inhibition as well. For example, a third ingredient such as cyclodextrin (CD), formed complexes with the drug-drug CAMS (darunavir-ritonavir) thereby enhancing the solubility and stability of the ternary CAMS [127]. Riekes et al. used Soluplus® as a carrier binary ezetimibe-lovastatin (EZE -LOV) CAMS and tested for enhancement in dissolution. As the drugs and polymer interact through hydrogen bonds, it showed great stability and high dissolution of 92% and 83% of EZE and LOV in 5 min [128]. Another study conducted by Arnfast et al. found that adding small amounts (5 %w/w) of polyethylene oxide prevented amorphous–amorphous phase separation in binary CAMS containing indomethacin–cimetidine [129]. Additionally, ARG–indomethacin CAMS tablet containing PVP extended indomethacin supersaturation for a prolonged period when compared to one without PVP as PVP inhibits precipitation. It was found that PVP increased the initial release rate of ibuprofen–ARG CAMS tablets compared with tablets without PVP. PVP is known to interact strongly with drugs [130]. Table 8 summarizes a list of publications relating to ternary CAMS based on polymers.

4.3. Binary CAMS + small molecule

In the presence of small molecules like AA, molecular interactions may dramatically increase the initial dissolution rate of a drug in ternary CAMS. Stabilizing AA was chosen after evaluating potential drug-AA interactions as well as prior knowledge of how to produce stable binary CAMS [5].

As a third water-soluble ingredient, ARG offers the best benefits for the improvement of T_g and stability of carbamazepine-citric acid CAMS as a result of the strong interaction between citric acid and ARG. It has been reported that simultaneous salt formation between citric acid and ARG in the ternary CAMS is responsible for this effect [113]. Another study used phenylalanine as a third ingredient for indomethacin-ARG CAMS. Upon storage at 40 °C or room temperature, the ternary CAMS remained stable for approximately 84 days. The authors found that the intrinsic dissolution rate of indomethacin was significantly higher in ternary systems than it was in the crystalline form. The interaction between proline and the other ingredients may determine its suitability in a co-amorphous mixture [83].

Recent studies have used dipeptides rather than AA to tailor the performance of CAMS. According to Wu et al., dipeptides show good conformability and physical stability when compared to individual AA [131]. Although dipeptides are useful, their affordability and practical availability limit their usefulness [131]. However, more systematic research also needs to be conducted in this field.

Other small molecules are involved in ternary CAMS. For example, Wairkar et al. employed Neusilin® as a small molecule in binary CAMS Nateglinide–Metformin hydrochloride (NT-MT). Hydrogen interactions between NT, MT, and Neusilin® confirmed amorphous form stabilization for this ternary CAMS. It was observed that *in-vitro* dissolution of NT, flow properties and compressibility of ternary CAMS were improved significantly [132]. In another study, Beyer et al., incorporated naproxen sodium as a small molecule into naproxen-indomethacin binary CAMS by quench-cooling. In the study, ternary CAMS demonstrated better physical stability and did not recrystallize during the 270 day period of study [133].

Table 8
An overview of studies on ternary CAMS based on polymers. HPMC: Hydroxyl propyl methyl cellulose, HP-b-CD: 2-Hydrox-propyl-b-cyclodextrin, PMMAEA: Poly methyl methacrylate-co-ethyl acrylate, PVP: Polyvinylpyrrolidone.

Binary CAMS	Polymer	Preparation method	Outcomes	Ref.
Flutamide–Bicalutamide	PMMAEA	Melt-quench	Inhomogeneity of the sample	[196]
Indomethacin–Citric acid	PVP	Solvent evaporation	Miscibility between two molecules was enhanced, but the effect is dependent on the amount of PVP.to indomethacin	[74]
Indomethacin– Arginine	Kollicoat® Protect	Coating	Drug release behaviour was improved	[125]
Indomethacin– Arginine	Co-povidone	HME	Improved dissolution behaviour	[159]
Ezetimibe–Lovastatin	PVP K30	Spray drying	One drug had a significant improvement in dissolution behaviour	[128]
Ezetimibe-lovastatin	Soluplus	Spray drying	In the ternary CAMS, the intrinsic dissolution rate of ezetimibe and lovastatin rose by up to 18 and 6 times, respectively. Enhanced physical stability of ezetimibe-lovastatin CAMS.	[128]
Ezetimibe–Simvastatin	Kollidon® VA64	Melt-quench	Enhancement of the physical stability at high temperature	[266]
Ibrutinib–Oxalic acid	Microcrystalline cellulose	Ball milling	Enhancement of solubility, dissolution rates and physical stability	[33]
Ritonavir –Darunavir	HPMC/PVP/HP-β-CD	Spray drying	Ritonavir–darunavir-HP-b-CD tertiary spray-dried powders improved the dissolution rate of both ritonavir and darunavir	[127]
Carvedilol–Aspartic acid	Eudragit® L 55	*In situ* amorphization and Coating	————	[219]
Carvedilol–Aspartic acid	HPMC	Spray drying	By reducing initial dissolution rate and extending the time of supersaturation, dissolution behavior was improved	[112]
Carvedilol-tryptophan	HPMC/Kollidon® VA64	Ball milling	Improvement in dissolution behavior. Increase in maintaining drug supersaturation	[267]
Sacubitril–Valsartan	Microcrystalline cellulose	Spray drying	The solubility of valsartan and sacubitril decreased slightly; phase transformation was delayed; *in-vivo* performance decreased; powder properties improved for compressibility.	[214]
Hydrochlorothiazide– Arginine	PVP	Cryo-milling	Dissolution of drugs improved; drug permeation decreased	[126]
Olmesartan medoxomil–Hydrochlorothiazide	HPMC	Solvent evaporation	Prevention of co-crystallization without a considerable increase in the dissolution profile.	[149]
Naproxen–Meglumine	Kollidon® K30	Reactive melt extrusion	Physical stability and dissolution properties were improved compared to drug-polymer systems	[268]

However, ternary systems can also have potential risks in spite of these promising examples. For example in TSD, researchers found that the addition of saccharin or tryptophan reduced the stability of binary ASD (PVP- carbamazepine) in both estimation and experiments [130].

In preparing ternary CAMS, it is important to keep in mind that it may present both opportunities and risks. Hence, there are still a number of questions to be answered about ternary amorphous drug delivery formulations.

5. Methods to prepare binary and ternary systems

CAMS can be prepared using many different methods. The circumstances of manufacturing can significantly affect the physicochemical properties of amorphous systems. There are two fundamentally different pathways for obtaining amorphous forms of drugs from their crystalline form, i.e., kinetic and thermodynamic pathways. By dissolving or melting of the drug, the thermodynamic pathway leads to the loss of crystal structure order, followed by rapid evaporation of the solvents or rapid cooling, which prevents the crystal formation of the drug [134].

The kinetic pathway leads to the conversion of the crystalline solid, into its amorphous form by mechanical activation. The excipients' crystallization is also relevant when selecting the method of preparing the drug, along with its thermal stability and melting point. Thus, selecting a suitable approach for preparing CAMS is essential for ensuring favourable stability and quality [134].

In general, the preparation of both CAMS and ASD is influenced by several crucial process parameters that require careful assessment. Firstly, the stoichiometric ratio between the components needs to be considered meticulously to achieve the desired properties [80,91]. Secondly, the selection of an appropriate polymer or co-former can have a significant impact on the stability, dissolution, and bioavailability of the product [75]. Thirdly, the intensity and duration of the mixing procedure can affect the homogeneity of the final product [135]. Fourthly, choosing an appropriate solvent is important to ensure the formation of a homogeneous mixture whilst minimizing potential interactions with the drug and excipients [136]. Fifthly, temperature and humidity levels during the preparation process should be controlled to prevent crystallization or degradation. Finally, the drying conditions or rate of cooling must be optimized to avoid any changes in the physical properties of the final product [137,138]. In summary, a careful consideration of these critical process parameters is essential to ensure the reproducibility, quality, and efficacy of both CAMS and ASDs.

The techniques used for both binary and ternary CAMS are classified into three categories include quench cooling, milling methods and solvent evaporation methods (as seen in Fig. 4). Furthermore, ASDs are produced using the same manufacturing processes as CAMS, including melting, solvent evaporation and milling [36], which are described in detail below.

5.1. Quench cooling

The most common method for converting crystalline physical mixtures to amorphous solids is quench cooling. This method employs heating a formulated sample and rapidly cooling the melt below freezing point by use of liquid nitrogen or ice to avoid recrystallization. Liquid nitrogen was used to quench the co-melted physical combination of curcumin and piperine to create binary CAMS. The resulting binary CAMS provided a significant yield (97%) and excellent stability with no thermal degradation for up to three months under accelerated testing circumstances (75% RH/40 °C). Beyer et al. also prepared ternary CAMS by quench cooling. The ternary CAMS prepared demonstrated improved physical stability during 270 days of storage with no recrystallization

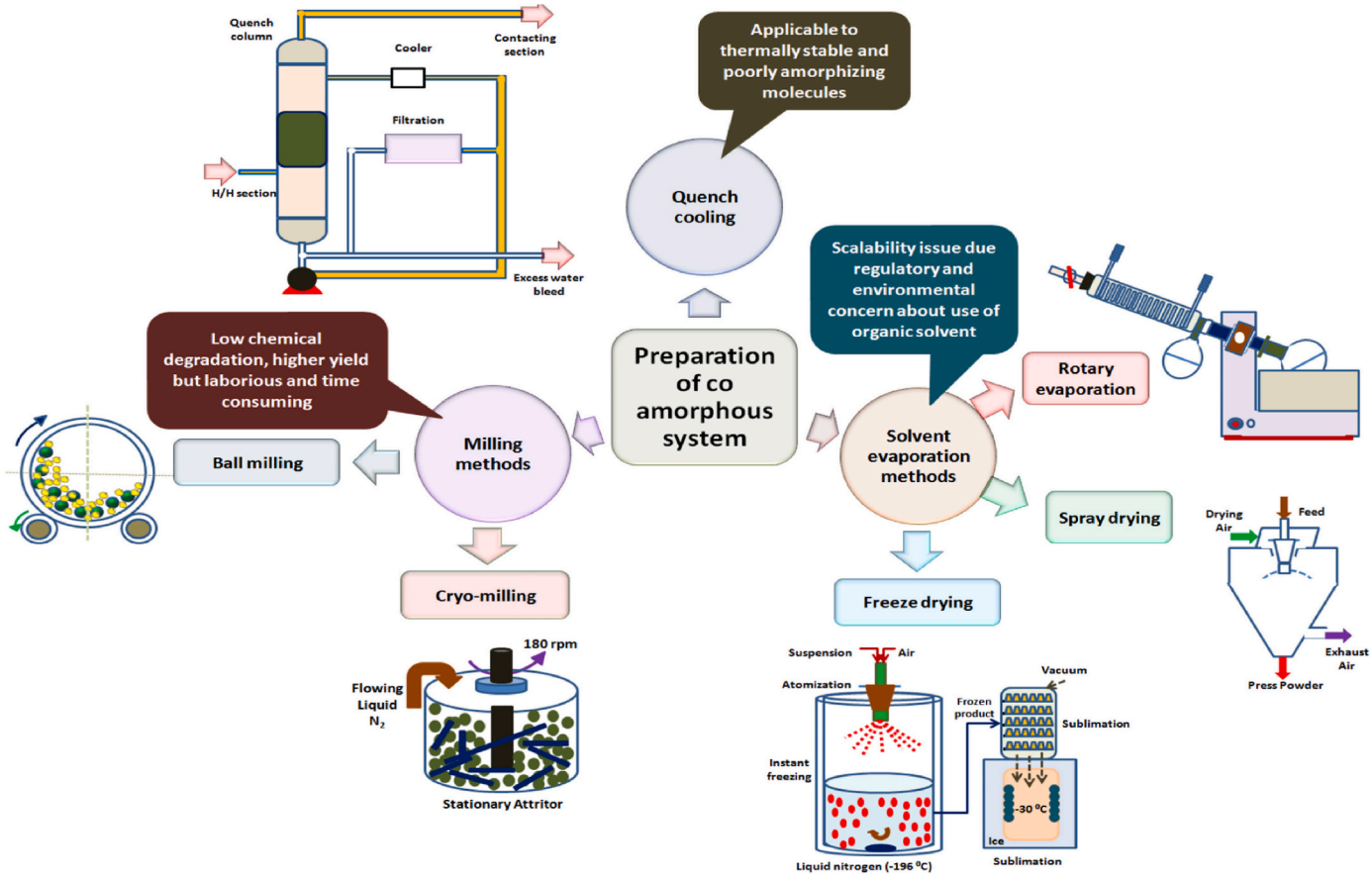

Fig. 4. Preparation methods of Co-amorphous systems. with permission from Ref. [137].

observed [133]. Although quench cooling is a simple and quick way to get CAMS, it is inappropriate for thermo-sensitive drugs such as atenolol and co-formers [134].

5.2. Milling methods

Utilizing mechanical activation such as ball milling or cryo-milling and liquid-assisted grinding causes disruption of the crystal lattice of the components and therefore leads to an amorphous state. In addition to using no organic solvents or high temperatures, ball milling is regarded as a "green" and high yield method of preparing CAMS [134,139]. However, ball milling has limitations, such as difficulty in attaining a homogeneous mix during large-scale procedures, phase transformation issues, and high mechanical stress [2].

The increasing temperature during the milling process affects the stability of the products, which may cause recrystallization and phase separation [140]. Descamps et al. showed that milling above a drug's T_g caused polymorphic transformations while milling performed below the drug's T_g in a cryo-miller was sufficient to cause amorphization [141]. The main benefits of cryo-milling are that it is solvent-free, and operating the ball mill at a low temperature minimizes recrystallization. Ojarinta et al. produced a binary CAMS containing indomethacin and AA using cryo-milling. To minimize deterioration or solid-state transformation due to overheating, a cooling in liquid nitrogen was used every 10 min to cool the milling cans [142]. A binary CAMS of hydrochlorothiazide and atenolol was prepared by cryogenic milling by Moinuddin and colleagues. The *in-vitro* results showed excellent physical stability, dissolution rate, and pharmacokinetics profile, which was attributed to strong molecular contacts between atenolol and hydrochlorothiazide [25].

Zhang et al. prepared ternary CAMS (Ibrutinib- Oxalic acid- Microcrystalline Cellulose) by ball milling. The novel ternary formulation showed good *in-vivo* and *in-vitro* performance compared to the binary formulation. Furthermore, the ion interactions in the ternary system greatly improved the solubility, dissolution rate, and stability of ternary CAMS [33].

Producing amorphous transitions by mechanical activation depends on many factors, such as temperature, vibration frequency, and milling time. Many examples in literature have also reported the amorphous form of drugs (famotidine, simvastatin) to be produced after milling [143,144]. There are, however some issues that remain unaddressed with the crucial challenge being the scalability of the process.

Another option for preparing CAMS when ball milling or cryo-milling isn't feasible is known liquid assisted grinding. This method involves adding a drop of solvent in the milling process. The liquid facilitates molecular diffusion and possible reactions between the drug and the co-former. It was reported by Pang et al. that piperazine-curcumin CAMS could be successfully prepared using ethanol-assisted grinding rather than ball milling. By partially dissolving components in ethanol, the reaction interfaces were increased, which triggered the formation of CAMS [145]. However, in another study, it was found that carvedilol was not able to form a CAMS after ball milling or liquid-assisted grinding with glutamic acid and aspartic acid but was able to form one after spray drying [146].

5.3. Solvent evaporation

In this methodology, the drugs and excipient are dissolved in a common solvent, after which the removal of the solvent is conducted by employing various processes, which include solvent evaporation, spray drying, and freeze-drying [147,148]. The most common method is rapid evaporation with a vacuum, since organic solvents can be eliminated rapidly, and the drugs precipitate out of solution [134]. Repaglinide and saccharin were successfully dissolved in methanol to achieve binary CAMS in an equimolar ratio and the solvent rapidly evaporated. The authors observed that the binary CAMS maintained stable stoichiometry with a high yield and almost no loss [107].

Abdelquader et al. co-evaporated olmesartan and hydrochlorothiazide with HPMC (as a third ingredient). As a result of co-processing with HPMC, the co-crystallization of drugs was eliminated, and the drug-drug interaction was minimized. The dissolution rate, however, was not significantly enhanced [149].

The main obstacle to this process is the removal of the solvent, phase separation, solvent choice for both drugs and co-former and environmental safety [150]. In addition, ICH guidelines suggest monitoring solvent residues that may cause instability during storage through solvent-mediated recrystallization [137,151].

5.4. Spray drying

Spray drying is a well-known process based on solvent removal by drying suitable solutions in a hot air stream with a spray nozzle atomizer. The benefits of this method include efficient scaling up, continuous manufacturing and suitability for drugs with a high melting point. The limitation of this method includes powder processability, APIs with low T_g, selection of suitable solvent, and residual solvent in the final products. Binary CAMS containing budesonide and ARG were developed by Luet al. through spray drying. ARG and budesonide were dissolved in ethanol/water binary co-solvent. In this system, ARG-budesonide CAMS with a spherical shape and ideal size of (1–5 μm) was obtained [152]. By spray drying, Liu et al. were able to produce ternary CAMS containing carvedilol–aspartic acid -HPMC. In these ternary systems, dissolution can be improved by decreasing the initial dissolution rate and prolonging the supersaturation [112].

5.5. Freeze-drying

Lyophilization, or freeze-drying, is a commonly used procedure for drying and enhancing the stability of a wide range of pharmaceutical products. It might also be utilized to develop porous and low-density CAMS [103,153]. Freeze drying consists of three basic steps: freezing, primary drying, and secondary drying. The primary drying step is the major focus of lyophilization optimization [154]. Researchers developed tryptophan-ofloxacin CAMS in water, then freeze-dried it. This freeze-dried CAMS produced a heterodimer and showed remarkable chemical and physical stability [153]. In terms of ternary systems, Wostry et al. developed a freeze-dried formulation of naproxen together with ARG and lysine as co-formers. The authors found that the freeze-dried ternary CAMS formed heterogeneous systems and improved sample stability at certain concentrations. Freeze-drying could be an effective production method for CAMS; however, it might only be applicable to a limited range of compounds [120].

5.6. Supercritical anti-solvent

Supercritical anti-solvent (SAS) technology has recently been employed in CAMS to increase the solubility and dissolution behaviour of drugs that are poorly water-soluble. SAS employs supercritical carbon dioxide (SC-CO_2) as an anti-solvent [155]. Since SC-CO_2 has a low critical condition and is easily accessible, it is the most commonly utilized supercritical fluid. Additionally, organic solvents can be avoided or minimized, residual solvents can be reduced, and non-flammability, non-toxicity, low price, and solvation power can be adjusted. In this regard, in ball milling, melt-quench, or solvent evaporation, glimepiride did not provide a binary CAMS, but a supercritical anti-solvent method did [156].

5.7. Hot melt extrusion (HME)

HME can be classified into melting techniques (Fig. 5). Under heating, the mixture is melted, and the molten mass is then extruded through the equipment to produce solid dispersions. This technology is a well-

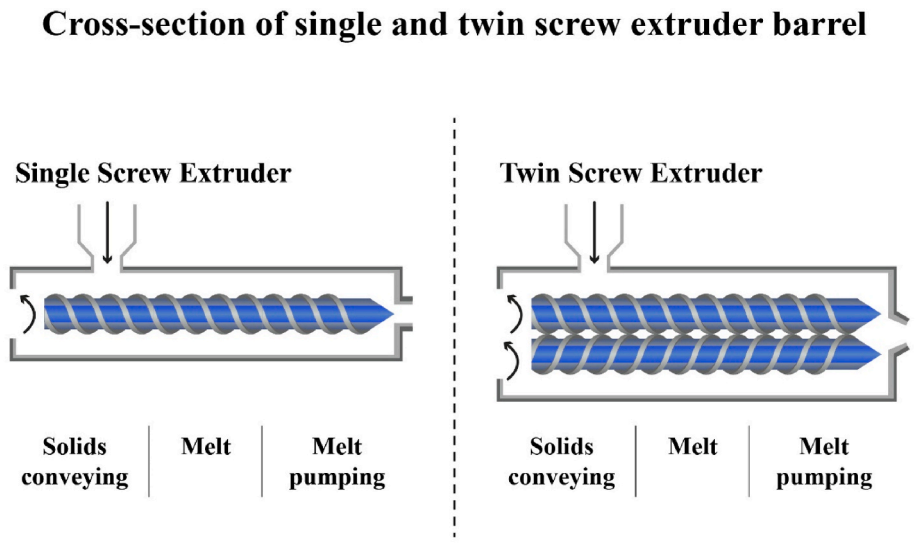

Fig. 5. Schematic of a single screw and twin-screw extruder.

accepted process in the pharmaceutical industry, involving drugs and excipients simultaneously melted (upon melting temperature), homogenized, and extruded. Subsequently, the final product is cooled, solidified, and milled into granules or powder form that is further subjected to downstream processes [157]. HME offers advantages over conventional methods, for instance: continuous process, solvent-free, and superior mixing with the feasibility of scale-up [158]. The significant advance in HME has been the introduction of twin-screw melt extrusion owing to its better mixing capability as described in Fig. 5.

Using two screws leads to the reduction of the residence time of materials and consequently constant mass flow with the improvement of mixing in the extruder. Secondly, it is applicable for drugs susceptible to hydrolysis and oxidation because of its ability to eliminate moisture and oxygen from the mixture. Except for screw design, other parameters are essential for defining the final product properties, including; temperature, feed rate, and rotation speed [158]. HME technology is a challenge for most drug-AA co-amorphization, due to the high thermal as well as mechanical energy. This makes it unsuitable for the disruption of the crystal lattice. Besides, AAs degrade above 200 °C. Regardless of that, Lenz et al. prepared the binary CAMS of arginine-indomethacin (ARG -IND) using HME. A stable co-amorphous formulation that had comparable molecular interactions to the spray drying product was produced, however, it was reported that there could be phase separation depending on the method of preparation [159]. With the help of a twin-screw extruder and monitoring process variables, Arnfast et al. designed ternary systems that included cimetidine and indomethacin combined with 5% polymer. The authors concluded that adding small quantities of polymer successfully reduced the viscosity of the melting materials. Furthermore, screw speed and the temperature had a substantial effect on the processability and viscosity of the ternary systems [129].

Another fusion-based method (KinetiSol®) is a novel approach for the processing of ASDs. There are blades within the chamber that rotate at a high velocity, creating heat through friction and shear force. While in a molten state, this process rapidly blends the drug with carriers to produce a single-phase amorphous product [160]. In general, it is difficult to prepare materials with melting points over 200 °C in HME. Consequently, KinetiSol® dispersing is suitable for processing compositions that contains viscous, high-molecular-weight polymers and compounds with a high melting point that are difficult to prepare by spray drying or HME [161,162]. Gala and colleagues used this technology to produce abiraterone TSD formulations with high melting points and limited solubility in organic solvents. With the KinetiSol® dispersion method, the TSD formulation was improved in dissolution and bioavailability [163].

Apart from the preparation methods used for creating these systems, there has been a gradual upward trend in the application of Design of Experiments (DoE) within this field over recent years. DoE plays a crucial role as a tool in Quality by Design (QbD), which is a systematic methodology utilized for screening and optimizing process parameters. This approach can be implemented to establish dependable and resilient processes for CAMS and ternary systems [164]. Beg et al. have utilized DoE in the development ASD using HME technology. The integration of DoE in ASD development presents benefits over a one-factor at a time approach in terms of resource conservation and minimizing the number of experimental trials needed to produce high quality results [165]. Another study explored the effect of process parameters on binary CAMS consisting of Levofloxacin-ARG. The samples were generated using various inlet temperatures and feed rates within a DoE setup, which is appropriate for producing the desired output [166]. Additionally, predictable dissolution attributes for etodolac ternary systems were successfully achieved via a DoE approach [167]. However, selecting an appropriate design with optimal factors and responses remains unclear and mandates a comprehensive knowledge of formulation and process variables.

6. Scale up

The main challenge in commercializing CAMS lies in their scalability for manufacturing purposes, as current preparation methods are only suitable for producing small quantities. Various factors, such as solvent properties, temperature, thermal and mechanical stress, and moisture content during processing, may cause the drug to recrystallize from its amorphous form. It is crucial to consider the critical physicochemical properties of the drug and its co-former when selecting an appropriate manufacturing method, particularly the melting point and thermal stability of the CAMS components. Overcoming the scalability issue requires careful consideration of several factors, including maintaining the amorphous state of the system, ensuring homogeneity and uniformity, and optimizing the manufacturing process to minimize costs [137].

One suggested method to address scalability concerns is to utilize advanced processing techniques involving constituent fusion, such as Hot-Melt Extrusion (HME), to achieve successful product scaling. HME offers several advantages, including continuous and solvent-free processing, as well as the availability of various equipment capacities for development and optimization at both bench and pilot plant levels [9, 140].

Ball milling has emerged as a viable alternative for scaling single-component amorphous systems due to its proven scalability. However, this method presents challenges such as elevated mechanical stress and difficulty in obtaining a homogeneous mix for large-scale processes. Additionally, issues such as charge build-up and phase transformation need to be taken into account. Consequently, the application of ball milling should be limited to thermally stable drugs and co-formers with higher glass transition temperature (Tg) values [137].

Solvent evaporation via spray drying has been reported as a reliable method for producing stable amorphous glass solutions that are scalable for solid dispersion production. However, the selection of appropriate solvents is a key factor that must be carefully considered to ensure effective large-scale production, taking into account solvent loading capacity and toxicity considerations [140]. In this regard, Jensen et al. have demonstrated the feasibility of utilizing spray drying to produce drug-amino acid (AA) CAMS formulations on a larger scale. The amorphous salt of indomethacin-ARG produced through spray drying exhibited properties comparable to those obtained through ball milling [28]. Despite these advancements, further research is necessary to optimize processing parameters and formulation design to ensure consistent product quality and stability at a larger scale.

7. Mechanism of stabilization and stability

7.1. Miscibility

One of the critical issues which are outstanding for co-amorphous formulations stabilization is the miscibility of components in these formulations. Mainly, observation of an obvious single T_g of a homogeneous single phase co-amorphous formulation could be an indicator of the miscibility of the components where both components are dissolved in each other [2]. By contrast, two T_gs imply non-miscible or rather miscible within the co-amorphous mixtures components that leads to phase separation [24]. There have however been reports of a single T_g being seen for phase-separated systems and two T_gs being seen for miscible systems [168,169].

For predicting the miscibility between the co-amorphous mixture components, Hildebrand first offered the theory of the solubility parameter [170]. The Hildebrand solubility parameter, however, has its limitations. The limitation of this concept is that it is insufficient for polar or specific interactions between components [171].

Hansen suggested a modified theory to estimate solubility parameters for polar components that are more practical [172]. Another alternative method that may be applied to predict the miscibility of components in CAMS is the use of the solubility parameter, which depends on the Flory-Huggins theory [173]. The Flory-Huggins (FH) interaction parameters can be successful in characterizing the behaviour of solid dispersion. A negative value of the FH favours miscibility, whereas a positive value indicates poor miscibility [174]. Marsac et al. [173] and Sun et al. [175] determined the FH interaction parameter for mixing drug-polymer systems comprising of nifedipine and indomethacin in PVP. In comparison to nifedipine, the indomethacin mixture showed more negative values of FH.

In a recent study, Pajula and colleagues calculated the FH interaction parameters for 1122 CAMS, showing that these parameters might be useful for a quick screening of a large set of drugs and co-formers [176]. In recent years, numerous techniques such as Raman mapping [177], and solid-state nuclear magnetic resonance (NMR) techniques [178] have increasingly been used along with theoretical calculations to estimate the miscibility of amorphous systems [2].

7.2. Glass transition temperature (T_g)

This term describes the critical temperature region at which the substance converts from a hard or glassy phase to a rubbery or viscous state upon heating and is usually measured with differential scanning calorimetry (DSC) or modulated DSC [179,180]. The T_g of co-amorphous mixtures is often noticed between the range of the T_g of the individual components [181].

In many cases, CAMS that have higher T_g could be an indicator attributed to enhanced physical stability. T_g is however not always credible for correlating to physical stability. For instance, the co-amorphous drug/drug combination between naproxen-indomethacin in 1:1 M ratio exhibits a favourable dissolution rate and the highest physical stability even though it does not show the highest T_g [21].

As the T_g is the point at which the material transitions from a solid to a viscous liquid form, its molecular mobility is modified. However, in the glassy state, the molecular motions are kinetically frozen in the systems but still show movement at a much lower rate. This change in molecular motion is commonly called relaxation, which causes the recrystallization behaviour of amorphous material at temperatures much below its T_g [180].

The Gordon-Taylor (GT) equation has been used for the anticipation of the T_g of amorphous multi-component systems theoretically (Eq. (1)). This equation has estimated the theoretical T_g values for co-amorphous blends, which consider ideal miscibility without interaction between two components [182].

$$Tgmix = \frac{w1Tg1 + Kw2Tg2}{W1 + KW2} \quad (1)$$

Where w_1 and w_2 represent the respective weight fractions of components, T_{g1} and T_{g2} are the glass transition temperatures, and K is an adjustable fitting parameter. If the estimated and experimental T_g differs by a positive or negative value, it indicates that the intermolecular interactions between the components are strengthening or weakening [26,40]. According to GT's theoretical value, furosemide-ARG CAMS deviated positively by 49.4 °C. According to this deviation, ARG and furosemide exhibit significant intermolecular interactions, which the authors confirmed with FTIR [88].

The miscibility of ketoconazole with PVP K25 polymer was calculated using T_g generated by the GT equations. The authors concluded that in order to keep ketoconazole formulations in the amorphous state, the materials had to be kept at least 50 K below their T_g [183]. At these temperatures, amorphous materials do not possess sufficient mobility due to the high viscosity of the system. Although this approach is widely accepted, recrystallization behaviour, even at these low temperatures, has been observed [184]. However, the parameters that cause the recrystallization behaviour are still poorly understood.

7.3. Molecular mobility

Molecular mobility is regarded as one of the main criteria, which influences the physical stability of the amorphous system. The impact of molecular mobility on the glass transition is known as "global mobility", and these molecular movements might appear as alpha (α)-relaxations [184]. The (α)-relaxations are linked to molecule rotation and translation and can vary depending on whether the system's temperature is above or below T_g. Because α-relaxations occur over a temperature zone where samples switch from a low mobility system (below T_g) to high mobility (above T_g), global mobility has been considered to play a significant part in crystallization. Vyazovkin and Dranca showed that when the temperature drops below T_g, the mobility associated with α-relaxations begins to rapidly decrease, despite the presence of physical instability [185]. Therefore, additional types of relaxation must also be taken into consideration. Furthermore, amorphous systems display intramolecular reorientations, referred to as beta (β)-relaxations, which are expressed as secondary relaxations or "local mobility" [186]. These secondary relaxations, which have been frequently connected to α -relaxations, can be caused by rotation about chemical bonds, as reported by Johari and Goldstein for entirely rigid molecules and termed as Johari-Goldstein (JG) relaxations [186–188].

There is evidence that at temperatures below T_g, β-relaxations play an instrumental role in assessing the probability of crystallization of amorphous materials, while at higher temperatures α-relaxations are considered trivial. Vyazovkin and co-workers stored amorphous indomethacin at 55 °C below the T_g for 149 days and observed a minor melting peak associated with the α polymorph. The authors proposed that β-relaxations are responsible for nucleation in the temperature region, while α -relaxations are too slow to measure [189].

Similar studies with nifedipine, and indomethacin, concluded with similar information about recrystallization below T_g [190,191]. Relaxation processes are however not fully comprehended.

Bhattacharya et al. provided information about the impact of local molecular mobility in amorphous pharmaceuticals as well as physical and chemical stability [184]. A correlation between molecular mobility and the enthalpy relaxation rate of amorphous drugs can be established. For instance, Ueda et al. [192] investigated the formation of CAMS between tranilast (TRL) and diphenhydramine hydrochloride (DPH). The data showed that the enthalpy relaxation rate and molecular mobility of formation of co-amorphous TRL-DPH decreased compared to the two individual amorphous drugs as presented in Fig. 6. Therefore, compared with every amorphous form, TRL-DPH CAMS had a lower enthalpy relaxation rate, resulting in slower molecular mobility and higher physical stability.

In humid conditions, it has been shown that moisture can negatively affect molecular mobility by acting as a plasticizer that lowers the T_g of the amorphous mixture and hence, enhancement in molecular mobility [193]. The plasticization effects of water would be notable to the physical and chemical stability of CAMS, and careful consideration should be given to this factor while developing a product [194].

7.4. Intermolecular interactions

To achieve good stability, it is crucial to mix binary or ternary CAMS at the molecular level [2]. Overall, CAMS exhibit higher physical stability than individual amorphous APIs. At the molecular level, homogeneous mixing inhibits the contact between drug molecules by the co-formers and also prevents drugs from recrystallizing [82]. In this regard, according to the research published by Beyer et al. the incorporation of naproxen sodium into binary CAMS (naproxen-indomethacin) improved physical stability [133]. It was found that no recrystallization occurred during the storage period of 270 days for the ternary CAMS, which were initially amorphous [133]. In the past few years, several mechanisms have been proposed to explain why CAMS exhibits a physical stability advantage, such as good miscibility, high T_g, reduced molecular mobility, strong intermolecular interactions, and intimate mixing at the molecular level.

Accordingly, the characterization of molecular interaction between components is one of the helpful methods for better understanding the physical stability of co-amorphous formulations at the molecular level. The molecular interaction is usually carried out via FTIR, NMR, X-ray diffraction (XRD), DSC, modulated differential scanning calorimetry (MDSC) and Raman spectroscopy. In this context, the interaction studies carried out by Alles et al. using Raman spectroscopy revealed an interaction between naproxen's carboxylic acid moiety and cimetidine's imidazole ring in the binary co-amorphous formulation. They suggested that their interactions probably caused the synchronized release of the two drugs in these systems [21]. Based on hydrogen bonds detected in FTIR studies of griseofulvin TSDs, FTIR was able to predict improvements in stability and solubility due to improved hydrogen bonding between the griseofulvin and carrier [195]. In another study, FTIR was used to investigate possible intermolecular interactions between the drug-polymer in the TSD formulation and the drug-drug interaction in the co-amorphous systems [128].

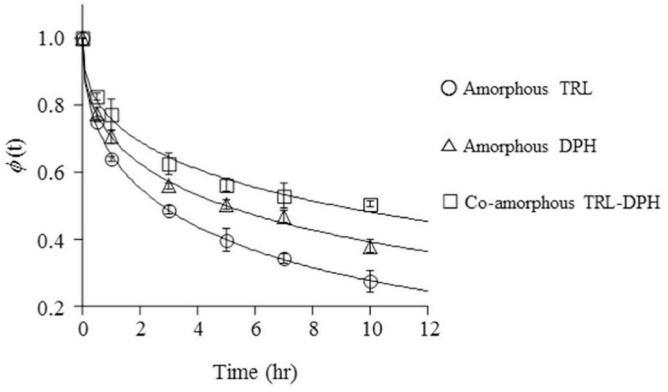

Fig. 6. Enthalpy relaxation profiles of amorphous tranilast (TRL) and diphenhydramine hydrochloride (DPH), and CAMS TRL-DPH (1:1) at Tg-20 °C. Reproduced from Ref. [192] with permission.

Likewise, Pacult et al. investigated the long-term stability of ternary mixtures of bicalutamide-flutamide and polymers using XRD and DSC analyses. A specific interaction between the drug and polymer molecules inhibited the tendency to crystallize and made the ternary CAMS stable at room temperature for at least 182 days [196]. A research team characterized polymer blends and ternary formulations using MDSC and concluded that multiple amorphous phases coexisted with crystallized itraconazole phases, depending on the TSD composition. Despite this, all of the ternary formulations appeared to be amorphous based on XRD results [197].

Also, Raman spectroscopy and solution ^{1}H NMR were used to characterize the polymorphic form of the drug from precipitation studies and also to assess the drug-polymer interaction in TSDs [198,199]. Besides, it has been shown that molecular interactions can be identified by a deviation of T_g determined experimentally compared to the calculated T_g according to the GT equation. So the deviation between calculated and experimentally obtained T_g values has been translated as the probability of intermolecular interactions [40].

7.5. Intimate mixing

For several co-amorphous formulations, satisfactory physical stability is related to intimate mixing between the components. It was noted that the presence of intermolecular interactions among the components of co-amorphous mixtures does not consistently appear to correlate with the attainment of satisfactory physical stability. Su et al. prepared co-amorphous tadalafil–repaglinide by solvent evaporation. It was found that both drugs in the CAMS showed significant increases in intrinsic dissolution rate, improved stability and maintained supersaturated levels. This stability advantage was attributed to the intimate molecular mixing of tadalafil and repaglinide [200].

It seems that intimate mixing provides benefits in terms of physical stability, as it was shown that the simvastatin and glipizide combination demonstrated enhanced physical stability without an increase in T_g or any recognizable intermolecular interactions [82]. Similar reports were also reported for ritonavir/indomethacin [81], and glipizide/atorvastatin [201].

It is suspected that slow de-mixing and phase separation are responsible for the recrystallization of these systems. According to Löbmann et al., molecular mixing and molecular interactions were responsible for the physical stability of ternary CAMS (indomethacin-carbamazepine with diverse AA) after ball milling. For co-amorphous mixtures, it should be noted that the solubility of the ingredients is the first necessity, while molecular interactions, intimate mixing, and elevated T_g, are caused by the ingredients' miscibility in the co-amorphous mixture.

Despite significant advancements in understanding the stabilization mechanism of CAMS, there are still several unanswered questions regarding their stability. The stability of CAMS is influenced by multiple factors. These include molecular mobility, co-former selection,

processing methods, storage conditions, and intermolecular interactions. Molecular mobility plays a crucial role in CAMS stability, as high molecular mobility in amorphous substances can lead to recrystallization or phase separation, resulting in decreased stability. This can however be mitigated by the incorporation of appropriate stabilizers or plasticizers to minimize molecular mobility and improve CAMS stability [2].

The selection of suitable co-formers is imperative to enhance stability. Research conducted by Yarlagadda and colleagues has shown that specific combinations of co-formers can positively impact stability, while others may have negative effects [75].

Controlled storage conditions, such as low humidity and temperature, are essential to prevent exposure to environmental factors that could degrade or crystallize the system, thereby reducing its stability [137,202].

To enhance the stability of CAMS, various preparation methods such as spray drying or co-grinding can be optimized to decrease intermolecular interactions and minimize the occurrence of recrystallization or phase separation. Additionally, protective coatings or packaging can act as physical barriers against environmental factors, further improving the stability of these systems [137].

The strength of intermolecular interactions between co-former molecules is another crucial factor influencing stability, as strong hydrogen bonding or other interactions enhance stability, while weak interactions can diminish it [138,203].

In conclusion, understanding and optimizing these factors are essential for improving the stability and shelf-life of CAMS, which is crucial for their practical applications as drug delivery systems.

8. Evaluation of in-vivo performance of binary and ternary systems

One of the primary motives behind CAMS is to enhance the physicochemical features such as an increase in solubility, dissolution and stability which bear significant consequences for their biopharmaceutical performances. As an example, indomethacin and ritonavir degrade at 40 °C immediately after their conversion into their amorphous forms. When formulated as co-amorphous mixtures, however, they exhibited improved physical and chemical stability during 90 days [81].

8.1. Dissolution properties

Due to the high internal energy and random orientation of molecules, amorphous forms possess an increased solubility and dissolution profile compared to their crystalline forms. Besides, co-amorphous formulations generally show higher dissolution performances than their crystalline and amorphous of individual drug counterparts. This was proved by the research carried out on the binary mixture of naproxen/cimetidine where the binary mixture showed a better dissolution rate than the individual crystalline forms and amorphous cimetidine [21].

Moreover, the selection of appropriate co-formers can efficiently help prevent solution-induced recrystallization. Several publications have indicated that the strength of intermolecular interactions between co-formers and APIs could also maintain supersaturation and inhibit crystallization tendency [2,76]. For example, charge-assisted hydrogen bonding interaction between components of lurasidone hydrochloride (LH) and saccharin formulation (SAC) resulted in prolonged physical stability and persistent supersaturated dissolution LH-SAC co-amorphous formulation [106]. However, in a subsequent study, it was demonstrated that the co-former solubility is another critical parameter for enhanced dissolution properties. In this regard, Löbmann et al. proved that dissolution test results of indomethacin/AA co-amorphous formulations were dependent on co-former solubility and strength of the interaction between drug-co-former [79]. However, if the solubility of the co-former is higher than a drug, and the interactions between the drug and co-former are weak, then the co-former dissolves too fast, and the drug becomes susceptible to recrystallization [28].

A non-sink dissolution condition is also essential to obtain supersaturated dissolution profiles, which indicate the degree of supersaturation and the ability of co-formers to inhibit solution-mediated recrystallization [76]. In this regard, it was found that the solubility and dissolution profiles of particularly binary drug-AA mixtures in phosphate buffer and non-sink conditions in bio-relevant (fasted and fed state simulated intestinal fluids) media showed that all the formulations provided long-lasting supersaturation and enhanced dissolution behaviours compared to amorphous and crystalline substances alone [123].

Despite the importance of molecular interactions in dissolution behaviour, Dengale et al. showed that ritonavir-indomethacin co-amorphous formulation had an effective enhancement in solubility and dissolution profiles of ritonavir because of it being intimately mixed without evidence of intermolecular interactions [81]. This was also the case when a co-amorphous combination of simvastatin-glipizide showed an improvement in stability and solubility without traceable intermolecular interactions after ball milling [82]. It is, therefore, still possible to stabilize amorphous drugs by physically separating similar molecules, known as intimate mixing or molecular mixing, when the drugs do not show any molecular interactions with the co-formers [24].

Aside from improving the dissolution of insoluble drugs, a synchronous release of drugs can sometimes be observed by CAMS as a result of pairwise interactions between molecules [21].

It was first reported by Alleso and co-workers that cimetidine-naproxen CAMS displayed a synchronized release for both drugs and no remarkable changes in intrinsic dissolution rate for the individual drugs, which could be ascribed to pairwise solvation and short-range order of the molecules of cimetidine and naproxen [21]. Similarly, Lobmann and co-workers suggested that the formation of heterodimer through hydrogen bonds is thought to be responsible for synchronizing intrinsic dissolution of the indomethacin-naproxen CAMS at a 1:1 M ratio combination as well as the higher stability co-amorphous blend [204] (Fig. 7).

As for ternary systems, ternary CAMS have performed better than binary CAMS for dissolutions [76,205]. In a study conducted by Riekes et al., ezetimibe-lovastatin-soluplus® ternary CAMS were compared to ezetimibe-lovastatin binary CAMS. According to their results, the intrinsic dissolution rate of ezetimibe and lovastatin increased 18 and 6-fold in ternary CAMS, respectively. As a result of the formation of intermolecular hydrogen bonds between Soluplus® and both of drugs, Soluplus® decreased recrystallization of ezetimibe-lovastatin binary CAMS and increased physical stability [128]. Another ternary co-amorphous formulation composed of Ibrutinib–oxalic acid–microcrystalline cellulose (IBR-OXA-MCC) displayed improved dissolution behaviour compared to crystalline IBR and binary IBR-OXA during dissolution. Accordingly, ternary IBR-OXA-MCC formulations showed cumulative releases of 97.38% after 4h, which is 5.33 and 1.65-fold higher than its crystalline and amorphous IBRs as shown in Fig. 8 [33].

Similarly, ternary co-amorphous mixtures containing naproxen (NAP- ARG)-proline (PRO), naproxen was stabilized with ARG using salt formation. The highly soluble AA PRO because of additional hydrogen bonding caused an improvement in the dissolution profile. Accordingly, ternary mixtures showed significantly improved dissolution properties compared to the binary mixture and crystalline naproxen as shown in Fig. 9 [206].

8.2. In-vivo evaluation

The purpose of CAMS is to increase drug solubility and dissolution rates, hence more free drug absorption which can lead to an improvement in the bioavailability of poorly soluble drugs. It is important to note, however, that the *in-vitro* benefits of CAMS may not always correspond well with their *in-vivo* benefits. Thus, a better in-vitro dissolution performance compared to a pure crystalline or amorphous

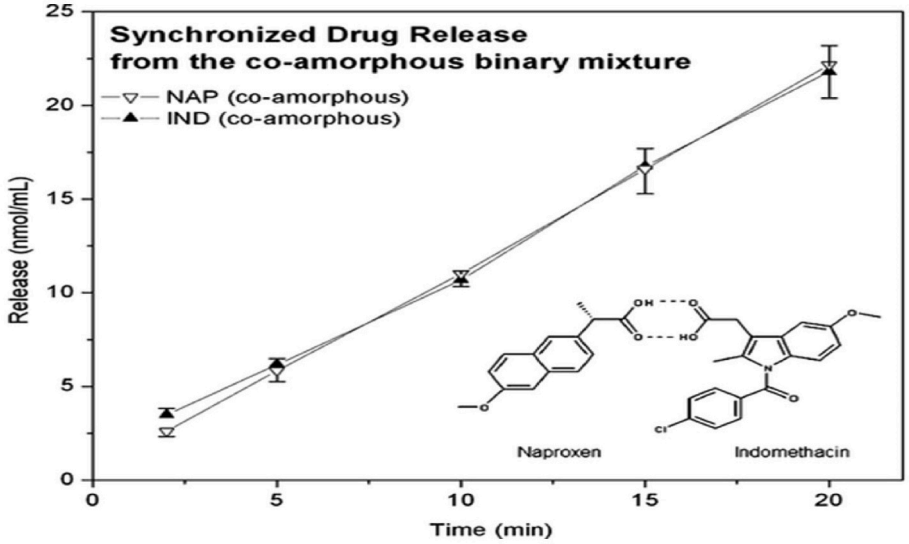

Fig. 7. Intrinsic dissolution rate of binary CAMS indomethacin (IND)-naproxen (NAP) exhibits a synchronized drug release. with permission from Ref. [204]. Copyright © 2011 American Chemical Society.

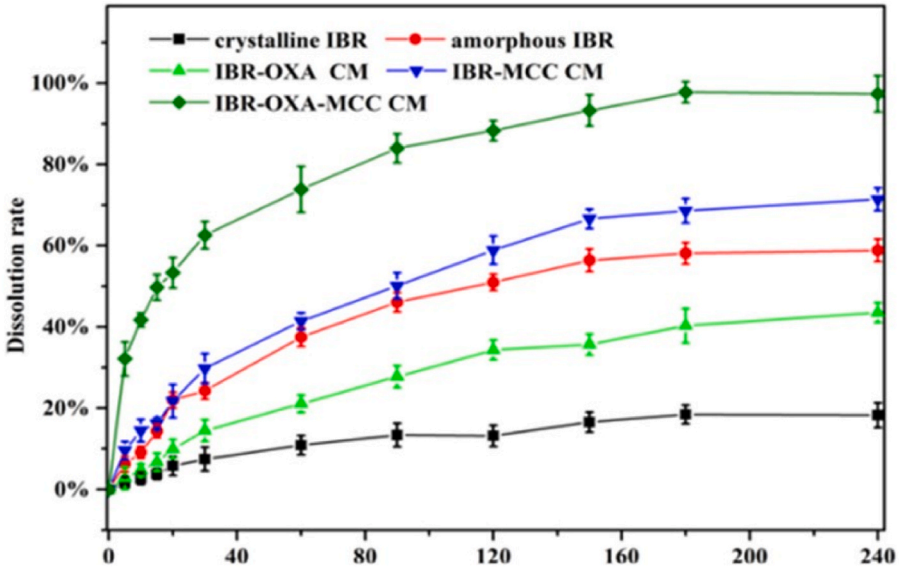

Fig. 8. The dissolution rate of ternary IBR-OXA-MCC CAMS is higher than that of binary IBR-OXA. Reproduced from Ref. [33] with permission.

form of the drug does not always translate into an improved bioavailability or dissolution *in-vivo*, because of different circumstances *in-vitro* versus in-vivo [207].

Even though the co-amorphous technology exhibits considerable privileges for increasing the dissolution and stability of amorphous drugs, there's limited research on the *in-vivo* study of co-amorphous formulations. An *in-vivo* study on male rats showed that, when curcumin was administrated in its co-amorphous form with artemisinin, a high amount of curcumin concentration in plasma was observed compared with the individual drugs, although it wasn't explicitly stated whether curcumin amorphization or co-amorphization was responsible for the increase [208]. Considering the previous findings, the maximum plasma concentration (C_{max}) and area under the curve (AUC) of concentration versus time of poorly soluble drugs indicated improvement in co-amorphous formulations [25,209,210]. An investigation of loratadine-citric acid CAMS oral administration showed that loratadine's C_{max} and AUC_{0-10h} increased respectively by 2.6- and 2.5-fold while its T_{max} decreased from 0.75 h to 0.5 h. The improved *in-vivo* performance was related to loratadine's enhanced dissolution in-vitro after co-amorphization. Similarly, there was a high bioavailability and maximum plasma concentration observed for the co-amorphization of olanzapine carboxylic acid dispersions compared with the marketed formulations [211]. In a recent study, Moinuddin et al. co-amorphized hydrochlorothiazide with atenolol to improve oral bioavailability. Studies in mice indicated that the bioavailability of hydrochlorothiazide (HCT) with atenolol co-amorphous mixtures was improved compared to the HCT in the physical mixture, amorphous and crystalline material [25] (As seen in Fig. 10).

There are other factors that can affect in-vivo performances. These include efflux transportation, drug metabolism and degradation. Particularly for BCS class IV drugs, poor dissolution behaviour and low membrane permeability can lead to poor oral bioavailability. The low permeability is most often caused by the physicochemical properties (size, polarity) of the drug molecule, as well as being substrates of the efflux pump [212]. Utilizing naringin as an efflux pump inhibitor, Teja and co-workers formulated a co-amorphous formulation that contained

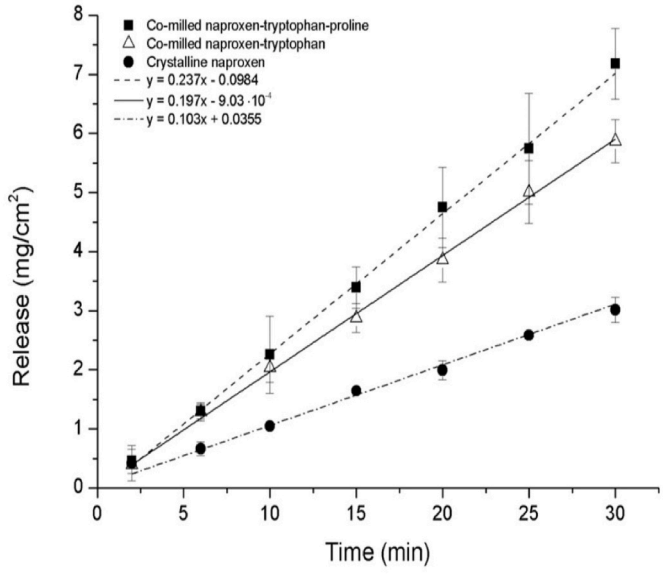

Fig. 9. Enhancement of dissolution rate in ternary system by incorporating an AA with a high water solubility.Reproduced from Ref. [206] with permission.

the low-permeability and poorly water-soluble drug talinolol. These formulations improved talinolol's dissolution profile and its permeability-absorption by inhibiting the action of P-glycoprotein (Pgp). The average $AUC_{(0-t)}$ of co-amorphous talinolol-naringin in rats had an approximately 5.4-fold increase in comparison with its crystalline counterpart. This contributed to the inhibition of P-gp as well as enhanced solubility [213]. The improved permeability and solubility resulted in higher *in-vivo* bioavailability. In Table 9, an updated overview of in-vivo studies on binary CAMS are presented.

Recently, a few publications have reported some *in-vivo* data on TSD as shown in Table 10. Zhang et al. found that co-spray drying lactose monohydrate (LM) as an inert excipient in a co-amorphous formulation containing sacubitril (SAC)-valsartan resulted in the highest solubility and excellent bioavailability for valsartan and metabolic product of SAC [214]. There have been some speculations that drug-excipient interactions can have considerable effects on effect on dissolution rate and bioavailability. Despite *in-vitro* studies showing improved solubility and dissolution of low solubility APIs after co-amorphization, little is known about the existing state and destiny of binary and ternary systems *in-vivo* [214].

9. Formulation of binary and ternary systems into tablets

Co-amorphous mixtures have rarely been used as oral dosage forms, despite their ability to stabilize amorphous drugs in the solid state and improve their dissolution properties. Co-amorphous products compressed into tablets or embedded into capsules run a risk that their amorphous structure, stability, or dissolution profiles may be altered by environmental factors (temperature and moisture) [201,215]. In addition to their soft and sticky nature, amorphous solid dispersion may have difficulty in granulating and sieving, as well as poor flowability and compressibility. On the other hand, wet granulation may not be a suitable granulation process, due to water having the tendency to cause plasticization and crystallization. Besides, during the process of melt granulation, the heat input can be above the T_g of components within the formulation and may therefore induce a risk for recrystallization [216]. Formulation of co-amorphous dispersion into tablets is generally demanded for oral delivery, as well as for other administration routes including the buccal, or pulmonary routes [134].

Lenz et al. were the first to develop a tablet containing indomethacin-ARG by means of the co-amorphous strategy. Compression had little effect on molecular connections, and there was no crystallization observed. Tablets demonstrated fast indomethacin release, higher supersaturation concentration, and long-term stability. Tableting had no effect on AUC as compared to spray-dried co-amorphous powder of indomethacin-ARG [215]. Tanaka et al. formulated co-amorphous tablets containing loratadine with several organic acids (malic acid, tartaric acid, citric acid and succinic acid) through injection-moulding (IM) as a single-step process (Fig. 11) [217]. The IM technique is most commonly used for making plastic objects, where hot melted thermoplastic is injected into a mould and allowed to cool [218]. It was found that the dissolution was greater in the loratadine–acids co-amorphous tablet than in the pure amorphous loratadine. Also, the co-amorphous tablet containing loratadine and each acid interacted ionically, and solubility, and stability were proportional to the strength of the interaction between the two acids.

The concept of adding a third excipient to binary CAMS was also used to optimize the preparation and to improve tabletting and coating [130,219]. In this regard, Petry et al. designed ARG-indomethacin CAMS by the spray drying method, and the obtained spray-dried powders were then converted into tablets and coated with Kollicoat® Protect (Fig. 12). It was found that the coated tablets had high physical stability, even when the formulation was stored at room temperature with 75% RH for a period of 91 days with no crystallization was observed [125]. Additionally, the AUCs of indomethacin–ARG CAMS tablets coated with the Kollicoat® protect polymer increased by 30% compared to their respective uncoated formulations [125].

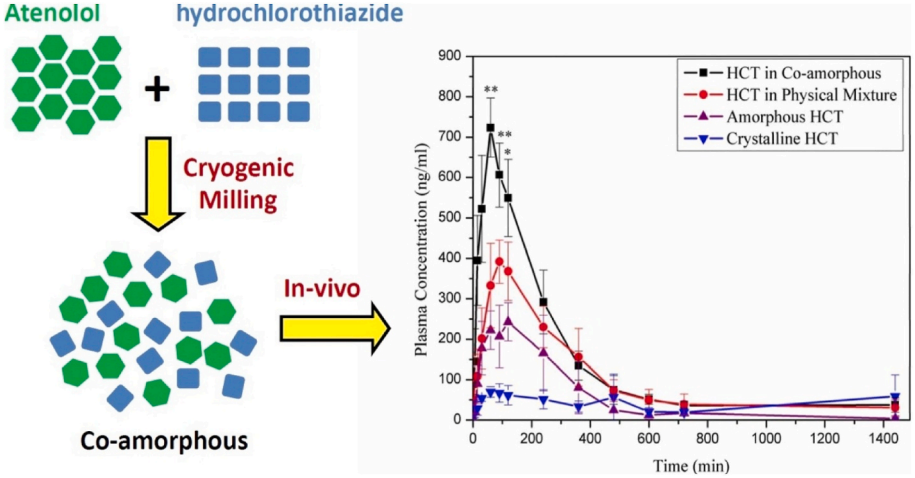

Fig. 10. Increased plasma concentration of hydrochlorothiazide – atenolol CAMS. Reproduced from Ref. [25] with permission.

Table 9
Recent In-vivo studies of binary CAMS.

Binary CAMS	In-vivo performance	Ref.
Simvastatin - epigallocatechin-3-gallate (SIM- EGCG)	SIM-EGCG systems at 1:3 M ratio had a significant increase in C_{max} of 1.81-fold and an AUC_{0-24h} 1.62-fold compared to the crystalline drugs	[108]
Nifedipine - epigallocatechin-3-gallate (NIF- EGCG)	NIF-EGCG systems at 1:3 M ratio has a significant increase of 5.69-fold and AUC_{0-24h} 4.57-fold compared to crystalline drugs	[108]
Apigenin- oxymatrine (APG-OMT)	The C_{max} and AUC_0 of APG-OMT was increased by 130% and 144% respectively and the T_{max} of APG-OMT was relatively shorter than pure APG.	[269]
Atorvastatin calcium (ATC)-nicotinamide	In comparison to the crystalline ATC group, C_{max} increased by 2.2-fold and $AUC_{0-6\ h}$ increased by 1.7-fold	[270]
Curcumin (CUR)-artemisinin	At shorter T_{max} (30 min), the CAMS provided a high C_{max} and $AUC_{0-24\ h}$, while the crystalline CUR did not give a detectable plasma drug concentration.	[208]
Telmisartan-Hydrochlorothiazide(TEL-HCT)	C_{max} and AUC_{0-48h} of TEL-HCT CAMS (1:3) were increased 10-fold and 3-fold compared to crystalline state	[257]
Curcumin(CUR)-piperine	Compared to CUR crystalline material, CAMS showed a 2.6-fold improve in C_{max} and 2.16-fold improvement in AUC_{0-24h}; in comparison with the piperine crystalline form, C_{max} was improved by 1.74-fold, while AUC_{0-24h} was enhanced by 1.52-fold.	[26]
Docetaxel - bicalutamide (DOX-BIC)	Compared with crystalline DOX group, C_{max} increased by 8.80- fold and $AUC_{0-24\ h}$ increased by 11.83 fold; compared with crystalline BIC group, C_{max} increased by 3.43-fold and AUC_{0-24h} increased by 3.22-fold	[209]
Docetaxel-myricetin(MYR)	In comparison to crystalline DOX, the C_{max} increased by 3.9-fold and the AUC0-∞ increased by 3.13-fold, whereas in comparison to crystalline MYR, the C_{max} increased by 2.1-fold and the $AUC_{0-\infty}$ increased by 1.9-fold.	[271]
Hydrochlorothiazide (HCT)-atenolol	In comparison to crystalline HCT group, C_{max} improved 7.30-fold, and AUC_{0-24h} improved 3.42-fold	[25]
Loratadine (LOR)-citric acid	As compared to the crystalline LOR group, C_{max} was 2.59 times higher and AUC_{0-10h} was 2.45 times higher	[272]

Similarly, R Ojarinta et al. developed tablets containing spray-dried co-amorphous ibuprofen-ARG or indomethacin-ARG, and PVP. As a result of significant interactions between PVP and the drug, ibuprofen-ARG CAMS tablets with PVP exhibited a higher initial drug release than tablets without PVP. It is important to note that PVP inhibits precipitation. This, therefore, allows the ARG-indomethacin CAMS tablets to remain supersaturated for a longer time when compared to the tablets without PVP [130]. Furthermore, adding a third ingredient to ASD improves the performance of binary ASD in tablets. For example, Hanada et al. examined the benefits of an immediate-release ternary ASD (itraconazole, hypromellose, mesoporous silica) with a high drug load to maintain high drug supersaturation during dissolution testing with the HME technique. In neutral conditions, the ternary ASD tablet showed higher itraconazole release than the binary ASD tablet. Furthermore, an ability to maintain supersaturation was observed in the dissolution behaviour of the ternary ASD tablet [220].

In recent years, there has been an expansion in the application of amorphous drug dispersions beyond oral administration, encompassing alternative drug delivery methods such as transdermal delivery. To enhance drug permeation and gain better control over drug release, several researchers have conducted experiments investigating the combination of amorphous drugs with transdermal delivery [221–223]. The findings of these studies indicate that amorphous drug dispersion shows promise as a valuable approach for efficient drug delivery via transdermal routes.

Table 10
Recent in-vivo studies on TSD. HPMCAS: hypromellose acetate succinate, HP-b-CD: 2-Hydroxypropyl-beta-cyclodextrin, SLS: Sodium lauryl sulfate, PVP: polyvinylpyrrolidone, SDS: Sodium dodecyl sulfate, HP: Hydroxypropyl cellulose.

TSD	*In-vivo* performance	Ref.
Ticagrelor-TPGS- NeusilinR	Compared to the pure drug, this formulation improved peak plasma concentration (C_{max}) and relative bioavailability by 238.09 ± 25.96% and 219.78 ± 36.33%, respectively.	[273]
Lopinavir(LPV) -Kollidon® VA 64-Soluplus	Bioavailability of LPV in Soluplus matrix extrudate was 1.70-fold greater than in Kollidon® VA 64 matrix extrudate and 3.70-fold greater than in LPV crystals	[274]
Abiraterone- HP-b-CD-HPMCAS	TSD enhanced Abiraterone bioavailability by 13.8-fold, the AUC_{0-10h} of ternary was higher than binary solid dispersion	[163]
Paclitaxel- PVP K30 -SLS	Paclitaxel plasma levels are within a therapeutic range for metronomic paclitaxel therapy.	[275]
Probucol- HPC-pluronic® F68 and SDS	The AUC value of the Probucol in ternary stabilizer systems is 15 times higher than that of coarse Probucal suspensions	[30]
Ibrutinib- Oxalic acid -microcrystalline cellulose	Approximately 1.49-fold higher than crystalline Ibrutinib	[33]

10. Transdermal application

The transdermal approach offers a promising alternative to traditional oral administration for delivering CAMS in the treatment of localized and systemic diseases. Transdermal formulations based on CAMS can help maintain drug supersaturation, prevent drug recrystallization, and enhance skin permeation [221]. Additionally, in certain cases, co-formers used in these systems can enhance drug permeation. For example, a supersaturated CAMS of atenolol was developed using urea as a co-former, resulting in the highest observed skin permeation through mice's skin [101]. In another study, a CAMS of piroxicam was developed with citric acid as a co-former. The cumulative amount of piroxicam and steady-state flux through mice skin was nearly doubled in the CAMS compared to a pure drug suspension and a physical mixture of the drug and co-former [99]. However, conducting a comprehensive stability study following regulatory guidelines, as well as *in vivo* pharmacokinetics and pharmacodynamics studies, would provide a more in-depth understanding necessary to advance amorphous drug-loaded supersaturated transdermal delivery systems.

11. Conclusion

In conclusion, significant progress has been made in the development of co-amorphous systems (CAMS) over the past decade, with the aim of improving the solubility and stability of water-insoluble drugs. Binary CAMS have been extensively researched and have demonstrated potential in enhancing the solubility and physical stability of numerous poorly soluble drugs. Researchers have however shifted their focus towards developing ternary CAMS and Ternary Solid Dispersions (TSD), which offer additional advantages such as enhanced stability and improved dissolution rates. Despite this, there are several challenges that still need addressing. These include the challenge of limited understanding of the underlying mechanisms underpinning these systems, a comparison of the impact of incorporating a third component in ternary systems versus binary CAMS and binary ASD, and the necessity to characterize ternary systems in terms of stability and dissolution behavior. To overcome these challenges, further research is required to

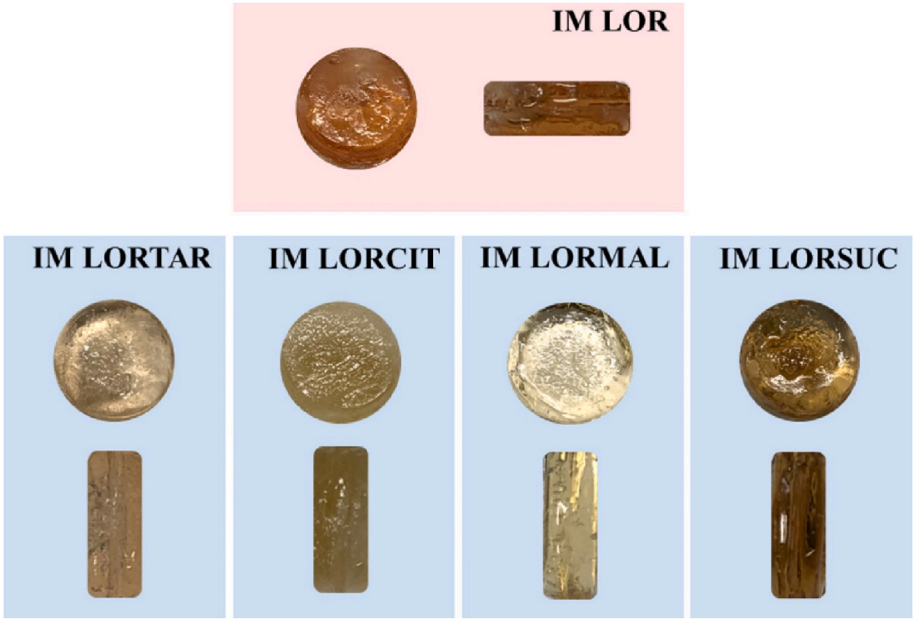

Fig. 11. Injection molded tablet of loratadine and loratadine -acid co-amorph. Reproduced from Ref. [217] with permission.

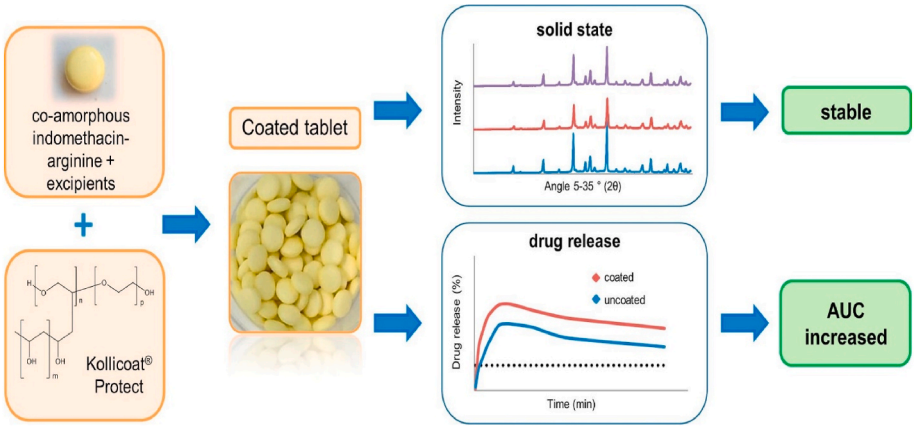

Fig. 12. Formulation of polymer-coated of co-amorphous tablets. Used with permission from Ref. [125].

comprehensively explore the advantages and drawbacks of each approach, optimize formulation parameters, and develop new technologies to advance drug delivery systems. Ultimately, the selection of a specific method will depend on various factors, including the unique characteristics of the drug, the other components involved, and the desired dosage form.

12. Future perspectives

In addition to the preparation methods used for creating these systems, there as been a gradual increase in the application of Design of Experiments (DoE) in this field in recent years. DoE plays a crucial role as a tool in Quality by Design (QbD), which is a systematic methodology utilized for screening and optimizing process parameters. This approach can be implemented to establish reliable and robust processes for CAMS and ternary systems [164]. Beg et al. utilized DoE in the development of Amorphous Solid Dispersions (ASD) using the Hot-Melt Extrusion (HME) technology. The integration of DoE in ASD development offers advantages over a one-factor-at-a-time approach in terms of resource conservation and minimizing the number of experimental trials needed to achieve high-quality results [165]. Another study investigated the effect of process parameters on binary CAMS comprising levofloxacin-ARG. The samples were generated using various inlet temperatures and feed rates within a DoE setup, which was suitable for producing the desired output [166]. Furthermore, a DoE approach was successfully employed to achieve predictable dissolution characteristics for etodolac ternary systems [167]. However, the selection of an appropriate design with optimal factors and responses remains unclear and requires a comprehensive understanding of formulation and process variables.

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Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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