REVIEW ARTICLE

Co-Amorphous Solid Dispersions: A Strategy for Improving Poorly Soluble Drug Delivery using Amino Acids and Hydrophilic Carriers

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Abstract

Class II drugs in the Biopharmaceutical Classification System (BCS) are characterized by low solubility and high permeability, necessitating enhanced dissolution to improve their bioavailability and therapeutic efficacy. This review focuses on solid dispersion (SD) strategies, particularly using amino acids (AAs), to enhance the aqueous solubility of compounds, including hydrogen bonding, ionic interactions, and π–π stacking. The review also outlines various techniques for preparing amorphous SDs, such as hot melt extrusion, spray drying, and solvent evaporation, highlighting their scalability and feasibility for pharmaceutical manufacturing. Due to their unique physicochemical properties, AAs serve as effective co-formers in SDs, contributing to the stabilization of the amorphous state and preventing drug recrystallization, a significant limitation in conventional approaches. Finally, the review discusses strategies to overcome key challenges associated with SD and concludes that AA-based systems offer a promising avenue for enhancing the solubility and bioavailability of BCS class II drugs, potentially leading to improved clinical efficacy and patient outcomes.

Key words: Amino acids, biopharmaceutical classification system-II drugs, co-amorphous solid dispersion, hydrophilic carrier, solubility

INTRODUCTION

The poor aqueous solubility of drug molecules is a significant challenge in the pharmaceutical industry. Around 90% of drugs in development and 40% of generic formulations suffer from low water solubility, leading to inadequate oral absorption, reduced bioavailability, and diminished therapeutic effectiveness.[1,2] According to the Biopharmaceutical Classification System (BCS), drugs are categorized into four categories based on permeability and solubility. Specifically, BCS class II drugs are characterized by low solubility and high permeability, where the dissolution rate is the primary factor limiting absorption. Therefore, effective formulation is crucial in optimizing their absorption from the gastrointestinal tract.[3,4]

Amino acids (AAs) are the fundamental building blocks of peptides and proteins and can be classified as hydrotropes because they can function as hydrogen bond donors or acceptors. There is considerable interest in using AAs as a natural and safe alternative. AAs are low-molecular-weight, water-soluble excipients or co-formers in co-amorphous (CAM) formulations. These formulations aim to enhance poorly soluble drugs' solubility and dissolution rate. Among the 20 natural AAs, each exhibits unique characteristics, including variations in size, hydrophobicity, and polarity. These differences contribute to various physicochemical properties that can benefit various drug molecules. A selection of AAs with diverse side chains, including neutral aromatic, aliphatic, and polar (both charged and uncharged) residues, was chosen to investigate how specific non-ionic interactions can improve drug solubility.

Several formulation strategies have been explored to improve the delivery of poorly soluble BCS class II drugs. These

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strategies focus either on enhancing the dissolution rate or improving solubility over time.[5] Techniques such as solid dispersion (SD), amorphous forms, and salt formation have been investigated. The amorphous solid state is particularly effective in improving solubility and dissolution rates due to its lower energy requirement for dispersion. The conversion of crystalline drugs to an amorphous form is a common approach for increasing solubility. However, the instability of amorphous systems, which can lead to recrystallization during storage, processing, or interaction with biological fluids, limits their effectiveness.[6]

To address the instability issues associated with amorphous systems, the development of amorphous solid dispersions (ASD) has emerged as a pronounced solution. SDs involve dispersing an amorphous active ingredient within an excipient matrix.[7,8] This approach leverages the enhanced solubility provided by the amorphous form of the active compound. ASDs improve drug delivery by increasing gastrointestinal tract supersaturation and enhancing bioavailability. Notably, incorporating hydrophilic polymers into SDs has been a significant advancement, as it increases their wettability, further improving solubility.[9]

SOLUBILITY ENHANCEMENT

Solubility enhancement is a key focus in pharmaceutical and chemical sciences, aiming to improve the dissolution and bioavailability of poorly soluble compounds. SD employs several techniques to enhance solubility, including reducing particle size, creating SDs, forming salts, employing co-solvency, and using surfactants. These methods contribute to improved drug absorption, which ensures better therapeutic efficacy and greater patient compliance.[10]

SD

SD is believed to be one of the earliest methods used to enhance the solubility and dissolution rates of active pharmaceutical ingredients, and it is widely researched in the pharmaceutical field. In the early 1970s, Chiou and Riegelman defined SD as the distribution of one or more active ingredients within an inert medium, achieved through techniques such as melting, dissolution, or a combination of both. SD can be classified into various categories shown in Figure 1.[8,11]

ASD

ASD is increasingly utilized for poorly soluble pharmaceutical compounds, as it enhances the solubility of the drug by disrupting its crystalline lattice, leading to a higher energy amorphous state. This technique allows for better dissolution rates and improved bioavailability, addressing challenges faced by many drugs that demonstrate limited solubility in their crystalline forms. In polymeric SDs, the drug is dispersed within a glassy polymer matrix, where stabilization occurs through the polymer chains' physical separation of drug molecules. These polymeric carriers often have a high glass transition temperature (T_g), resulting in a rise in the T_g of the amorphous drug. Polymers stabilize the system by limiting molecular mobility and reducing nucleation and crystallization. Furthermore, interactions among the polymers and the drug can assist in inhibiting recrystallization.[12]

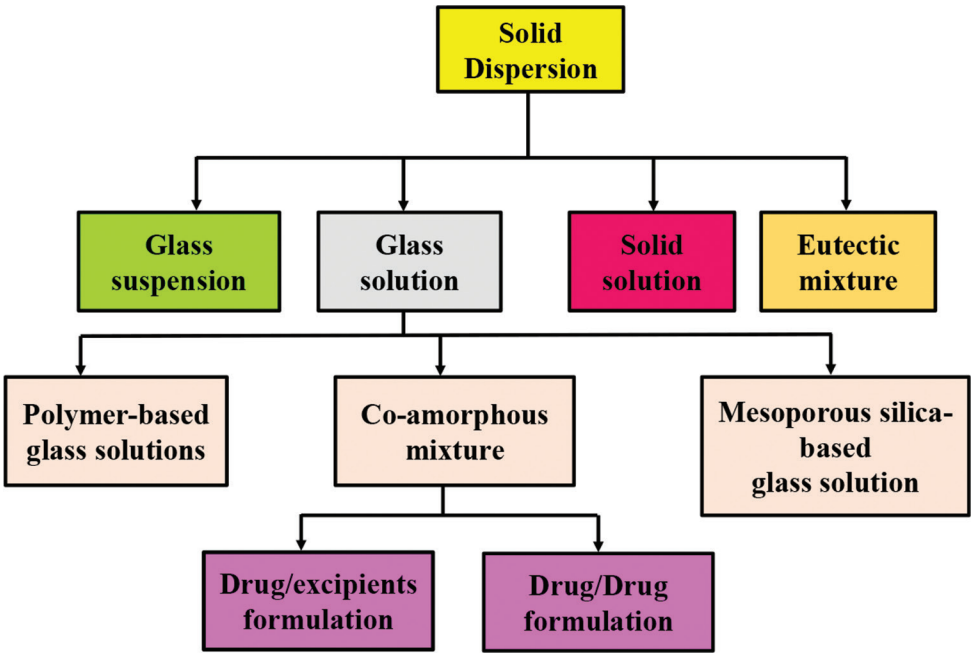

Figure 1: Classification of Solid dispersion.

CO-AMORPHOUS SOLID DISPERSIONS (CAM-SD)

Recent advancements have introduced a novel method to enhance the solubility and stability of amorphous pharmaceutical formulations: CAM-SD. This technique combines two or more small-molecule constituents into a single homogeneous amorphous phase, which helps stabilize poorly soluble drugs in their amorphous form. Because these dispersions utilize small molecular weight components, only a minimal amount of stabilizer (co-former) is required, reducing the necessity for large dosage sizes and addressing the hygroscopic issues often associated with polymeric ASD.[13]

CAMs offer enhanced drug solubility because of the increased energy state of the amorphous form, which minimizes the energy required for crystal lattice rearrangement during dissolution. These systems demonstrate superior stability and dissolution characteristics compared to crystalline drugs and other amorphous forms. In one study, it was suggested that CAM systems can significantly elevate the maximum concentration of a drug by 1.3–30 times, the area under the curve by 1–5 times, and decrease the time to reach maximum concentration.[14]

In research, the stability of CAM systems is primarily attributable to the elevated T_g and the homogenous distribution of molecules attained by proper mixing.[14,15] AA hinders recrystallization by increasing physical stability through interactions such as π–π stacking, hydrogen bonding, and ionic interactions.[16] In another research, CAM dispersions enhance stability through molecular mixing.

SELECTION OF AA AS A CO-FORMER FOR CAM FORMULATION

Developing CAMs often requires systematic studies to select suitable co-formers, mainly when particular AA work with specific drugs but not others. Techniques such as Fourier-transform infrared, near-infrared (N-IR), and Raman spectroscopy are crucial for investigating intermolecular interactions and ensuring the stability of these dispersions. Computational methods, including quantum molecular theory, density functional theory, and natural bond orbital, have ensured the formation of heterodimers, such as amoxicillin–omeprazole.[17] The researcher explored how co-formers' physicochemical properties affect CAM's stability through various analyses, emphasizing factors such as T_g to melting temperature proportion, molecular flexibility, H-bond acceptor count, and polarizability. They highlighted the successful co-amorphization with the flexible AA tryptophan versus the rigid proline, which tends to crystallize.[18]

The research indicated that co-milling these substances accelerated the formation of amorphous powders, with amorphization confirmed by decreased XRPD reflections and principal component analysis of NMR spectra. DSC results suggested that the AA dissolved into the amorphous drug in the indomethacin system, whereas in the furosemide system, the drug dissolved into the amorphous AA. The miscibility of compounds was assessed using the Flory interaction parameter (χ) and the Hansen solubility parameter (δ). For stable compounds, phase diagrams are employed in research[19] to measure melting point (MP) reduction and help determine miscibility. Miscible systems showed a more significant decrease in MP, whereas immiscible or partially miscible systems showed minimal change. More systematic approaches for co-former selection are needed, as noted by Korhonen *et al*.[20]

METHODS OF PREPARATION OF CAM-SD

The most common methods for drug formulation include the fusion (or melting) method and the solvent evaporation method. The drug and carrier are melted and then rapidly cooled to form a solid matrix using the fusion method. The solvent evaporation method involves dissolving both components in a volatile solvent and removing the solvent to create a uniform dispersion. Advanced techniques, such as hot-melt extrusion, spray drying, and supercritical fluid technology, offer improved scalability and stability [Figure 2].

Solvent evaporation

Solvent evaporation is commonly used to prepare CAMs. Among these, solvent evaporation under vacuum is a widespread technique because it enables the swift removal of organic solvents and facilitates the precipitation of the drug before it can reorganize, nucleate, or crystallize. For example, the researcher combined saccharin and ibrutinib in methanol and then rapidly evaporated the solution under a vacuum at 40°C to produce CAMs.[21] Similarly, another study effectively formulated repaglinide-saccharin CAMs by rapidly evaporating a methanol solution containing these components at an equimolar ratio.[22]

A study concluded that CAMs from these processes were obtained with high yield and consistent stoichiometry, as verified by yield and stoichiometric measurements. However, selecting a specific solvent that can dissolve the drug and co-former remains challenging in the solvent evaporation technique. In addition, adhering to ICH guidelines is crucial to managing solvent residues that could cause instability through solvent-mediated recrystallization during storage.[23-25]

Quench cooling

Quench cooling is a widely employed approach for transforming crystalline mixtures into CAMs. This technique

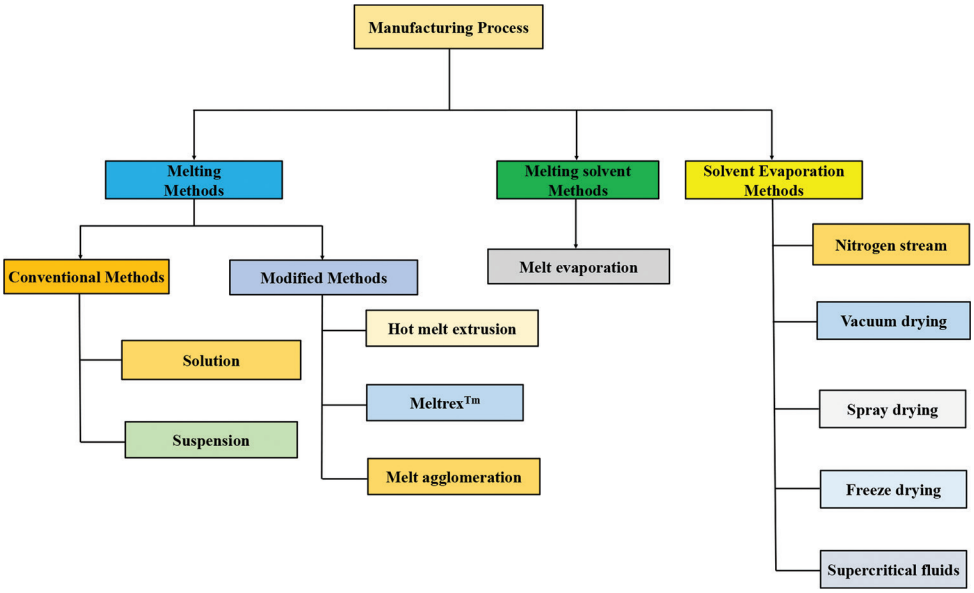

Figure 2: Effective production technique for the large-scale production of solid dispersion

involves rapidly cooling the melted physical mixture using liquid nitrogen or ice after it has been heated in a vessel with vigorous agitation.[24,26,27] The cooling rate helps prevent nucleation/crystal formation, which is crucial for successfully producing CAMs. For example, the researcher employed liquid nitrogen to quench the co-melted mixture of curcumin and piperine, achieving a high yield (~97%) with excellent stability under specific conditions (40°C/75% relative humidity) over 3 months without thermal degradation.[28]

Spray drying

Spray drying is a well-known technique where solutions are atomised through a nozzle into a hot air stream, allowing for the quick removal of solvents. This method offers several advantages, including continuous production capability, efficient scalability, and compatibility with drugs that have high MPs. However, challenges include processing powders, handling APIs with low T_g, selecting a suitable solvent, and dealing with residual solvents in the end product. For instance, scientists used spray drying to create binary CAMs of budesonide and arginine (ARG). They dissolved both components in a co-solvent of ethanol/water, resulting in ARG-budesonide CAMs with an optimal particle size of 1–2 µm and a spherical morphology [Table 1]. An increase in dissolution could be obtained by lowering the initial dissolution rate and exceeding supersaturation in such ternary systems.[29,30]

Freeze drying

Freeze drying is used to dry and stabilize various pharmaceutical dosage forms. This method also applies to creating CAMs with low-density and porous structures. This process involves stages, including freezing and primary and secondary drying. Among these, the primary drying step is particularly critical as it greatly influences the overall quality and efficiency of the process. Optimizing the circumstances for primary drying is essential for achieving a successful outcome.[31] In a study, the scientist mixed tryptophan and ofloxacin in water at a 1:1 ratio and then subjected the mixture to freeze-drying. This process produced a fluffy CAM powder with good chemical and physical stability, particularly during the initial drying phase.[16]

Hot melt extrusion (HME)

HME is a popular, solvent-free approach used widely in the medicinal field for the large-scale production of ASDs. This method is advantageous for scaling from small-batch processes to commercial production. The process involves using a temperature-controlled extruder equipped with a barrel and rotating screws to blend and process ingredients through a die. The characteristics of the extrudate are influenced by both the properties of the materials used and the operational parameters, such as screw speed and temperature settings.[26,32] The researcher employed a twin-screw extruder to create the CAMs of indomethacin and cimetidine with 5% polymer content, carefully monitoring process variables such as temperature, screw speed, and force.[33] Their findings indicated that incorporating small amounts of polymer effectively reduced the viscosity of the melt CAM. The viscosity and processability of the melt CAM were also significantly affected by the temperature settings and screw speed. In another study, scientists developed CAMs of indomethacin and ARG by feeding an indomethacin co-povidone mixture into the extruder barrel with a powder feeder. An ARG solution was introduced into the barrel through a nozzle with the help of a peristaltic pump [Table 1].[34]

Table 1: Methods involved in solid dispersion (CAM/ASD) formulations, mechanism of stabilization, and solubility enhancement of poorly water-soluble drugs using amino acids/hydrophilic carriers

Drug	BCS class	Amino acid	Molar ratio	Stabilization mechanism	Method	Outcome	References
Ofloxacin	II	tryptophan	1:1	Hydrogen bonds	Lyophilization method	Increasing the ofloxacin solubility by about 10 times.	[16]
Indomethacin	II	ARG, histidine, lysine	1:1	Salt formation	Ball-milled and spray-dried	200-fold increment in spray-dried indomethacin-ARG.	[43]
Indomethacin	II	Lysine	1:1	Salt formation	Ball milling and liquid-assisted grinding	The co-amorphous salt had a high dissolution rate (2.70 μg/cm^2/min), 2.7, 38.5, and 90-fold higher than those of the individual components.	[44]
Indomethacin	II	L-Proline	3:1	Two-dimensional hydrogen bonding	Liquid-assisted grinding method	Indomethacin with L-proline co-crystal increases the solubility by approximately 2–3-fold.	[52]
Telmisartan	II	Arginine	1:2	Hydrogen bonding interaction	Freeze-drying method	Telmisartan complexed with arginine at a ratio of 1:2 showed an enhancement of solubility of about 57-fold.	[53]
Griseofulvin	II	Tryptophan, L-aspartic acid, L-lysine, L-valine, DL-methionine	1:1	Hydrogen bonding interaction	Ball milling and quench cooling method.	Griseofulvin-tryptophan amorphous system positively impacted drug dissolution, showing AUC improvements of 88.6% and 58.2% FaSSGF and FaSSIF, respectively.	[54]
Budesonide	II	ARG	1:1	Hydrogen bonds	Spray drying and ball milling method	A co-amorphous system of budesonide and arginine obtained by spray drying enhanced physical stability compared to the drug alone.	[55]
Glibenclamide	II	Serine (SER) and ARG	1:1	Salt formation, hydrogen bonds	Cryo-milling	Glibenclamide-ARG-SLS mixture exhibited a 9-fold higher activity.	[56]
Indomethacin	II	ARG, phenylalanine, and tryptophan	1:1	Salt formation	Cryo-milling method	Precipitation reveals the formation of a co-amorphous mixture, which enhances the AA capacity to resist precipitation and increases the dissolution rate by 4–17-fold.	[39]
Indomethacin	II	ARG	1:1	Molecular interactions	Hot melt extrusion method	Drug-AA combinations are used to prepare a co-amorphous system using a spray drying approach to improve the dissolution of non-sink, poorly water-soluble drugs.	[34]
Naproxen	II	Arginine	1:1	Salt formation	Liquid-assisted grinding and ball milling	Pharmacokinetic results revealed a 1.5-fold rise in AUC_{0-t} and a 2.15-fold rise in maximum plasma concentration.	[41]
Naproxen	II	ARG, lysine	1:1	There was no interaction between molecules	Freeze-drying	Applying surfactants to a co-amorphous system was found to be successful, with certain surfactants increasing the ability to sustain it for at least 18 weeks. The lysine-based system proved to be more stable than the Arginine-based one.	[57]

(Contd...)

Table 1*(Continued)*

Drug	BCS class	Amino acid	Molar ratio	Stabilization mechanism	Method	Outcome	References
Indomethacin, carvedilol	II	TRY	1:1	Hindered molecular motions	Vibrational ball milling	Carvedilol-TRY has an excess of carvedilol and will recrystallize when the drug concentration is 50% or higher.	[58]
Glibenclamide	II	ARG	1:1	Salt formation and H-bonding	Ball milling	Amorphous Glibenclamide-ARG had a greater dissolution rate than glibenclamide pure drug, by about 10-fold.	[59]
Lurasidone hydrochloride	II	L-cysteine	1:1	Hydrogen bonding interaction	Solvent evaporation	An amorphous system of lurasidone hydrochloride-L-cysteine increased solubility by at least 50-fold and dissolution by 1200-fold.	[60]
Mebendazole	II	Proline/tryptophan	1:1	NA	Ball milling	Mebendazole-aspartic acid-tyrosine and mebendazole-histidine-glycine had a higher dissolution rate by about 3-fold and 19-fold, respectively, as compared to amorphous and crystalline mebendazole.	[61]
Valsartan	II	L-HIS/L-ARG/ L-lysine	1:1	Hydrogen bonding interaction	Ball milling	The drug AA co-amorphous method significantly improves the solubility and intrinsic dissolution rate of valsartan by about 1000 times.	[62]
Hydrochlorothiazide	IV	D-ARG, L-ARG	1:1	Hydrogen bond formation	Cryomilling method	Co-amorphization resulted in a 1.5-fold increase in AUC values for hydrochlorothiazide.	[63]
Glimepiride	II	L-ARG	1:1	Hydrogen bond with hydrophobic interaction	Physical mixture, melt quenching, and solvent evaporation method	The interaction between L-arginine and glimepiride in the CAMS improved glimepiride dissolving rates through solubility.	[64]
Diclofenac	II	L- Proline	1:1	Hydrogen bond	Liquid-assisted grinding	The solubility of zwitterionic diclofenac-proline cocrystals was 7.5 times higher than that of diclofenac crystals.	[65]
Diclofenac acid	II	Proline	1:1	Hydrogen bond	Fast evaporation	The study demonstrates a 1.32-fold improvement in the release of nano-diclofenac-proline cocrystals.	[66]
Diclofenac potassium	II	L-proline	1:1	Hydrogen bond	Solent evaporation	Solubility was enhanced up to 3.5-fold, and the intrinsic dissolution rate was increased by 3.4-fold.	[67]
Carvedilol	II	L-aspartic acid	1:1	Ionic interaction	Spray drying	The dissolution drug concentration was maintained at a level 4 times higher than that of the crystalline drug.	[30]
Carvedilol	II	TRY	1:1	Hydrogen bond and pi-pi interaction	Ball milling method	This ternary complex can enhance the dissolution rate by boosting it and sustaining supersaturation for extended periods.	[68]
Ibrutinib	II	ARG	1:1	Ionic bond interaction	Ball milling method	The study showed 2.8 times more solubility.	[69]

(Contd...)

Table 1 (*Continued*)

Drug	BCS class	Amino acid	Molar ratio	Stabilization mechanism	Method	Outcome	References
Mebendazole	II	ARG	1:1	Salt formation	Ball milling	Salt-formation mixtures exhibited a higher Tg, a higher dissolution rate, greater physical stability, and higher solubility than non-salt-formation mixtures.	[70]
Carvedilol	II	Glutamic acid, aspartic acid	1:1	Salt formation	Spray drying, ball milling, and liquid-assisted grinding	The dissolution rate increased with the spray-dried mixture.	[71]

ASD: Amorphous solid dispersion, CAM: Co-Amorphous, ARG: Arginine

Ball milling

Mechanical milling, encompassing techniques such as ball milling, liquid-assisted grinding, and cryomilling, is a highly effective method for creating disordered materials through mechanical activation. This process converts crystalline materials into amorphous forms while introducing defects into the crystal lattice. Particularly, ball milling is regarded as a sustainable and efficient approach for producing CAMs because it avoids the use of organic solvents and high temperatures.[26,35] The duration of ball milling is critical in the production of CAMs. For instance, the researcher used ball milling to create CAM with furosemide-TRY and indomethacin-TRY, observing a progressive reduction in crystal diffraction peaks that eventually led to an amorphous state as milling time increased [Table 1].[36]

Cryomilling

Conventional ball milling can be limited in converting crystalline materials into amorphous solids because the heat generated during the process often leads to recrystallization. To mitigate this issue, cryomilling is commonly used, especially at elevated temperatures. This technique involves sealing samples in milling jars and immersing them in liquid nitrogen before milling. This method proves effective, given that the T_g of many amorphous drugs is well below the temperature used in cryomilling.[37,38] For example, scientists applied cryogenic milling to develop a combined CAM of hydrochlorothiazide and atenolol, taking advantage of atenolol's low Tg [Table 1].[39]

Liquid-assisted grinding

Liquid-assisted grinding becomes valuable when ball milling or cryomilling fails to create combined CAMs. This method involves adding a small amount of solvent to the milling process.[24,26] The solvent facilitates molecular diffusion and interactions between the co-former and the drug. For example, the researchers successfully used ethanol-assisted grinding to produce curcumin-piperazine CAMs.[40] They enhanced the formation of the desired CAM by incorporating a small amount of ethanol, which slightly dissolved the CAMs and improved the reactions' interfaces.

DRUG-AA CAM

AA are zwitterionic compounds that readily form intermolecular interactions with H-bonding receptors/donors in pharmaceutical compounds [Table 1]. They are frequently utilized as co-formers in CAMs [Figure 3(a)]. For instance, ionic interactions between AA and drug molecules in CAM salts enhance both the stability and the water solubility of these drug-AA CAMs [Table 1].[41-43]

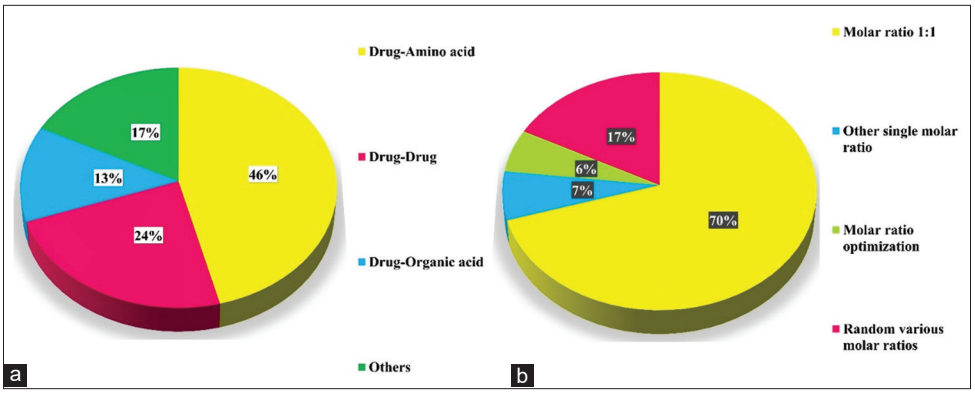

Figure 3: (a) Comparative study of CAM formulations (%) using amino acids and other carriers. (b) Percentage of different molar ratios used for CAM formulations. CAM: Co-amorphous

In one study, the researcher used vibrating ball milling to combine indomethacin with lysine, resulting in a CAM salt. This salt exhibited a solubility rate 90 times higher than the crystalline form and 38.6 times higher than the amorphous form of indomethacin. In addition, CAMs maintained physical stability over 9 months at 25° and 40°C.[44] Another study demonstrated that ARG could be co-former bearing ibuprofen to produce a CAM salt, which showed improved dissolution and physical stability when stored below 40°C for up to a year.[45]

DRUG-AA CAM COMPOSITION AND ITS SALTS

AA are biocompatible co-formers and anti-plasticizers, enhancing T_g, minimizing drug interactions, and preventing recrystallization. Due to their low molecular weight, only small quantities of AAs are needed compared to polymeric SDs, and the molar ratio of 1:1 is mainly preferred [Figure 3(b)]. The choice of AAs is guided by their potential interactions with drug-receptor sites in biological systems.[46,47] Due to molecular interactions, CAM complexes formed with drugs and AAs generally exhibit improved dissolution rates and physical stability over their amorphous counterparts.[46-49] Stable systems with non-interactive components can also be achieved.[50]

The researcher investigated the effectiveness of co-amorphization by varying the milling time of six drugs combined with different AAs in equimolar amounts for rapid screening and assessment of suitable AAs co-formers. Their research identified that non-polar AAs such as tryptophan, phenylalanine, leucine, isoleucine, valine, proline, and methionine are effective co-formers. Essential AAs are more suitable for forming amorphous salts with acidic drugs, whereas acidic AAs are often less effective as co-formers.[51]

CONCLUSION AND FUTURE PERSPECTIVES

Developing ASDs and CAM systems represents a significant advancement in the pharmaceutical field, particularly in enhancing poorly soluble drugs' solubility, dissolution rate, and bioavailability. The innovative use of AAs as co-formers in CAM dispersions has demonstrated considerable potential in enhancing physical stability and mitigating the risk of recrystallization, a prevalent issue in ASDs. Despite these merits, challenges remain, particularly in the selection of appropriate carriers and optimization of formulation techniques. Looking ahead, continued research is essential to overcome these obstacles and fully realize the clinical potential of these systems. Future investigations should aim to refine formulation strategies, improve long-term stability, and expand the range of drug candidates suitable for these delivery platforms, ultimately contributing to developing more effective and reliable therapeutic solutions.

ANIMAL STUDIES

None

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AUTHOR CONTRIBUTIONS STATEMENT (CREDIT FORMAT)

Mr. Gaurang Sharma (GS): Original draft, language, figures, tables, data curation. Jitendra Gupta (JG): Reviewing, editing, and conceptualization.

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