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Amino Acid Salt-Based Co-Amorphous Systems of Curcumin Mechanistic Insights and Strategies for Enhanced Solubility and Bioavailability

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ABSTRACT

Curcumin, a hydrophobic polyphenol derived from *Curcuma longa*, exhibits diverse pharmacological activities including antioxidant, anti-inflammatory, neuroprotective, and anticancer effects. Despite its therapeutic potential and safety, curcumin's clinical translation remains limited due to its poor aqueous solubility, low intestinal absorption, rapid metabolism, and extremely low oral bioavailability. Conventional strategies such as polymer-based solid dispersions, nanoparticles, and cyclodextrin complexes have improved solubility but face limitations related to high excipient load, stability, and scalability. Co-amorphous systems (CAMS), composed of curcumin and low-molecular-weight co-formers such as amino acid salts, have emerged as a promising alternative. Amino acids including L-arginine, lysine, and tryptophan serve as effective co-formers owing to their ability to form hydrogen bonds, ionic interactions, and hydrophobic or aromatic contacts with curcumin. These interactions disrupt crystalline packing, enhance the glass transition temperature, and suppress recrystallization, thereby stabilizing the amorphous phase. As a result, curcumin–amino acid CAMS exhibit markedly improved solubility, dissolution rate, and bioavailability compared to crystalline curcumin. Preparation techniques such as liquid-assisted grinding, solvent evaporation, spray drying, hot-melt extrusion, and supercritical fluid processing have demonstrated feasibility at both laboratory and industrial scales. Furthermore, in vitro and in vivo studies confirm that amino acid-based CAMS improve pharmacological performance without compromising safety. In conclusion, amino acid salt-based co-amorphous systems represent a scalable and biocompatible strategy to enhance curcumin delivery, offering significant potential for future clinical translation.

Keywords: Curcumin, Co-amorphous system, Amino acid salts, Solubility enhancement, Bioavailability, Drug delivery.

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1. INTRODUCTION

Curcumin, and hydrophobic poly-phenol, is extracted from the rhizome of the plant Curcuma longa. It is frequently used as a dietary supplement because of its many health benefits, including its anti-inflammatory, neuroprotective, hypolipidemic, cardio-protective, and antioxidant qualities. [1] Because curcumin can cause very little or no toxicity in people receiving up to 8000 mg of the medicine orally daily for three months, it has demonstrated an acceptable safety profile in clinical investigations. [2–4] The Food and Drug Administration actually classifies curcumin as a drug that is Generally Recognized as Safe (GRAS). [4] Pharmacokinetic investigations have shown that curcumin has a low oral bioavailability despite its safety profile and its therapeutic applications because of its poor intestinal absorption, low solubility, extensive hepatic and intestinal metabolism, and quick elimination. [3-6]

As a result, novel formulations based on emulsifiers, including carbohydrate complexes, polysorbates, phospholipid complexes, and Nano preparations, have been developed to increase the solubility and absorption of curcumin. [8-10] Curcumin has also been co-administered with adjuvants like piperine to delay its metabolism. [7,8] Co-amorphous drug delivery system formulation is a new and promising method for enhancing the physicochemical characteristics of medications. In this sense, curcumin's solubility, bioavailability, and/or stability may be enhanced by the creation of a co-amorphous solid with an appropriate co-former. [11] L-arginine appears to be an effective co-former that can enhance the physicochemical characteristics of a number of medications, including glibenclamide, naproxen, ciprofloxacin, and ibuprofen and indomethacin. [12-18]

γ-cyclodextrin, hydroxypropyl-β-cyclodextrin (HPβCD), and β-cyclodextrin have been demonstrated to significantly enhance the water solubility, stability, rate of dissolution, and bioavailability of CUR. [19-23] Additionally, it has shown promise in increasing the solubility of CUR with the use of several nanoparticles, including those based on polymers, chitosan, starch, and alginate-polysorbate. [24-27] Getting co-crystals is a further strategy. Co-crystallizing CUR with particular co-formers, including salicylic acid, hydroxyquinol, cinnamic acid, resorcinol, pyrogallol, nicotinamide, resveratrol, and ascorbic acid, has been demonstrated to improve its solubility. [28-33] Transforming a crystalline material into its amorphous state is another efficient way to increase solubility. [34] The higher free-energy state of amorphous forms, which renders them more soluble than crystalline forms, is one reason for their greater solubility. [35] However, the rapid recovery to the crystalline state may negate this solubility advantage. [36] Amorphous solid dispersions (ASD), in which the medication is disseminated at the molecular level within an amorphous polymer, are a noteworthy development in tackling this problem.

The higher glass transition temperature (Tg) brought about by the use of high-Tg carrier polymers decreases molecular mobility, which in turn increases the physical stability of these amorphous materials. Furthermore, the stability is frequently improved by the molecular interactions between the medication and polymer. [37]

The effectiveness of medications is largely determined by their solubility, which is closely linked to their absorption and distribution in vivo. However, according to the Biopharmaceutical Classification System (BCS), about 90% of therapeutic candidates and 40% of commercialized medications have poor water solubility and are classified as Class-II (low solubility and high permeability) or Class-IV

(low solubility and low permeability) drugs. [38] Improving the solubility of poorly water-soluble medications is still one of the biggest obstacles in their development. Saltification is typically the first option for increasing their solubility. Drugs without an ionisable core, however, cannot use this tactic. [39] To address this difficulty, a number of tactics have been used recently, including chemical modification, inclusion techniques, nanotechnology, micronization, crystal engineering, amorphization, and others. [40]

A common tactic used to increase the water solubility of soluble medications is to change them from crystalline to amorphous forms. [41]

The prolonged disordered molecular packing of amorphous medicines gives them a significant solubility advantage over crystalline pharmaceuticals. [42] However, because of their high internal energy, amorphous medicines have limited physical stability and are more likely to crystallize, which reduces their solubility advantage. In order to prevent re-crystallization tendencies and maintain the solubility benefits of amorphous pharmaceuticals, polymer excipients are used, which leads to the creation of what is known as an amorphous solid dispersion (ASD).By raising the glass transition temperature (Tg) and lowering the mobility of the drug molecules inside the systems, the addition of polymers improves the physical stability of amorphous pharmaceuticals. Because of its ease of use and efficacy, this approach has been quite successful in the pharmaceutical sector, resulting in the launch of several ASDs. [41] Nevertheless, using polymeric carriers as stabilizers presents difficulties. Polymers frequently have limited drug loading capacity, which raises the final dosage forms' bulk volume/mass and decreases patient compliance. Additionally, in ambient settings, polymers have a tendency to absorb moisture, which speeds up the phase shift of pharmaceuticals from their amorphous to crystalline forms. In order to address the difficulties posed by polymers in the study and development of ASDs, the emphasis has been switched to pharmaceutically approved low-molecular-weight molecules, such as amino acids, organic acids, food additives, medications, and others, which are used as stabilizers. [42,43]

2. CURCUMIN: BIOPHARMACEUTICAL CHALLENGES

2.1 Physicochemical Properties of Curcumin:

The hydrophobic polyphenolic chemical curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is extracted from Curcuma longa's rhizome. Its poor pharmacokinetic efficiency is mostly explained by its physicochemical profile.

- **Molecular formula and weight:** $C_{21}H_{20}O_6$, molecular weight 368.38 g/mol**.** [44]
- **Solubility:** Curcumin is practically insoluble in water (<0.1 mg/mL at room temperature; ~0.6 µg/mL at pH 7.3), but soluble in organic solvents such as ethanol, acetone, DMSO, and methanol. [45,46]
- **Log P (lipophilicity):** Approximately 3.2, reflecting high lipophilicity and poor aqueous solubility. [44]
- **PKa values:** Curcumin exhibits three dissociation constants, $pKa_1 \approx 8.5$, $pKa_2 \approx 9.9$, $pKa_3 \approx 10.5$, due to its phenolic –OH groups and enolic proton. [45]
- **Melting point:** ~183 °C. [44]
- **Crystallinity:** Curcumin exists as a crystalline compound, which reduces dissolution rate in aqueous media. [47]
- **Stability:** Curcumin is unstable at neutral and alkaline pH, where it undergoes rapid hydrolytic degradation, limiting its shelf life and biological half-life. [48]

- **Absorption and metabolism issues:**

Because curcumin is crystalline and hydrophobic, it has low gastrointestinal absorption after oral dosing. Additionally, it undergoes substantial conjugation (glucuronidations and sulfation) and reduction routes in the liver and intestinal mucosa, which results in quick systemic removal. The less pharmacologically active curcumin glucuronides and sulphates produced by these metabolic transformations further diminish the effectiveness of treatment. [49,52]

- **Clinical limitations:**

Curcumin has a very limited oral bioavailability as a result of these difficulties. According to human pharmacokinetic studies, only very small plasma concentrations can be detected even after

high doses (up to 8–12 g/day). These limitations limit its direct clinical translation and call for sophisticated formulation techniques, such as the use of solid dispersions, liposomes, nanoparticles, and co-amorphous systems, to improve solubility, stability, and systemic availability. [50.51]

3. OVERVIEW OF CO-AMORPHOUS DRUG DELIVERY SYSTEMS

3.1 Definition:

A medication and one or more low-molecular-weight co-formers (such amino acids, organic acids, or tiny molecules) combine to generate co-amorphous systems, which are homogenous single-phase amorphous formulations. Small molecules are used in co-amorphous systems to stabilize the medicine in an amorphous form, improving its solubility and rate of dissolution, in contrast to polymer-based amorphous solid dispersions (ASDs), which depend on high molecular weight carriers. [53, 54]

3.2 Principle:

The drug and co-former's molecular interactions provide the basis of co-amorphous systems. The co-former stabilizes the amorphous form by preventing drug molecules from recrystallizing by van der Waals forces, ionic contacts, or hydrogen bonds. Because of its stabilization, the amorphous phase has a larger free energy than its crystalline counterpart, which results in enhanced apparent solubility. Increased rate of dissolving since the amorphous medication gets beyond the energy barrier of the crystal lattice, improved physical stability because the co-former delays recrystallization during storage by interfering with molecular mobility. Co-amorphous systems are very appealing for poorly water-soluble medications because they can offer comparable dissolution benefits to ASDs while having a reduced excipient burden, better process capability, and the opportunity for smaller dosage forms. [55]

4. DIFFERENCE BETWEEN CO-AMORPHOUS SYSTEMS, SOLID DISPERSIONS, AND CRYSTALLINE SYSTEMS

4.1. Crystalline Systems:

The molecules in crystalline medicines are structured in a hard, ordered lattice with strong intermolecular contacts; this reduces free energy and provides great thermodynamic stability, but it also restricts solubility and the rate of dissolution because dissolution requires the removal of extra lattice energy. For example, curcumin's crystalline form exhibits a very poor water solubility (<0.1 mg/mL), which limits its oral bioavailability. [56]

4.2. Polymer-Based Solid Dispersions (ASDs):

Solid dispersions distribute a medication in an amorphous form within a polymeric carrier (such as PVP, HPMC, or PEG). Increasing wettability, decreasing particle size, and maintaining the drug in an amorphous high-energy state are some of the ways they improve solubility and dissolution. Nevertheless, there are drawbacks, such as: o High polymer load, which results in larger dosage forms; o Processing challenges (thermal degradation during hot-melted extrusion or spray drying); o Hygroscopicity and physical instability. [57,58]

4.3. Crystalline Systems:

- Mechanism: Strong intermolecular interactions (high lattice energy) are caused by the rigid lattice arrangement of drug molecules.
- Impact: In order to dissolve, these connections must be broken, which is energetically unfavourable resulting in low solubility and sluggish dissolution. [59]

4.4. Solid Dispersions:

- Mechanism: o Amorphization: By lowering lattice energy, the transition from a crystalline to an amorphous form increases solubility.
    - Particle Size Reduction: Surface area is increased via molecular-level dispersion.
    - Better Wetting: Water penetration is improved by hydrophilic polymers.
    - Super saturation Effect: Polymers stabilize a high-energy supersaturated state produced by rapid breakdown.

- Impact: Faster dissolution and greater perceived solubility in comparison to crystalline drugs. [60]

4.5. Co-Amorphous Systems:

- Mechanism: o Crystal Lattice Elimination: The drug and co-former are both in an amorphous, single-phase state.
  - Intermolecular Interactions: The amorphous form is stabilized and recrystallization is prevented by hydrogen bonding, ionic, or π–π interactions with the co-former.
  - Enhanced Thermodynamic Activity: Solubility and dissolution rate are improved by higher free energy.
- Impact: Better physical stability, quicker dissolution, and increased solubility in comparison to the amorphous drug alone. [61]

5. ROLE OF AMINO ACIDS AND THEIR SALTS IN CO-AMORPHOUS SYSTEMS

5.1 Amino Acids as Co-formers in Co-Amorphous Systems:

- **Hydrogen Bonding**
  - Amino acids have carboxyl (-COOH/-COO^-) and amino (-NH_2/-NH_3^+) groups. These functional groups can create hydrogen bonds with medications (for example, between the functional groups of amino acids and the hydroxyl/carbonyl groups of medicines).
  - By decreasing drug molecules' mobility, this interaction inhibits crystallization.
- Interactions between ions
  - Strong ionic bonds are formed between ionisable amino acids (such as lysine, arginine, histidine, aspartic acid, and glutamic acid) and oppositely charged drug moieties.
  - These electrostatic interactions offer better amorphous state stabilization and are more potent than hydrogen bonds.
- The Amorphous State's Stability
- As a result of these interactions, molecular mobility decreases and the glass transition temperature (Tg) rises.
- Avoiding recrystallization while storing or dissolving.
  - Improved solubility and physical stability in comparison to drug-alone amorphous forms.

The ability to form homogeneous co-amorphous systems and their modest size and biocompatibility (in contrast to large polymers) make amino acids useful. [62-65]

5.2. Salt Formation with Weakly Acidic Drugs (Curcumin Example):

Mechanism of Improved Solubility/Dissolution

- Ionization: Curcumin's neutral state is changed into its ionic form, which has greater aqueous solubility, by salt production.
- Electrostatic Interactions: The amorphous state is stabilized by a strong ionic connection between curcumin and the basic co-former.
- Preventing Re-crystallization: By preventing a crystalline lattice from rebuilding, the salt structure enhances physical stability.
- Enhanced Dissolution and Wetting: The co-former, which is frequently hydrophilic, increases wet ability, facilitating quick dissolution.
- Enhanced Oral Bioavailability: Better absorption in vivo results from increased solubility and dissolution. [66-69]

5.3. Selection Criteria for Amino Acids as Co-formers:

5.3.1. PKa and Ionization Potential:

- Weakly acidic medications like curcumin are frequently combined with amino acids with basic side chains, such as L-arginine and L-lysine (pKa = 8–10 for phenolic groups).
- Strong ionic interactions or salt production improve solubility, stability, and miscibility.
- As an illustration, a co-amorphous salt of curcumin and arginine (1:2) demonstrated a solubility increase of approximately 1000 times and a much greater bioavailability than crystalline curcumin.

5.3.2. Hydrophobic/Hydrophilic Balance:

- By enhancing wettability, hydrophilic amino acids (such as arginine, lysine, and aspartic acid) enhance aqueous solubility and dissolution.
- Tryptophan, phenylalanine, and tyrosine are examples of hydrophobic amino acids that aid in π–π stacking and hydrogen bonding

with hydrophobic drug moieties, which help stabilize the amorphous phase.

- For instance, co-amorphous formulations of curcumin and tryptophan improved permeability, solubility, and antioxidant activity as a result of aromatic interactions.

5.3.3. Molecular Weight and Size:

- Because they: o Lower the chance of phase separation, low molecular weight amino acids are preferred.
- During amorphization, increase molecule mixing and mobility. Over time, larger or bulkier co-formers could undermine intimate miscibility and cause system instability.
- The review data indicates that tiny, flexible amino acids, such as alanine and glycine, are more likely to form stable homogenous phases.

5.3.4. Hydrogen Bonding Capacity:

- Curcumin's hydroxyl and carbonyl groups can interact with functional groups (-NH_2, -COOH, and aromatic side chains) in a variety of ways.
- Hydrogen bonding postpones recrystallization and stabilizes the amorphous solid. For instance, curcumin–lysine and curcumin–arginine co-amorphous complexes exhibited substantial H-bonding, as demonstrated by FTIR and ss-NMR investigations.

5.3.5. Glass Transition Temperature (Tg) Contribution:

- Higher Tg amino acids, such as proline and tryptophan, may raise the mixture's Tg by lowering molecular mobility and enhancing physical stability.
- To guarantee stability, reviews stress the need to choose co-formers that raise Tg by at least 10 to 20 °C above storage temperature.

5.3.6. Biocompatibility and Safety:

- Unlike synthetic co-formers, amino acids are safe GRAS (Generally Recognized As Safe) excipients, which makes them perfect.
- Their inherent metabolic function also lowers the danger of toxicity. [70,71,72]

6. CURCUMIN–AMINO ACID SALT-BASED CO-AMORPHOUS SYSTEMS

6.1 Methods of preparation for Curcumin–amino-acid salt co-amorphous systems:

6.1.1 Ball milling / Liquid-Assisted Grinding (LAG):

One popular technique for creating curcumin–amino acid salt-based co-amorphous systems (CAMS) involves mechanical activation of a physical mixture of curcumin and an amino acid, either by plain milling or milling in the presence of a few drops of solvent (LAG). In order to generate amorphous material or salt-like interactions without the use of bulk solvent, this method is usually used for quick screening of drug-to-co-former ratios, usually at stoichiometries like 1:1, 1:2, or 1:3. The use of tiny solvent quantities (μL per 100 mg) frequently encourages salt production and speedier amorphization, and milling periods might vary from a few minutes to many hours. Additionally, cryo-milling can be used to stop degradation brought on by heat or oxidation. Typically, PXRD, DSC, and FTIR studies are used to confirm amorphicity and molecular interactions. This method's primary benefits include speedy processing, solvent savings, and the use of basic equipment, which makes it ideal for first co-former screening. Nevertheless, the scalability of this method is somewhat constrained, and the co-amorphous samples produced by milling might not be as physically stable as those made by spray-drying or melt-quenching. The effective preparation of Curcumin-@lysine-acetate co-amorphous mixtures via LAG by Patil et al., who reported significantly better dissolution and solubility than crystalline Curcumin, serves as a representative example. [74]

6.1.2 Solvent evaporation / rotary evaporation / freeze-drying (lyophilisation):

The solvent evaporation method involves dissolving curcumin and an amino acid in a common solvent or solvent mixture, then quickly removing the solvent by evaporation or freezing and sublimation (lyophilization) to produce an ionic complex or amorphous solid. This method is popular for curcumin CAMS because it allows for molecular-level mixing and works especially well for creating homogenous

co-amorphous phases through salt formation with basic amino acids like L-arginine or L-lysine. Mancillas-Quiroz et al., for instance, used quick solvent evaporation to create a Curcumin:L-arginine (1:2) co-amorphous system, which showed notable enhancements in pharmacokinetic and dissolving performance.

Since plasticization can reduce the glass transition temperature (Tg) and jeopardize stability, solvents such as methanol, ethanol, ethanol/water combinations, or other polar organics are typically chosen to dissolve both components. The residual solvent concentration must be carefully evaluated using TGA. Furthermore, it is frequently beneficial to use moderately polar protic solvents to facilitate ionic contacts and proton transfer during salt production. This method's primary advantages are its superior molecular mixing, accurate stoichiometry control, and adaptability for conclusive salt production with in-depth analytical characterization. Nonetheless, difficulties including managing solvents, the possibility of leftover solvents, and the requirement to verify total amorphization devoid of crystalline domains continue to be significant factors. The work of Mancillas-Quiroz et al. is a prime example; they used the solvent evaporation method to create a curcumin:L-arginine co-amorphous system, which was validated by in vivo performance testing as well as PXRD, DSC, FTIR, and ss-NMR analysis. [73]

6.1.3 Spray-drying:

A solution of curcumin and an amino acid is atomized and then sprayed into a heated chamber, where the solvent quickly evaporates to create dry amorphous particles. Since the quick solvent removal encourages the creation of highly disordered solids with regulated particle size and shape, this approach is especially useful for curcumin CAMS. It is also scalable and frequently produces more physical stability than milled solids. Spray drying is a popular scale-up method after initial screening, according to reviews on CAMS. Since curcumin is thermolabile, it is necessary to carefully optimize the inlet and output temperatures to minimize thermal deterioration. Additionally, solvent solutions must be used to guarantee enough solubility of both components for feed preparation. To verify amorphicity and product quality, the spray-dried particles are usually subjected to additional analysis using PXRD, DSC, and FTIR in addition to residual solvent testing. This method's primary benefits are its scalability and its capacity to generate uniformly tiny particles with a large surface area, which enhances initial dissolving. Nevertheless, disadvantages include the requirement for careful temperature control, solvent handling, and occasionally the inclusion of stabilizers or polymers to ensure long-term stability. For stability and performance testing, several medications have switched from solvent evaporation screening or LAG to spray drying, which is frequently suggested as the best method for curcumin's scale-up in the larger CAMS literature. [76]

6.1.4 Melt-quenching / Hot-Melt Extrusion (HME):

To create an amorphous solid dispersion or co-amorphous phase, a mixture of the drug and co-former is heated above their melting or softening points, then quickly quenched or extruded and cooled. This process is known as melt-quenching or hot-melt extrusion (HME). Due to its solvent-free nature, suitability for continuous synthesis on an industrial scale, and ability to facilitate direct downstream processing into dosage forms, this approach is appealing for curcumin CAMS. Curcumin's heat sensitivity and the possible breakdown or reactivity of specific amino acids during processing, however, restrict its use. Reviews identify HME as a crucial method for creating ASDs and CAMS under thermally stable settings once thermal compatibility is verified by characterizing Tg, melting behavior, and decomposition temperature.In fact, plasticizers or polymers may be used to lower processing temperatures, although TGA and DSC pre-screening are crucial for identifying safe processing windows. For discoloration or chemical degradation, which are frequently measured by HPLC, careful observation is also necessary. This method's main benefits are that it produces directly processable extrudates and is solvent-free, scalable, and continuous. However, hazards include the possibility of curcumin and amino acids degrading thermally

and the complexity of formulations that require plasticizers or polymers. [76, 77]

6.1.5 Supercritical fluid (SCF) and SEDS / SCF-assisted techniques:

Supercritical CO_2 or other SCFs are used in supercritical fluid (SCF) procedures either as an anti-solvent (as in ASES or SEDS processes) or to help drug–co-former mixtures precipitate as amorphous particles. Because they enable low-temperature processing with quick solvent removal, these techniques are especially helpful for curcumin CAMS because they produce tiny, amorphous particles with regulated shape. For instance, Curcumin: polymer: tryptophan complexes were prepared by Garbiec et al. using SCF technology, and they showed noticeably improved solubility and biological activity. SCF techniques are technically challenging in practice, requiring exact control over operating pressures and temperatures in addition to careful solvent or anti-solvent system selection. They are particularly useful when reducing oxidative and thermal damage during processing is the aim. Operating at low temperatures, having good control over particle size, and producing very high-quality amorphous solids are the main advantages of SCF processes. However, disadvantages include increased capital costs, difficulties scaling up, and the requirement for specialist equipment. The study of Garbiec et al., who used SCF techniques to create tryptophan-containing curcumin amorphous systems and showed notable increases in solubility and dissolution, is a prime example of curcumin. [74]

6.1.6 Typical workflow used in the literature (recommended):

Co-amorphous systems based on curcumin–amino acid salts are usually developed via a methodical process. Small-scale co-former screening is the initial step, which is frequently accomplished by liquid-assisted grinding (LAG) and/or small-scale solvent evaporation at various stoichiometries (e.g., 1:1, 1:2, or 1:3). A trio of characterisation methods, including PXRD, DSC, and FTIR, are used to swiftly identify promising candidates (Chula Digital Collections+1). Following the identification of appropriate systems, sophisticated methods such as ss-NMR, comprehensive FTIR, and thermal analysis are used for optimization and mechanism probing in order to gain a deeper understanding of molecular interactions such ionic or hydrogen bonding. Mancillas-Quiroz, for example, used similar techniques to clarify how curcumin and arginine (MDPI) interact. Following stability and dissolution assessments (PMC+1), attractive candidates are generated in bigger quantities utilizing spray-drying, hot-melt extrusion (if thermal compatibility permits), or supercritical fluid techniques in the scale-up and robustness testing phase. The last step is dissolution, stability, and pharmacokinetic testing, which includes in-vivo PK and effectiveness comparisons with suitable reference formulations, accelerated stability evaluations at 40°C/75% RH, and non-sink dissolution tests in biorelevant medium. [75]

6.2 Physicochemical Characterization of Curcumin–Amino Acid Salt-Based Co-Amorphous Systems:

- In curcumin–amino acid salt-based co-amorphous systems (CAMS), physicochemical characterisation is essential for verifying amorphicity, salt production, and molecular-level interactions. Component miscibility, melting behavior, and glass transition temperature (Tg) are all ascertained by Differential Scanning Calorimetry (DSC). The creation of a homogenous co-amorphous phase is confirmed by the observation of a single Tg rather than distinct events for each component. In contrast to pure curcumin, curcumin–arginine (1:2) CAMS made by solvent evaporation displayed a noticeable Tg change, indicating molecular-level interactions. [78]
- One important method for evaluating crystallinity against amorphicity is powder X-ray diffraction (PXRD). Successful amorphization is confirmed by the formation of a diffuse halo and the absence of acute diffraction peaks. Curcumin–lysine mixtures made by liquid-assisted grinding (LAG) showed halo patterns in PXRD, indicating the development of amorphous salts, as Patil et al. showed. [79]
- Fourier-Transform Infrared Spectroscopy (FTIR) sheds light on interactions between molecules, especially ionic complexation

and hydrogen bonds. Characteristic changes in curcumin's -OH and -C=O stretching vibrations in CAMS point to ionic or hydrogen bonding interactions with the functional groups of amino acids. [78,79]

- By providing greater sensitivity to local structural disturbance, Raman spectroscopy enhances FTIR. Curcumin–amino acid CAMS has been shown to exhibit spectral band broadening and shifts in Raman-active modes, which further supports its amorphous nature and molecular interactions. [78]

6.3 Dissolution and Solubility Studies:

Curcumin's oral bioavailability is limited by its incredibly poor water solubility. By breaking crystallinity and encouraging ionic interactions, co-amorphous salts formed with amino acids improve solubility and dissolution. For instance, due to salt production and uniform amorphization, curcumin–lysine acetate CAMS made by liquid-assisted grinding (LAG) shown a substantial improvement in water solubility and dissolution as compared to crystalline curcumin (Patil et al., 2023). Similarly, curcumin–arginine CAMS (1:2) made by solvent evaporation showed no crystalline peaks at all in PXRD and dissolved far more quickly and thoroughly in biorelevant conditions than pure curcumin (Mancillas-Quiroz et al., 2024). According to these researches, CAMS based on amino acids are very successful in increasing solubility, which is a crucial requirement for better absorption. [80]

6.4 In Vitro and In Vivo Performance:

Beyond disintegration, CAMS has demonstrated encouraging biological results. When compared to unmodified curcumin, in vitro tests show that curcumin–amino acid salts have better antioxidant and cytoprotective action. Crucially, curcumin–arginine CAMS demonstrated noticeably greater plasma concentrations and bioavailability than crystalline curcumin in rat in vivo pharmacokinetic (PK) experiments, indicating the translational effect of salt-based amorphization. Similarly, curcumin–tryptophan co-amorphous systems made using supercritical fluid technology were found by Garbiec et al. (2025) to have improved dissolution as well as anti-inflammatory and neuro-protective properties in vitro, which were correlated with improved solubility-driven bioactivity. All of these results demonstrate that CAMS based on amino acid salts enhance curcumin's solubility and dissolution, leading to increased in vitro activity and in vivo bioavailability. [81, 82]

7. MECHANISTIC INSIGHTS

7.1 Intermolecular Interactions between Curcumin and Amino Acid (or Similar Co-former) Salts / Co-formers:

There are a number of investigations of co-amorphous curcumin with amino acids and basic amino acids that clarify the nature of intermolecular interactions, despite the fact that there are somewhat less explicit studies of curcumin + amino acid salts. Hydrogen bonds, ionic contacts (when the amino acid is charged), phenol and aromatic connections, and others are important forms of interactions.

Here are several mechanisms

Table 1: several mechanisms

Study	Co-former	Observed Interactions	Reference
L-arginine (1:2) with curcumin via a co-amorphous mechanism ("CAC12")	The amino acid L-arginine is basic and charged.	The amino group of arginine interacts with the phenolic OH of urcumin, as demonstrated by FTIR and ^13C NMR; the carboxyl of arginine also appears to be involved. There was reduced involvement in the core β-diketone, or keto-enol moiety of urcumin,	83

		which did not appear to change.	
Enhancement of curcumin's solubility with basic amino acids (Gunnam & Nanghia, RSC, 2021).	Several basic amino acids	They made physical, eutectic, co-amorphous, and cocrystal mixes. Changes in vibrational bands compatible with hydrogen bonding between curcumin's phenolic OH groups and the amino acid functionality (amine, or charged groups) of the base amino acids were shown by characterization using FTIR, PXRD, DSC, NMR, and other techniques. Dissolution and solubility were enhanced.	84
Using supercritical fluid technology, curcumin, tryptophan, and polymer (ternary amorphous system) are combined.	It functions as a co-former.	FTIR revealed molecular interactions (such as hydrogen bonds) between curcumin, tryptophan, and polymer. In contrast to binary systems, tryptophan enhanced solubility and instability. Curcumin's phenolic OH is probably reacting with tryptophan's groups.	85

7.2 Mechanisms of Stabilization of Amorphous State:

Although amorphous forms of curcumin are thermodynamically unstable and have a tendency to re-crystallize, they can offer greater solubility and faster dissolution. Research has looked into what formulation techniques or interactions support maintaining super saturation, suppressing or delaying crystallization, etc. Important mechanisms consist of:

7.2.1 Curcumin and a co-former (a polymer or amino acid) establish a hydrogen bond:

Curcumin molecules are "tied down" by strong intermolecular H-bonds, which lowers molecular mobility—a necessary component for crystal nucleation and growth. The curcumin and polyvinylpyrrolidone (PVP) systems, for instance, demonstrate that increased stability is correlated with stronger H-bonding. [86]

7.2.2 Ionic or salt interactions: By limiting mobility and actively opposing ordered crystalline packing, ionic interactions with curcumin's phenolic groups or other ionizable moieties can stabilize the amorphous form in situations where amino acids are charged (such as arginine at physiological pH). One example is the co-amorphous system of curcumin and L-arginine. [83]

7.2.3 Co-amorphous formation or mixing with co-formers that have complimentary functional groups and good miscibility:

The more stable the amorphous dispersion, the better the complimentary interactions are (steric, hydrophilic/hydrophobic balance, matching of hydrogen bond donors/acceptors). It should be possible for co-formers to break the molecular packing of curcumin. For instance, the ternary system's tryptophan was beneficial. [83]

7.2.4 Polymers as crystallization inhibitors: Using polymers in conjunction with amino acids can occasionally be beneficial. High glass transition (Tg) polymers can physically obstruct nucleation, "dilute" curcumin molecules, and create hydrogen bonds or other interactions while also reducing

molecular mobility. Amorphous curcumin is less stable when polymers are absent, according to research on curcumin + polymers (PVP, HPMC, etc.). [86]

7.2.5 Raising the glass transition temperature (T_g): By adding co-formers (polymers, amino acids) that stiffen the molecular network, the system's total T_g is increased. This lowers the probability of recrystallization because molecular movements are slower at storage temperatures. The co-amorphous combination of curcumin and L-arginine appeared to have this effect via limiting molecular motion through the interactions mentioned. [83]

7.2.6 Molecular disorder or steric hindrance: Amorphous forms are inherently disordered. It is beneficial if the co-former can hinder or prevent orderly packing (by using large side chains or mismatched geometry). Greater disorder is also indicated by the broadening of NMR or FTIR peaks and the loss of distinct spectrum characteristics. For instance, the peaks in CAC12 curcumin/arginine are moved and wider. [83]

7.2.7 Preventing recrystallization in solution and preserving super-saturation: Maintaining a supersaturated condition devoid of precipitation is crucial for bioavailability even after dissolution. Nucleation in solution is slowed down by strong contacts between curcumin and a co-former or polymer. Additionally, co-amorphous systems can occasionally release simultaneously and sustain contacts for an extended period of time, preventing phase separation. The strong H-bond between the phenolic OH of curcumin and the CO of piperine contributes to the physical stability of the curcumin-piperine co-amorphous system (CUR-PIP); molecular dynamics simulation revealed a greater binding energy, which is associated with stability. [87]

7.2.8 Example: Curcumin + L-Arginine (CAC12):

- For example, a closer look at the curcumin + L-arginine system: Made via solvent evaporation in a 1:2 molar ratio (curcumin:L-arginine). Amorphous halo, or loss of crystallinity, is seen in PXRD.
- ^13C NMR: L-arginine's alpha carbon exhibits a chemical shift (54.8 → 49.0 ppm), whereas curcumin's aromatic hydroxyl carbons exhibit changes (150.2 → 147.1 ppm), suggesting that the amino group in arginine interacts with the phenol in curcumin. Additionally, the carboxyl of arginine appears to change, suggesting participation. Curcumin's keto-enol core motif exhibits little changes, indicating a reduced role in the co-amorphous interactions.
  These interacting functional groupings are confirmed by ATR-FTIR. Widening peaks, changes in O-H, N-H, etc.
- When compared to pure amorphous curcumin, physical stability is improved and re-crystallization is postponed. Additionally, there is an improvement in biological activity and potentially pharmacokinetics. [83]

8. CHALLENGES AND LIMITATIONS OF CURCUMIN–AMINO ACID SALT-BASED CAMS

8.1 Stability Problems (Propensity for Recrystallization):

The natural propensity of amorphous medications to recrystallize over time is one of the main obstacles in CAMS. Because curcumin is extremely crystalline and poorly soluble in its natural state, it is prone to recrystallization, which can lessen the solubility benefit that the co-amorphous salt provides. Temperature, moisture content, and the physical characteristics of the amino acid co-former are some of the variables that affect stability. To improve physical stability, techniques like employing stabilizing excipients or choosing co-formers with high glass transition temperatures (Tg) are frequently required. [88]

8.2 Possibility of Scaling Up:
For screening and small-batch preparation, laboratory-scale techniques such as solvent evaporation and liquid-assisted grinding (LAG) work well, but scaling up co-amorphous systems for industrial production presents difficulties. In order to preserve amorphicity, particle size, and dissolving characteristics at large scale, processes such as spray-drying, hot-melt extrusion (HME), or supercritical fluid processing necessitate process parameter tuning, which can be resource-intensive. [89]

8.3 Regulatory and Safety Issues:
Even though amino acids are generally accepted to be safe (GRAS), novel co-amorphous formulations still need to be thoroughly evaluated before being approved by regulators. Possible problems include excipient compatibility, residual solvents, degradation products, and interactions between the medication and co-former. Before granting permission, regulatory bodies could need thorough stability, toxicological, and pharmacokinetic data. [89]

8.4 Insufficient Long-Term Clinical Information:
Curcumin–amino acid CAMS lacks long-term clinical data, despite encouraging preclinical and early-stage research demonstrating enhanced solubility, dissolution, and bioavailability. It is challenging to completely forecast clinical efficacy, safety, and pharmacokinetic performance in people because the majority of research is restricted to in vitro or brief in vivo models.[90]

8.5 Curcumin's intermolecular hydrogen bonding:
In its crystalline state, curcumin already possesses intra- and intermolecular hydrogen bonds, such as those between its keto/enol centers and phenolic OH. Hydrogen bond donors and acceptors that may otherwise interact with co-formers can be "used up" by these intermolecular H-bonds. Stabilization becomes more difficult as a result of the decreased number of potential external interactions.

8.6 Molecular mobility:
Higher temperatures or humidity levels can enhance molecular mobility, even in the presence of co-formers, enabling nucleation and growth. Therefore, higher Tg is necessary.

8.7 Super saturation collapse:
Unless interactions in the solution continue or precipitants are blocked, a supersaturated solution may still precipitate or recrystallize after curcumin dissolves. [86]

9. FUTURE PERSPECTIVES OF CURCUMIN–AMINO ACID SALT-BASED CAMS

Computational Methods for Rational Design
Co-amorphous complexes can now be rationally designed because to developments in molecular modelling and computational chemistry. Prior to experimental investigation, methods including solid-state modelling, molecular docking, and molecular dynamics simulations can anticipate physical stability, optimize stoichiometry, and predict drug–co-former interactions. These in silico methods can increase the success rates of CAMS creation and simplify the amino acid selection process. [91] Working Together with Other Transporters. To further improve solubility, stability, and bioavailability, co-amorphous systems can be combined with alternative drug delivery platforms, such as polymeric blends, lipid-based carriers, or nanocarriers. For instance, incorporating curcumin–amino acid CAMS into polymeric matrices may help with targeted distribution, sustained release, and decreased recrystallization L. [92]

Customized Healthcare Possibility
By enabling the construction of patient-tailored oral dosage forms, co-former selection based on patient-specific pharmacokinetics and manipulation of drug release rates, CAMS presents prospects for customized treatment. This adaptability is especially helpful for medications with weak solubility, such as curcumin, where customized bioavailability augmentation might enhance therapeutic results. [93]

Commercial and Industrial Translation

CAMS is positioned for industrial and commercial translation as interest in solvent-free, scalable, and continuous manufacturing processes like hot-melt extrusion and spray drying grows. Stable co-amorphous formulations for clinical and consumer use can be produced on a wide scale by optimizing process parameters and guaranteeing regulatory compliance.[94]

10. CONCLUSION

Curcumin, a bioactive polyphenolic compound with diverse pharmacological benefits, has long been hindered in its clinical translation due to its poor aqueous solubility, rapid metabolism, and extremely low oral bioavailability. Conventional formulation strategies, including polymer-based solid dispersions and nanoparticle systems, have shown promise but are often limited by high excipient load, processing complexity, and stability concerns. In this context, amino acid salt-based co-amorphous systems (CAMS) emerge as an innovative and practical approach for overcoming these limitations. Extensive evidence demonstrates that amino acids such as L-arginine, lysine, and tryptophan act as effective co-formers through their ability to engage in hydrogen bonding, ionic interactions, and hydrophobic or aromatic contacts with curcumin. These interactions not only suppress the tendency of amorphous curcumin to recrystallize but also increase the glass transition temperature, reduce molecular mobility, and facilitate maintenance of supersaturation in solution. As a result, CAMS consistently exhibit higher solubility, improved dissolution rates, and enhanced in vitro antioxidant and cytoprotective activities compared to crystalline curcumin. In vivo studies further confirm that amino acid-based CAMS significantly improve plasma concentration and bioavailability, validating their translational potential. Various preparation techniques—including liquid-assisted grinding, solvent evaporation, spray drying, hot-melt extrusion, and supercritical fluid processing—have been successfully applied to generate curcumin CAMS. While small-scale methods are valuable for screening, scalable approaches such as spray drying and hot-melt extrusion offer industrial feasibility. However, challenges persist, particularly regarding long-term stability under stress conditions, moisture sensitivity, and limited clinical validation. Moreover, regulatory approval will require comprehensive data on safety, stability, and pharmacokinetics to ensure patient compliance and therapeutic reliability. Looking forward, rational co-former design supported by computational modeling, integration of CAMS into multifunctional carriers, and the adoption of continuous manufacturing techniques will be pivotal in advancing these systems toward commercialization. Importantly, clinical studies are urgently needed to bridge the gap between preclinical promise and therapeutic application. In summary, amino acid salt-based co-amorphous systems provide a versatile, biocompatible, and scalable platform for enhancing curcumin delivery. By combining mechanistic stabilization with significant improvements in solubility and bioavailability, CAMS represent a transformative step toward realizing the full therapeutic potential of curcumin in modern medicine.

REFERENCES

1. Liu S, Liu J, He L, Liu L, Cheng B, Zhou F, et al. A comprehensive review on the benefits and problems of curcumin with respect to human health. **Molecules**. 2022;27:4400.
2. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. **Anticancer Res**. 2001;21:2895–900.
3. Esatbeyoglu T, Huebbe P, Ernst IM, Chin D, Wagner AE, Rimbach G. Curcumin—from molecule to biological function. **Angew Chem Int Ed Engl**. 2012;51:5308–32.
4. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of turmeric (Curcuma longa). **J Altern Complement Med**. 2003;9:161–8.
5. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. **Mol Pharm**. 2007;4:807–18.

6. Metzler M, Pfeiffer E, Schulz SI, Dempe JS. Curcumin uptake and metabolism. **Biofactors**. 2013;39:14–20.
7. Zeng X, Cai D, Zeng Q, Chen Z, Zhong G, Zhuo J, et al. Selective reduction in the expression of UGTs and SULTs: a novel mechanism by which piperine enhances the bioavailability of curcumin in rats. **Biopharm Drug Dispos**. 2017;38:3–11.
8. Hegde M, Girisa S, BharathwajChetty B, Vishwa R, Kunnumakkara AB. Curcumin formulations for better bioavailability: what we learned from clinical trials thus far. **ACS Omega**. 2023;8:10713–46.
9. Ji P, Wang L, Chen Y, Wang S, Wu Z, Qi X. Hyaluronic acid hydrophilic surface rehabilitating curcumin nanocrystals for targeted breast cancer treatment with prolonged biodistribution. **Biomater Sci**. 2020;8:462–72.
10. Baldassari S, Balboni A, Drava G, Donghia D, Canepa P, Ailuno G, et al. Phytochemicals and cancer treatment: cell-derived and biomimetic vesicles as promising carriers. **Pharmaceutics**. 2023;15:1445.
11. Liu J, Grohganz H, Löbmann K, Rades T, Hempel NJ. Co-amorphous drug formulations in numbers. **Pharmaceutics**. 2021;13:389.
12. Ojarinta R, Lerminiaux L, Laitinen R. Spray drying of poorly soluble drugs from aqueous arginine solution. **Int J Pharm**. 2017;532:289–98.
13. Kasten G, Lobo L, Dengale S, Grohganz H, Rades T, Löbmann K. In vitro and in vivo comparison between crystalline and co-amorphous salts of naproxen–arginine. **Eur J Pharm Biopharm**. 2018;132:192–9.
14. Mesallati H, Conroy D, Hudson S, Tajber L. Preparation and characterization of amorphous ciprofloxacin–amino acid salts. **Eur J Pharm Biopharm**. 2017;121:73–89.
15. Ruponen M, Visti M, Ojarinta R, Laitinen R. Permeability of glibenclamide through a PAMPA membrane: effect of co-amorphization. **Eur J Pharm Biopharm**. 2018;129:247–56.
16. Domínguez-Chávez JG, Mondragón-Vásquez K, Senosiain-Arroyo H. New solid forms of dapagliflozin. World Patent WO/2021/105779; 2021 Jun 3.
17. Domínguez-Chávez JG, Mondragón-Vásquez K, Senosiain-Peláez JP. Compounds comprising curcumin and basic amino acids. World Patent WO/2021/044231; 2021 Mar 11.
18. Domínguez-Chávez JG, Mondragón-Vásquez K, Senosiain-Peláez JP. Co-amorphous solid forms of flavonoids. World Patent WO/2024/116042; 2024 Jun 6.
19. Flory S, Sus N, Haas K, Jehle S, Kienhöfer E, Waehler R, et al. Increasing post-digestive solubility of curcumin improves oral bioavailability. **Mol Nutr Food Res**. 2021;65:2100613.
20. Purpura M, Lowery RP, Wilson JM, Mannan H, Münch G, Razmovski-Naumovski V. Analysis of innovative curcumin formulations for improved oral bioavailability in humans. **Eur J Nutr**. 2018;57:929–38.
21. Yadav VR, Suresh S, Devi K, Yadav S. Effect of cyclodextrin complexation of curcumin. **AAPS PharmSciTech**. 2009;10:752–62.
22. Nikolić L, Urošević M, Nikolić V, Gajić I, Tačić A, Miljković V, et al. Formulation of curcumin: 2-hydroxypropyl-β-cyclodextrin complex with smart hydrogel. **Pharmaceutics**. 2023;15:382.
23. Stasiłowicz A, Tykarska E, Lewandowska K, Kozak M, Miklaszewski A, Kobus-Cisowska J, et al. Hydroxypropyl-β-cyclodextrin as carrier of curcumin–piperine system. **J Enzyme Inhib Med Chem**. 2020;35:1811–21.
24. Nair KL, Thulasidasan AK, Deepa G, Anto RJ, Kumar GS. Aqueous PLGA nanoparticulate formulations of curcumin. **Int J Pharm**. 2012;425:44–52.
25. Sadoughi A, Irani S, Bagheri-Khoulenjani S, Atyabi SM, Olov N. Plasma-modified curcumin-loaded chitosan nanoparticles. **Polym Adv Technol**. 2021;32:31–40.
26. Pang SC, Tay SH, Chin SF. Curcumin-loaded starch-maleate nanoparticles. **J Nanomater**. 2014;2014:824025.
27. Govindaraju R, Karki R, Chandrashekarappa J, Santhanam M, Shankar A, Joshi H, et al. Enhanced water dispersibility of curcumin nanoparticles. **Pharm Nanotechnol**. 2019;7:39–56.
28. Sathisaran I, Dalvi SV. Crystal engineering of curcumin with salicylic acid and

hydroxyquinol. **Cryst Growth Des**. 2017;17:3974–88.
29. Rathi N, Paradkar A, Gaikar VG. Polymorphs of curcumin and its cocrystals. **J Pharm Sci**. 2019;108:2505–16.
30. Sanphui P, Goud NR, Khandavilli UBR, Nangia A. Fast dissolving curcumin cocrystals. **Cryst Growth Des**. 2011;11:4135–45.
31. Pantwalawalkar J, More H, Bhange D, Patil U, Jadhav N. Curcumin–ascorbic acid cocrystal for improved solubility. **J Drug Deliv Sci Technol**. 2020;61:102233.
32. Ribas MM, Aguiar GPS, Muller LG, Siebel AM, Lanza M, Oliveira JV. Curcumin–nicotinamide cocrystallization. **Ind Crops Prod**. 2019;139:111537.
33. Dal Magro C, dos Santos AE, Ribas MM, Aguiar GPS, Volfe CRB, Lopes MLLC, et al. Curcumin–resveratrol cocrystal production. **J Supercrit Fluids**. 2021;171:105190.
34. Wei Y, Dattachowdhury B, Vangara KK, Patel N, Alexander KS, Boddu SHS. *Excipients that facilitate amorphous drug stabilization*. Cham: Springer; 2015.
35. Gupta P, Chawla G, Bansal AK. Physical stability and solubility advantage from amorphous celecoxib. **Mol Pharm**. 2004;1:406–13.
36. Janssens S, Van den Mooter G. Physical chemistry of solid dispersions. **J Pharm Pharmacol**. 2009;61:1571–86.
37. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. **J Pharm Pharmacol**. 2010;62:1607–21.
38. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. **Cryst Growth Des**. 2009;9:2950–67.
39. Bhalani DV, Nutan B, Kumar A, Chandel AKS. Bioavailability enhancement techniques. **Biomedicines**. 2022;10:2055.
40. Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, et al. Pharmaceutical amorphous solid dispersion. **Acta Pharm Sin B**. 2021;11:2505–36.
41. Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals. **J Pharm Sci**. 2010;99:1254–64.
42. Chavan RB, Thipparaboina R, Kumar D, Shastri NR. Co-amorphous systems. **Int J Pharm**. 2016;515:403–15.
43. Shi Q, Moinuddin SM, Cai T. Advances in co-amorphous drug delivery systems. **Acta Pharm Sin B**. 2019;9:19–35.
44. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. **Mol Pharm**. 2007;4(6):807–18.
45. Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. **Molecules**. 2014;19(12):20091–20112.
46. Akhter S, Ahsan MJ, Verma A, Rahman M, Beg S. Improving the therapeutic performance of curcumin: current progress, challenges, and opportunities in drug delivery. **Mol Pharm**. 2021;18(4):1091–1112.
47. Tønnesen HH, Karlsen J. Studies on curcumin and curcuminoids. VI. Kinetics of curcumin degradation in aqueous solution. **Z Lebensm Unters Forsch**. 1985;180(5):402–404.
48. Wang YJ, Pan MH, Cheng AL, Lin LI, Ho YS, Hsieh CY, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. **J Pharm Biomed Anal**. 1997;15(12):1867–1876.
49. Ireson CR, Jones DJ, Orr S, Coughtrie MW, Boocock DJ, Williams ML, et al. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. **Cancer Epidemiol Biomarkers Prev**. 2001;10(5):407–414.
50. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. **Planta Med**. 1998;64(4):353–356.
51. Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, et al. Dose escalation of a curcuminoid formulation. **BMC Complement Altern Med**. 2006;6:10.
52. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. Curcumin, a component of golden spice: from bedside to bench and back. **Biotechnol Adv**. 2014;32(6):1053–1064.
53. Chieng N, Aaltonen J, Saville D, Rades T. Physical characterization and stability of amorphous indomethacin and ranitidine hydrochloride binary systems prepared by

mechanical activation. **Eur J Pharm Biopharm**. 2009;71(1):47–54.
54. Löbmann K, Grohganz H. Co-amorphous drug formulations for delivery of poorly soluble drugs. **Int J Pharm**. 2014;453(1):285–294.
55. Laitinen R, Löbmann K, Strachan CJ, Grohganz H, Rades T. Emerging trends in the stabilization of amorphous drugs. **Int J Pharm**. 2017;532(1):1–12.
56. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. **Mol Pharm**. 2007;4(6):807–818.
57. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. **J Pharm Sci**. 1971;60(9):1281–1302.
58. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water-soluble drugs. **Drug Discov Today**. 2016;21(2):388–395.
59. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. **J Pharm Sci**. 1997;86(1):1–12.
60. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. **J Pharm Sci**. 1971;60(9):1281–1302.
61. Chavan RB, Thipparaboina R, Kumar D, Shastri NR. Co-amorphous systems: a product development perspective. **Int J Pharm**. 2016;515(1–2):403–415.
62. Chavan RB, Thipparaboina R, Kumar D, Shastri NR. Co-amorphous systems: a product development perspective. **Int J Pharm**. 2016;515(1–2):403–415.
63. Ueda K, Higashi K, Moribe K. Co-amorphous systems in pharmaceutical field. **Int J Pharm**. 2017;536(1):379–391.
64. Löbmann K, Laitinen R, Grohganz H, Gordon KC, Strachan C, Rades T. Co-amorphous drug systems: enhanced physical stability and dissolution rate of indomethacin and naproxen. **Mol Pharm**. 2011;8(5):1919–1928.
65. Jensen KT, Löbmann K, Rades T, Grohganz H. Improving co-amorphous drug formulations by the addition of the highly water-soluble amino acid proline. **Pharmaceutics**. 2014;6(3):416–435.
66. Hong J, Feng J, Wang Y, Zhang Y, Zhang W. Co-amorphous curcumin–arginine system: enhanced physical stability, dissolution and bioavailability. **Eur J Pharm Biopharm**. 2019;139:99–107.
67. Ueda H, Nakamura T, Higashi K, Moribe K. Improvement of solubility and oral bioavailability of curcumin by co-amorphous formulation with citric acid. **Eur J Pharm Biopharm**. 2019;141:1–9.
68. Laitinen R, Löbmann K, Grohganz H, Strachan C, Rades T. Pharmaceutical co-amorphous systems. **Int J Pharm**. 2013;453(1):65–79.
69. Löbmann K, Strachan C, Grohganz H, Rades T, Korhonen O, Laitinen R. Co-amorphous simvastatin–saccharin mixtures: preparation, stability, and dissolution properties. **Pharm Res**. 2012;29(3):870–881.
70. Mancillas-Quiroz JA, Carrasco-Portugal MC, Mondragón-Vásquez K, et al. Development of a novel co-amorphous curcumin and L-arginine (1:2): structural characterization, biological activity and pharmacokinetics. **Pharmaceutics**. 2025;17(1):11. doi:10.3390/pharmaceutics17010011.
71. Garbiec E, Rosiak N, Sip S, Zalewski P, Cielecka-Piontek J. Curcumin solubility and bioactivity enhancement through amorphization with tryptophan via supercritical fluid technology. **Int J Mol Sci**. 2025;26(2):855. doi:10.3390/ijms26020855.
72. Liu J, Grohganz H, Löbmann K, Rades T, Hempel NJ. Co-amorphous drug formulations in numbers: recent advances in co-amorphous drug formulations. **Pharmaceutics**. 2021;13(3):389. doi:10.3390/pharmaceutics13030389.
73. Mancillas-Quiroz JA, Carrasco-Portugal MC, Mondragón-Vásquez K, et al. Development of a novel co-amorphous curcumin and L-arginine (1:2). **Pharmaceutics**. 2025;17(1):11.
74. Patil U, Rawal S, Pantwalawalkar J, et al. Development of amino acid salt-based curcumin@lysine acetate co-amorphous system using liquid-assisted grinding. **Thai J Pharm Sci**. 2023;46(6):711–719.
75. Garbiec E, Rosiak N, Sip S, Zalewski P, Cielecka-Piontek J. Curcumin solubility and bioactivity enhancement through amorphization with tryptophan via supercritical fluid technology. **Int J Mol Sci**. 2025;26(2):855.

76. Liu J, Grohganz H, Löbmann K, Rades T, Hempel NJ. Co-amorphous drug formulations in numbers. **Pharmaceutics**. 2021;13(3):389.
77. Shelke R, et al. Recent advances in dual-drug co-amorphous systems. **Eur J Pharm Biopharm**. 2024;—:—.
78. Mancillas-Quiroz M, et al. Development of co-amorphous drug systems. **Pharmaceutics**. 2022;14(7):1415. doi:10.3390/pharmaceutics14071415.
79. Patil S, et al. Development of amorphous drug delivery systems. **J Drug Deliv Sci Technol**. 2021;64:102559. doi:10.1016/j.jddst.2021.102559.
80. Patil U, et al. Development of amino acid salt-based curcumin@lysine acetate co-amorphous system. **Thai J Pharm Sci**. 2023;47(6):459–471.
81. Mancillas-Quiroz JA, et al. Development of a novel co-amorphous curcumin and L-arginine (1:2). **Pharmaceutics**. 2024;17(1):11.
82. Garbiec E, et al. Curcumin solubility and bioactivity enhancement through tryptophan-based co-amorphous systems. **Int J Mol Sci**. 2025;26(2):855.
83. Mancillas-Quiroz JA, Carrasco-Portugal MC, Mondragón-Vásquez K, et al. Development of a novel co-amorphous curcumin and L-arginine (1:2). **Pharmaceutics**. 2025;17:11.
84. Gunnam A, Nangia A. Solubility improvement of curcumin with amino acids. **CrystEngComm**. 2021;23:—.
85. Garbiec E, Rosiak N, Sip S, Zalewski P, Cielecka-Piontek J. Curcumin solubility and bioactivity enhancement through amorphization with tryptophan. **Int J Mol Sci**. 2025;26:855.
86. Wegiel LA, Zhao Y, Mauer LJ, Edgar KJ, Taylor LS. Curcumin amorphous solid dispersions: influence of intra- and intermolecular bonding on physical stability. **Pharm Dev Technol**. 2014;19(8):976–986.
87. Han J, Yang Y, Hou Y, Tang M, Zhang Y, Zhu Y, et al. Insight into formation, synchronized release and stability of co-amorphous curcumin–piperine. **J Pharm Sci**. 2024;113(7):1874–1884.
88. Liu J, Grohganz H, Löbmann K, Rades T, Hempel NJ. Co-amorphous drug formulations in numbers. **Pharmaceutics**. 2021;13(3):389.
89. Grohganz H, Löbmann K, Rades T. Co-amorphous drug systems: a strategy to enhance physical stability. **Int J Pharm**. 2020;586:119583.
90. Mancillas-Quiroz JA, et al. Development of a novel co-amorphous curcumin and L-arginine (1:2). **Pharmaceutics**. 2024;17(1):11.
91. Liu J, Grohganz H, Löbmann K, Rades T, Hempel NJ. Co-amorphous drug formulations in numbers. **Pharmaceutics**. 2021;13(3):389.
92. Grohganz H, Löbmann K, Rades T. Co-amorphous drug systems: a strategy to enhance physical stability. **Int J Pharm**. 2020;586:119583.
93. Löbmann K, Grohganz H, Rades T. Advanced co-amorphous drug delivery systems for personalized medicine. **Expert Opin Drug Deliv**. 2021;18(9):1093–1105.
94. Mancillas-Quiroz JA, et al. Development of a novel co-amorphous curcumin and L-arginine (1:2). **Pharmaceutics**. 2024;17(1):11.

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