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Solid-State Modification Strategies for Alpha-Mangostin Solubility Enhancement: A Review on Recent Progress

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Abstract

Introduction: Enhancing the therapeutic efficacy of active pharmaceutical ingredients requires addressing the persistent challenge of improving their solubility. Alpha-mangostin (AM), a promising natural compound with various pharmacological properties, faces significant limitations due to its low aqueous solubility. This review focuses on evaluating solid-state modification (SSM) techniques developed to enhance AM solubility. It aims to identify the most effective SSM approaches, analyse their advantages, and provide insights for future research directions in addressing solubility challenges for poorly water-soluble compounds. **Methods:** This review article is based on a comprehensive analysis of the literature from databases like Scopus, Google Scholar, ScienceDirect, Springer, and PubChem, covering studies published in the past 15 years. Keywords such as "solubility," "alpha-mangostin," and "solubility improvement" were utilised, with a focus on scientific articles and reviews. **Results:** Several strategies, such as nanoparticle technology, particle size reduction, amorphous formation, and solid dispersion, have been used to enhance AM solubility. Solid dispersion with polyvinylpyrrolidone achieved the highest solubility (2743 µg/mL), while the AM-chitosan-oleic acid complex using nanotechnology improved AM solubility to 160 µg/mL, an 800-fold increase from 0.2 µg/mL. **Conclusion:** The reviewed methods have significantly enhanced the aqueous solubility of AM, with solid dispersion and nanotechnology showing the most promising results. These findings highlight the potential of solubility enhancement strategies to optimise AM's pharmaceutical applications and provide a framework for improving the bioavailability of other poorly water-soluble compounds. Future research should explore alternative methods, such as co-crystallisation and advanced nanotechnologies, to further enhance solubility and formulation efficiency.

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Introduction

Solubility denotes the maximum quantity of a compound that can dissolve in a solvent at equilibrium, with solubility generally increasing with temperature (Savjani et al., 2012). In pharmaceuticals, solubility is essential for achieving effective active pharmaceutical ingredient (API) concentrations in plasma, as the API must be dissolved in a non-toxic solvent at the necessary concentration to ensure proper bioavailability. This ensures that the API reaches its target site and elicits the desired therapeutic effect (Savjani et al., 2012).

The solubility of APIs can be improved through solid-state modification (SSM), which involves altering the structure or form of the APIs, sometimes with the incorporation of excipients (Jain et al., 2005; Lavilla et al., 2013). SSM is commonly used to enhance the solubility, stability, and bioavailability of poorly water-soluble compounds. Methods such as solid dispersion, nanoparticle formulation, and amorphous formation are considered SSMs because they involve changes in the physical form of APIs while preserving their molecular structure. Unlike chemical modifications or liquid formulations, which alter the molecular structure and produce compounds with different properties, SSMs retain the original molecular structure. The focus on SSM is driven by its proven effectiveness in addressing the solubility challenges of APIs while offering additional advantages, such as cost-effectiveness, energy efficiency, and environmental sustainability.

Alpha-mangostin (AM) is a naturally occurring xanthone isolated from various parts of the mangosteen (*Garcinia mangostana Linn*) tree, including its pericarps (Ahmad Izuren Shah et al., 2025). The compound is attractive due to its potent pharmacological actions such as anticancer (Zhang et al., 2017), renal and hepatic protective, anti-diabetes (Tatiya-Aphiradee et al., 2019), antioxidant (Suthammarak et al., 2016; Akhmad et al., 2018), antibacterial and antifungal properties (Narasimhan et al., 2017), and a promising candidate for the treatment of obesity (Ardakanian et al., 2022; Taher et al., 2015), Alzheimer's disease, Parkinson's disease, and depression (Do & Cho 2020). However, the compound's poor aqueous solubility and low oral bioavailability are the major obstacles to its development. It is classified as a Class II substance in the Biopharmaceutical Classification System (BCS), characterised by low solubility and high permeability. The low aqueous solubility of 0.2 ± 0.2 μg/mL at room temperature, as reported by Aisha et al. (2012), impairs its dissolution in the upper gastric fluid (Savjani et al., 2012), which alters bioavailability and deters its therapeutic application. The low aqueous solubility of AM correlates with its molecular structure, as shown in Fig. 1. AM consists of an unsubstituted tricyclic xanthone core, three hydroxy groups at positions 1, 3, and 6, a methoxy group at position 7, a carbonyl group at position 9, and two isopentene groups at positions 2 and 8. The unsubstituted tricyclic rings lack polar functional groups capable of interacting with water molecules through hydrogen bonding or dipole-dipole interactions. In addition, the structure of AM lacks hydrogen bond donors and acceptors, restricting its ability to form favourable interactions with solvent molecules, resulting in poor solvation in water.

This review focuses on evaluating SSM techniques developed to enhance AM solubility. It aims to identify the most effective SSM approaches, analyse their advantages, and provide insights for future research directions in addressing solubility challenges for poorly water-soluble compounds. It is based on a comprehensive literature review of

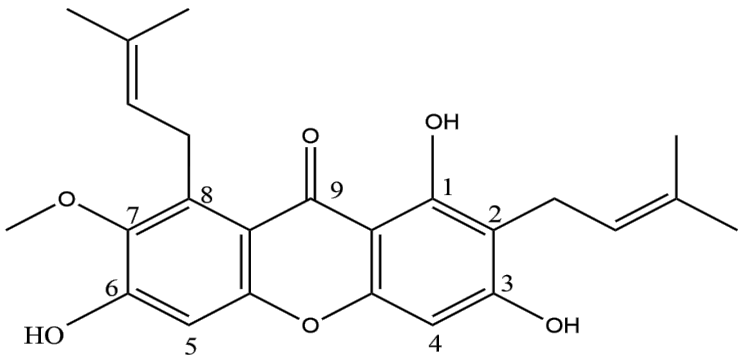

Fig. 1: The structural formula of alpha-mangostin (AM). (Reproduced from Ahmad Izuren Shah et al., 2025)

studies from databases like Scopus, Google Scholar, ScienceDirect, Springer, and PubChem, published in the past 15 years. Keywords such as "solubility," "alpha-mangostin," and "solubility improvement" were utilised, with a focus on scientific articles and reviews.

Factors affecting solubility.

The solubility of a compound is determined by both its intrinsic characteristics and the conditions of the solution. Key attributes such as particle size, crystalline order, and polarity influence how the compound interacts with various solvents (Kasimedua et al., 2015). Moreover, solution conditions, including pH, the presence of co-solvents, temperature, and pressure, play a significant role in affecting solubility (Kasimedua et al., 2015).

Particle size

Solubility enhancement is achieved through the reduction of particle size, which increases the surface area-to-volume ratio by providing more surface for interaction with the solvent. This principle is supported by the following equation (Chaudhary et al., 2012):

$$log\frac{S}{So} = \frac{2\gamma V}{2.303\ R.T.r} \qquad (1)$$

Where S_o = the solubility of large particles (mol/L), S = the solubility of fine particles (mol/L), V = the molar volume (L/mol), γ = the surface tension of the solid (N/m), r = the radius of the fine particles (m), R = gas constant (J/mol·K), and T = temperature (K).

This increase in surface area exposes more of the AM particles to the solvent, thereby facilitating improved solubilisation through enhanced solvent interaction. For AM, this is particularly significant due to its bulky xanthone core and limited aqueous solubility, as smaller particles can increase the likelihood of hydrogen bonding with solvents. Additionally, smaller particles present a higher number of high-energy sites, further augmenting their interaction with liquid solvents. The process of reducing particle size often introduces crystal defects or imperfections, which weaken AM's crystalline structure, characterised by strong intramolecular interactions, thereby promoting easier dissolution (Łuczak et al., 2023). Furthermore, smaller AM particles generally exhibit a lower melting point, leading to reduced intramolecular forces within the xanthone tricyclic ring system and promoting solubility (Alshora et al., 2016).

Crystalline order

Crystalline forms of APIs are generally the most stable, characterised by high density, high melting points, and minimal Gibbs free energy, which contribute to their low solubility (Peltonen & Strachan 2020). The well-ordered molecular arrangement in crystalline states limits interaction with solvent molecules, reducing solubility.

Although crystalline forms of APIs are typically the most stable, some compounds can be processed into an amorphous form to enhance their solubility. The amorphous state is generally the least stable, but it exhibits significantly higher solubility due to its disordered molecular arrangement (Babu et al., 2011). These high-entropy phases are produced by rapidly freezing molecular motion before it can organize into a crystalline lattice. Amorphous compounds, which can exist as solids or supercooled glassy states, lack the long-range order and periodicity of crystalline structures (Peltonen & Strachan, 2020). This structural disorder increases surface area and functional group exposure, allowing better solvent interaction and enhancing solubility. However, the metastable nature of amorphous compounds, combined with their susceptibility to recrystallisation during storage, poses challenges for drug development and necessitates stabilisation strategies to preserve the solubility advantage (Babu et al., 2011).

Polarity

The capacity of a compound and solvent to form hydrogen bonds is intrinsically linked to their polarity. Compounds and solvents with higher polarity typically exhibit a stronger tendency to function as hydrogen bond donors and acceptors (Mudalip et al., 2013; Hassan et al., 2018). AM, with its three hydroxyl groups and xanthone core, can form hydrogen bonds with polar solvents, enhancing its solubility. However, AM's limited

solubility in highly polar solvents, such as water, arises from its bulky, hydrophobic structure, which reduces compatibility with such solvents. Van der Waals interactions, though secondary to hydrogen bonding, play a more prominent role in AM's solubility in non-polar or semi-polar solvents, where intermolecular interactions better accommodate its unsaturated tricyclic xanthone ring (Guo et al., 2016).

Solution conditions

Solubility is also influenced by solution conditions such as pH, the presence of co-solvents, and temperature. For weakly ionisable APIs like AM, solubility can exhibit substantial variability with pH fluctuations (Taniguchi et al., 2014). AM, being a polyphenolic compound with weakly acidic properties, exhibits solubility dependence on pH, particularly in its crystalline form. Small changes in pH can lead to noticeable shifts in AM's solubility, similar to the behaviour of other BCS Class II substances, which are characterised by high permeability but low solubility. As pH decreases, AM's solubility increases due to its enhanced ionisation (Asasutjarit et al., 2019). In addition, an increase in pH can reduce AM particle size from 548 nm to 200 nm, with crystallisation occurring at lower pH levels and physical changes observed around pH 6 (Ahmad et al., 2013).

Co-solvents can enhance the solubility of low polarity compound, such as AM. The use of co-solvents reduces solvent-solvent interactions, thereby lowering surface tension and the dielectric constant, improving AM's solubility in polar solvents by reducing the incompatibility between its hydrophobic core and the solvent (Mantri et al., 2017). Temperature also plays a role in enhancing AM's solubility, especially when using endothermic processes. As temperature increases, the kinetic energy of molecules intensifies, leading to more frequent and energetic collisions between AM and solvent molecules (Hassan et al., 2018). Elevated temperatures may help overcome some of AM's inherent molecular structure, increasing AM solubility. Furthermore, temperature increases may lead to the formation of larger micelles, facilitating AM's dispersion in solution. Pressure typically has less of an impact on AM's solubility compared to gases, but variations in pressure can influence the solubility of AM in certain solvents, particularly under supercritical conditions (Lee et al., 2019).

To enhance solubility, various techniques can be used for AM, including physical modifications such as reducing particle size through micronisation or nanosuspension, and altering crystal forms. The use of co-solvents, surfactants, and other excipients can help to solvate AM more effectively (Lee et al., 2019). Moreover, chemical modifications, such as adjusting pH or derivatives formation, may improve AM's dissolution rate (Savjani et al., 2012).

Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) categorises substances into four classes based on their solubility and permeability characteristics, in accordance with the International Conference on Harmonisation (ICH) guidelines (2019), as depicted in Fig. 2. This system has become crucial in recent years for guiding the development of oral formulations and establishing bioavailability standards (Dahan et al., 2009).

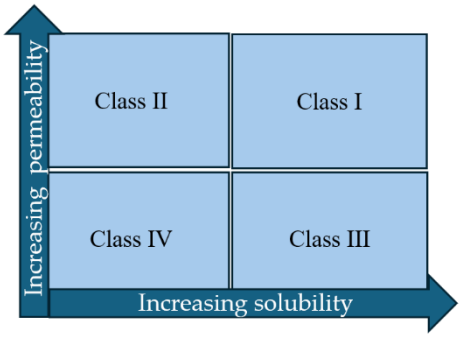

Fig. 2: API classification based on the Biopharmaceutics Classification System (BCS)

BCS Class II substances are characterised by high permeability but low solubility, which limits their bioavailability (Yasir et al., 2010). As of recent reports, 60–70 % of API candidates in development and 30 % of APIs that have reached the market belong to BCS Class II (Ting et al., 2018). AM is classified as a BCS Class II compound (Li et al., 2011). Its solubility in water at room temperature is 0.2 ± 0.2 μg/mL (Aisha et al., 2012). It is significantly

lower compared to ibuprofen (21 µg/mL) (National Center for Biotechnology Information, 2024) and atorvastatin (100 µg/mL) (Rodde et al., 2014), but comparable to curcumin (0.6 µg/mL) (Górnicka et al., 2023). In terms of permeability, AM shows high membrane permeability, similar to curcumin (apparent permeability (P_{app}) ≈ 0.07×10^{-6} cm/s) (Dempe et al., 2012) and atorvastatin (P_{app} ≈ 28.1×10^{-6} cm/s) (Li et al., 2011), though slightly lower than ibuprofen ($P_{app} \approx 1.8\times10^{-4}$ cm/s) (National Center for Biotechnology Information, 2024).

To enhance the solubility of BCS Class II substances, techniques are generally categorised into two main groups: physical modification and chemical modification. Physical modification involves particle and crystal engineering, along with amorphous systems, incorporating methods such as nanoparticle synthesis, particle size reduction, amorphous solid formation, and solid dispersion techniques (Jain & Chella, 2020). In contrast, chemical modification includes prodrug strategies and API derivatisation to modify physicochemical properties and biodistribution while preserving pharmacological activity, along with the formation of complex compounds using surfactants or co-solvents (Jain & Chella, 2020). To date, numerous attempts using various techniques have been employed to improve the solubility of AM.

Nanotechnology

While physical and chemical modification techniques offer various approaches for enhancing the solubility of BCS Class II substances, nanotechnology has emerged as a powerful strategy to further address these challenges. Nanotechnology is a key component of nanomedicine, enabling advancements in targeted treatments and enhancing therapeutic efficacy in clinical applications. Nanoparticles, which are around 10^{-9} meters in size, have a significantly larger surface area, leading to greater contact with solvents. In addressing the challenges of poor API solubility, nanoparticles increase the API surface area, thus improving dissolution rates and stabilising the API in a nanoscale form. Nanoparticle technology facilitates improved solubility through mechanisms such as solid dispersion formation and enhanced dissolution rates (Chen et al., 2011). By encapsulating the API in a nanoscale carrier, nanoparticles address solubility issues, making them an effective method for improving the solubility of poorly soluble APIs. Cellulose derivative polymers have the ability to form nanoreservoirs using particle technology (Pan-in et al., 2014; Kim et al., 2014). These enhancements are further amplified when coupled with polyethylene glycol-2000 (Sakpakdeejaroen et al., 2022). In addition, the combined application of letichin and propolis extract has demonstrated enhanced efficacy and solubility of AM (Suhandi et al., 2023).

The AM encapsulation procedure involved the use of a self-assembly technique (Pan-in et al., 2014) and a solvent displacement method, employing a mixture of ethylcellulose and methylcellulose polymers to form nanoparticles (Kim et al., 2014). The resulting nanoparticles were characterised to ascertain their loading capacity and encapsulation efficiency, in vitro release, cellular uptake, and susceptibility testing (Pan-in et al., 2014; Kim et al., 2014). The morphology of the nanoparticles encapsulated with AM showed their spherical form (Kim et al., 2014). The nanoparticles displayed favourable stability in suspension and excellent drug-loading and encapsulation efficiencies. The results demonstrate the effectiveness of cellulose-derivative nanoparticles in enclosing the hydrophobic AM, enhancing its solubility and bioavailability of AM, as well as successfully improving the delivery of AM into cancer cells (Kim et al., 2014).

Furthermore, nanotechnology enhances AM solubility through SSM to form proniosomes. The amphiphilic nature of proniosomes allows them to interact with both hydrophilic target molecules and the hydrophobic regions of APIs, thereby improving therapeutic agent delivery (Shah et al., 2021). Proniosomes are dehydrated powders made of nonionic surfactants and lipids (see Figure 3(b)). When these powders contact water, they transform into niosomes, encapsulating AM, a poorly soluble API, which improves its solubility and stability. Chin et al., (2016) used the coacervation phase separation method to prepare AM proniosomes, creating a stable system that enhances the transportation of lipophilic AM. The study reported that AM proniosomes had numerous significant advantages, including improved skin permeability, high entrapment efficiency, successful deposition in

the viable epidermis, better vesicle stability, and no agglomeration.

Pham et al. (2019) formulated AM-loaded fibroin nanoparticles using fibroin extracted from Bombyx mori silk, combined with carbodiimide and polyethylenimine. The resulting nanoparticles, averaging 300 nanometres in size with surface charges between −15 and +30 millivolts, exhibited a significantly enhanced solubility of 1.091 µg/mL, which is nearly a threefold increase compared to the 0.386 µg/mL solubility of free AM. In contrast, Yang et al. (2019) employed biodegradable monomethoxy poly(ethyleneglycol)-polycaprolactone copolymer nanomicelles. By re-suspending AM and the copolymer in methanol, followed by a self-assembly process in water, they fabricated nanomicelles with high encapsulation efficiency.

Micelles are colloidal structures formed by the self-assembly of amphiphilic molecules, as schematically shown in Fig. 3 (c). In an aqueous environment, the hydrophilic regions of these molecules' orient outward, interacting with the solvent, while the hydrophobic regions aggregate inward to form the particle's core (Ducheyne et al., 2017). The concentration at which micelles begin to form is referred to as the critical micelle

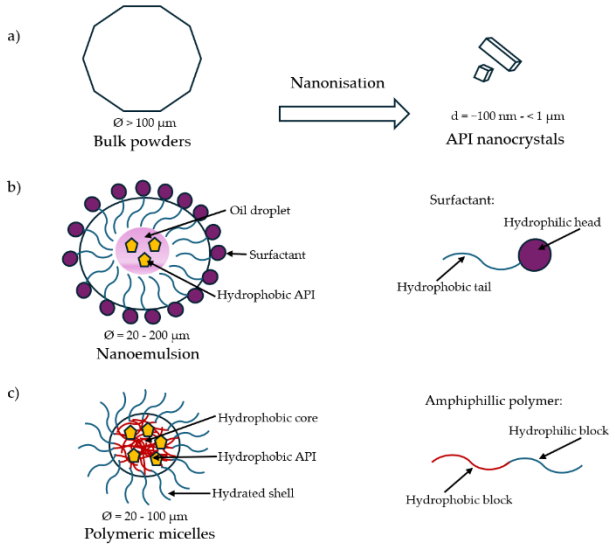

Fig. 3: Schematic overview of different nanotechnology techniques. (Modified from Chen et al., 2011)

concentration (CMC). A lower CMC is typically preferred in functional applications, as it indicates greater micelle stability, even under dilution (Meylina et al., 2021). These nanomicelles not only improved solubility but also demonstrated controlled drug release.

Both Samprasit et al., (2014) and Kalidason & Kuroiwa (2023) improved AM solubility using chitosan, albeit through different methods: thiolated chitosan polymer solutions and chitosan-oleic acid complexes, respectively. Samprasit et al., (2014) enhanced AM solubility by incorporating it into nanofiber mats using a polymer matrix. A composite solution of thiolated chitosan and polyvinyl alcohol was prepared to achieve a homogeneous dispersion of AM, followed by electrospinning to fabricate nanofibre mats. The resulting mats exhibited potent antibacterial activity and facilitated the rapid release of bioactive compounds. In contrast, Kalidason & Kuroiwa (2023) utilised nanoencapsulation technology to enhance the aqueous solubility of AM by preparing a chitosan solution from chitosan flakes dissolved in acetic acid and oleic acid, into which the AM extract was incorporated. Following stirring and centrifugation, a stable chitosan-oleic acid complex with a particle size of 830 nm was formed. The thiolated chitosan improved the prolonged release and efficacy of the mats when taken orally, while the chitosan-oleic acid complex exhibited excellent stability and efficient controlled delivery to the intestine, significantly increasing AM's solubility by over 800 times, from an initial 0.2 µg/mL. Nanoparticle drug delivery systems offer significant benefits, including enhanced solubility, controlled release, and targeted delivery, all of which improve the bioavailability and therapeutic effectiveness of AM. These systems also provide versatile formulations, reduce toxicity, and enhance pharmacokinetic properties (Wathoni et al., 2020). Nevertheless, scaling up nanoparticle formulations for industrial production is complex and costly. Stability, biocompatibility, and toxicity must be carefully managed, as environmental conditions and potential adverse effects can impact AM efficacy (Wathoni et al., 2020).

Size reduction

Nanotechnology uses the properties of nanoparticles, whereas size reduction techniques, such as high-pressure homogenisation, offer a more direct approach to improving AM's solubility. AM was dispersed in deionised water with stabilisers

such as sodium lauryl sulphate and poloxamer 188. The dispersion was sonicated to improve uniformity. High-pressure homogenisation was conducted at different pressures while maintaining temperature control to prevent excessive heating and reduce particle size (Limwikrant et al., 2019). The stability and efficacy of the particles were evaluated by monitoring their size and zeta potential. The study found that sodium lauryl sulfate resulted in the highest solubility for AM, with a value of 57.81 ± 0.21 μg/mL. This was attributed to its lower CMC compared to poloxamer 188 (Limwikrant et al., 2019).

Ball milling techniques were also used for the size reduction of poorly soluble APIs, with the potential to increase AM solubility. The API powders were weighed inside a glove box under a high-purity argon atmosphere (oxygen <25 ppm) to maintain inert conditions and prevent oxidation during milling. The powders were then loaded into hardened stainless-steel jars with stainless-steel balls, and stearic acid was added as a process-controlling agent. High-energy ball milling was performed at 280 and 350 rotations per minute, with a 30-minute pause after each hour of milling (Witharamage et al., 2021). The milled powders were subsequently cooled and compacted.

This technique effectively reduced particle size, increasing the surface area and active sites, which led to enhanced solubility. Reducing particle size offered significant advantages, such as improved emulsion stability and energy efficiency (Dumay et al., 2013). It also enhanced the functional properties and bioavailability of the API. While size reduction provided various benefits, it also required high operational costs, significant energy consumption, and potential temperature effects that could degrade the API. Additional challenges included scale-up difficulties, limited long-term data, microbial resistance, and the need for precise viscosity control, which complicated product formulation and consistency (Dumay et al., 2013).

Amorphous formation

The formation of amorphous solids is one of the SSM strategies used to enhance AM solubility. The amorphous form of a substance is characterised by its irregular structure and higher energy state compared to its crystalline counterpart, as shown in Fig. 4. This form generally enhances API dissolution, solubility, and bioavailability due to its less ordered lattice, which improves solvent contact and wetting (Iqbal et al., 2018). Amorphous solids exhibit elevated free energy, enthalpy, and entropy due to their disordered structure (Gurunath et al., 2013). A study indicated that rice husk ash mesoporous silica effectively facilitated the transformation of AM into its amorphous form, thereby enhancing its solubility (Iqbal et al., 2018). Rice husk was processed by washing, filtration, and rinsing, followed by calcination to produce rice husk ash. Mesoporous silica was synthesised from this ash using Pluronic 123, followed by additional calcination. The sol-gel method was then employed to load AM onto the rice husk ash mesoporous silica. Both AM and the mesoporous silica were dissolved in ethanol, concentrated, and dried (Iqbal et al., 2018). Amorphous AM enhances solubility, improves physical stability, and inhibits recrystallization. However, amorphous AM has limitations, such as high recrystallisation tendencies, agglomeration issues, and dependence on polymer choice and ratio. These challenges, along with storage difficulties and regulatory concerns, complicate its practical use in pharmaceutical formulations (Budiman et al., 2023).

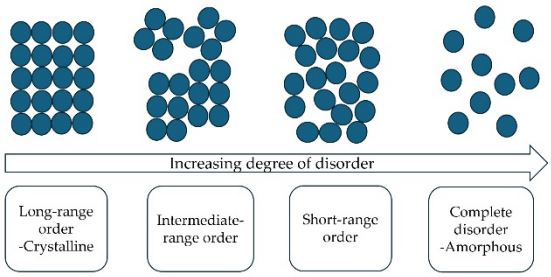

Fig. 4: The structural transition from crystalline to amorphous states. (Modified from Peltonen & Strachan 2020)

Solid dispersion

Solid dispersions, which are a method of enhancing the solubility of poorly soluble drugs by dispersing them in a solid matrix, are illustrated by the process flow shown in Fig. 5. They typically consist of a hydrophilic matrix and a hydrophobic API, with the matrix existing in either crystalline or amorphous states (Singh et al., 2013). This method

enhances API concentrations in gastrointestinal fluids by employing particle size reduction, improving wetting, and reducing agglomeration (Kumar et al., 2017). The inclusion of surfactants further minimises recrystallisation, improving both dissolution and stability (Chaudhari et al., 2017). Solid dispersions offer advantages over other systems by enhancing oral bioavailability without altering the API's active targets, often through salt formation or by incorporating polar or ionised groups (Kaur et al., 2012).

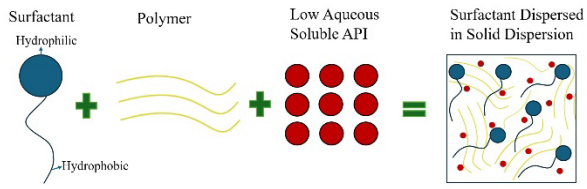

Fig. 5: Schematic representation of a technique for incorporating surfactant and polymer into solid dispersions.

The study by Aisha et al. (2012) employed solid dispersion techniques to enhance solubility and elucidate the underlying mechanisms. Solid dispersions were prepared through the solvent evaporation method using polyvinylpyrrolidone (PVP), resulting in a substantial increase in AM solubility from 0.2 ± 0.2 µg/mL to 2743 ± 11 µg/mL. Characterisation was performed using Fourier Transform Infrared (FTIR) spectroscopy to analyse API-polymer interactions and X-ray Diffraction (XRD) to verify the transition of AM to an amorphous state. Solubility studies involved dissolving the solid dispersions in phosphate-buffered saline. This study also confirmed the formation of spherical anionic nanomicelles with particle sizes ranging from 99 to 127 nm, which enhance tissue and cellular penetration. Solid dispersions provide versatility in AM formulation, stability for sensitive compounds, ease of manufacturing, and potential for combination therapies, while also reducing side effects by lowering required dosages. However, solid dispersions face challenges such as stability issues, limited drug loading, and complex formulation development, which can affect their efficacy and application (Tran et al., 2019).

Complex formation

Besides solid dispersions, complex formation with cyclodextrins provides another effective strategy for enhancing AM solubility. Cyclodextrins, cyclic oligosaccharides derived from starch, form non-covalent bonds with APIs, preserving their physicochemical properties. They possess primary and secondary hydroxyl groups that act as potential modification sites (Phunpee et al., 2018). Structurally, cyclodextrins resemble a truncated cone with a hydrophilic exterior and a hydrophobic interior, which facilitates the formation of inclusion complexes with non-polar molecules (Phunpee et al., 2018). This configuration, combined with the increased free energy and complex energy from such interactions, makes cyclodextrins effective carriers (Hotarat et al., 2020). Specifically, the glycerol ester group of dimethylcyclodextrin interacts with AM through hydrogen bonding, suggesting the permeation of the inclusion complex into the inner phospholipid membrane (Hotarat et al., 2020).

The phase solubility studies consisted of introducing AM into cyclodextrin solutions in a 1:1 stoichiometry ratio until the point of saturation was reached (Hotarat et al., 2019). Solutions were sonicated and incubated until equilibrium, then the supernatants were filtered and analysed. The experimental results showed that the formation of complexes with 2, 6-dimethyl-beta-cyclodextrin was the most favourable, as validated by molecular dynamics simulations. The simulations further demonstrated that AM could adopt two orientations inside cyclodextrin cavities, primarily stabilised by van der Waals forces (Hotarat et al., 2019). The results confirmed that 2, 6-dimethyl-beta-cyclodextrin significantly enhanced the solubility of AM, increasing its concentration from 1 µM in pure water to 104 µM, compared to 22 µM with beta-cyclodextrin and 28 µM with 2-hydroxypropyl-beta-cyclodextrin (Hotarat et al., 2019).

The enhanced AM solubility reached 2743 µg/mL using PVP through the solid dispersion method, which includes the solvent evaporation technique. FTIR and XRD analyses confirmed the formation of an amorphous AM-PVP solid dispersion. Moreover, the study observed no significant variation in pyrene fluorescence

intensity, indicating the physical stability of the AM-PVP complex and reinforcing the micellar stability. Complex formation techniques improved pharmacokinetics and reduced toxicity, making it safer for therapeutic use. However, limitations include the need for extensive in vivo and clinical trials, synthesis challenges, potential API interactions, and variability in individual responses. Regulatory hurdles, stability issues, and high production costs may delay approval and clinical use (Mardianingrum et al., 2024).

Summary

Nanotechnology using cellulose derivatives enhance AM's solubility and bioavailability but face challenges in preparation and stability. Proniosomes improve solubility, stability, and skin permeability, though phase separation can be problematic. Fibroin nanoparticles and nanomicelles offer biocompatibility and controlled release but are costly and hard to scale. Chitosan-based formulations are effective but affected by variability in quality. Size reduction techniques like high-pressure homogenisation and ball milling are simple and scalable but prone to aggregation and stability issues. Amorphous formation using mesoporous silica enhances solubility but is complex and costly. Solid dispersions improve wetting but face scaling and recrystallisation challenges, while cyclodextrin complexation significantly enhances solubility, with effectiveness depending on the cyclodextrin type. Each method improves AM's therapeutic potential but involves trade-offs in complexity, scalability, and stability.

Among the methods reviewed, as summarised in Table 1, Aisha et al., (2012) achieved the highest enhancement in AM solubility, reaching 2743 µg/mL using PVP via the solid dispersion method, which includes the solvent evaporation technique. FTIR and XRD analyses confirmed the formation of an amorphous AM-PVP solid dispersion. In

Table 1: Methods to enhance the aqueous solubility of AM.

Method	Free AM (µg/mL)	Enhanced AM (µg/mL)	Excipient	References
Solid dispersion, Amorphous formation	0.2	2743	Polyvinylpyrrolidone	Aisha et al., 2012
Nanoparticles	0.2	160	Chitosan-oleic acid complexes	Kalidason & Kuroiwa 2023
Particle size reduction	-	57.81	Sodium lauryl sulphate and poloxamer 188	Limwikrant et al., 2019
Complex formation	0.412	42.88	Beta cyclodextrin	Hotarat et al., 2019
Nanoparticles	0.386	1.091	Fibroin, carbodiimide, and polyethylenimine.	Pham et al., 2019
Nanoparticles (nanocarrier)	-	-	Ethylcellulose, methylcellulose (1:1)	Pin et al., 2014 Kim et al., 2014
Nanoparticles (nanocarrier)	-	-	Proniosomes	Chin et al., 2016
Nanoparticles (nanomicelles)	-	-	Monomethoxy poly(ethyleneglycol)-polycaprolactone	Yang et al., 2019
Nanoparticles (nanofiber)	-	-	Thiolated chitosan	Samprasit et al., (2014)
Amorphous formation			Rice husk, pluronic 123	Iqbal et al., 2018
Complex formation	-	-	Beta cyclodextrin	Phunpee et al., 2018

comparison, Kalidason & Kuroiwa (2023) obtained the second highest AM aqueous solubility enhancement, with 160 μg/mL, by developing an AM-chitosan-oleic acid complex. This complex exhibited excellent stability and controlled intestinal release, boosting AM's solubility over 800-fold from an initial 0.2 μg/mL.

Future strategies

In order to explore effective strategies for enhancing AM solubility, it is useful to examine similar approaches applied to other polyphenols, such as curcumin. Co-crystallisation of curcumin with resorcinol and pyrogallol has shown significant improvements in solubility and bioavailability (Sanphui et al., 2011). It was found that curcumin-resorcinol cocrystals have a solubility increase of 2.7 to 4.7 times, while curcumin-pyrogallol cocrystals show an increase of 6.7 to 11.8 times compared to the stable form of curcumin. These findings highlight the potential of using co-crystallisation to improve AM's solubility and therapeutic effectiveness.

Conclusion

This review examines both established and emerging SSM strategies for enhancing the solubility of AM, including nanoparticle technology, solid dispersions, particle size reduction, amorphous formation, and complexation. These strategies are discussed in the context of recent advancements and relevant research that highlight their effectiveness in improving AM solubility. As a BCS Class II substance, AM faces formulation challenges due to its low solubility and poor bioavailability, which limit its therapeutic effectiveness.

Solid dispersion (Aisha et al., 2012) and AM-chitosan-oleic acid complexation via nanotechnology (Kalidason & Kuroiwa, 2023) have demonstrated promising results, with AM solubility increasing by over 2700 μg/mL in the former and 160 μg/mL in the latter. These enhancements increase the potential for AM-based treatments for diseases like cancer, inflammation, and microbial infections, where AM shows significant bioactivity. Furthermore, scalable and reproducible solubility enhancement methods could facilitate the development of commercially viable AM formulations, making these therapies more accessible to patients.

Future research should focus on co-crystallisation, advanced nanotechnologies, lipid-based delivery systems, and long-term stability studies to ensure consistent solubility improvement. *In vivo* pharmacokinetic studies are also essential to assess absorption and therapeutic efficacy. Furthermore, exploring synergistic strategies for solubility enhancement and developing scalable, cost-effective formulations will be key to translating these findings into practical clinical applications

Authors contributions

Conceptualisation: M. R. A. B.; Writing—original draft preparation: N. S. A. I. S.; Writing—review and editing: M. R. A. B.; Visualisation: N. S. A. I. S.; Supervision: M. R. A. B., M. T. B, F. A., S. A. R. and W. H. D.; Project administration: M. R. A. B.; Funding acquisition: M. R. A. B. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that ChatGPT and QuillBot were used in order to improve readability and language. After employing this tool, the author meticulously assesses and modifies the text as necessary, taking full responsibility for the content of the publication.

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