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Review Article

Recent Strategies for Enhancing the Solubility and Dissolution of Poorly Water-Soluble Curcumin for Therapeutic Purposes and Beyond

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ABSTRACT

Curcumin, a natural compound with significant therapeutic potential, has been the subject of extensive research due to its anti-inflammatory, antioxidant, and anticancer properties. However, its clinical application has been hindered by poor aqueous solubility and low bioavailability, presenting significant challenges for effective drug delivery. This review provides a comprehensive overview of recent strategies aimed at improving the solubility and dissolution of poorly water-soluble curcumin. Key approaches discussed include conventional solubilization methods, such as particle size reduction, solid dispersions, co-crystals, complexation, and deep eutectic solvents, alongside more advanced delivery systems, including nanoparticles and bioconjugates. Each approach is critically evaluated in terms of its solubilizing mechanism, advantages, limitations, and applicability to large-scale production. The review also addresses challenges and future directions that offer promises for overcoming existing barriers, paving the way for the development of efficient, biocompatible, and sustainable curcumin-based therapeutics.

Keywords: Curcumin, Natural compound, Solubility, Dissolution, Stability, Bioavailability.

Introduction

Despite the growing production of synthetic active pharmaceutical ingredients (APIs), naturally derived therapeutic agents remain popular due to their effectiveness in treating various diseases. Their availability and affordability contribute to lower production cost and market costs, benefiting the pharmaceutical industry. However, natural drugs often face challenges related to stability and solubility, as they are typically poorly water-soluble and are prone to degradation when exposed to environmental factors such as oxygen, light, or temperature.[1] Therefore, a thorough investigation into scalable formulations of natural compounds is essential for their successful commercialization. Curcumin (CCM), one of the most commonly used natural compounds, is a yellow-orange polyphenolic compound extracted from the rhizome of turmeric.[2] It is also known as diferuloylmethane, or (1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione), with the chemical formula of $C_{21}H_{20}O_6$.[3] Structurally, CCM consists of a β-diketone moiety linked to two symmetrical aromatic rings of ortho-methoxy phenolic groups. The β-diketone moiety is stable at neutral or acidic pH while being a 3 is often desirable due to its higher solubility, despite its lower thermodynamic stability, whereas Form 1 is favored when stability is prioritized.[6] The solubility of CCM is pH-dependent, being highly soluble in alkaline environments but exhibiting very low solubility in neutral and acidic conditions due to the presence of ionizable functional groups.[7,8]

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Despite the increased solubility of CCM in alkaline conditions, it is not chemically stable. High pH values can lead to the autoxidation of CCM, resulting in the degradation into bicyclopentadione, vanillin, and ferulic acid.[9] CCM exhibits three distinct pKa values, one corresponding to enol proton dissociation and two associated with phenolic proton dissociation.[10] The physicochemical properties of CCM are summarized in Table 1. CCM and its derivatives have demonstrated a wide range of beneficial biological effects, promoting health and preventing various diseases. Its most notable property is the antioxidant activity, achieved through the neutralization of reactive oxygen species (ROS) via electron donation, hydrogen transfer, and direct binding to free radicals.[14] CCM inhibits ROS formation and lipid peroxidation, thereby reducing oxidative stress.[3,15] CCM's anti-inflammatory properties stem from the modulation of multiple signaling pathways. A key mechanism involves suppressing NF-κB (nuclear factor κB), a pro-inflammatory transcription factor, thereby preventing its DNA binding and subsequent activation of pro-inflammatory genes, such as the matrix metalloproteinase family. This suppression leads to reduced levels of pro-inflammatory cytokines, which include TNFα, IL-1β, IL-2, IL-6, IL-8, and MIP-1α.[16] CCM also interacts with COX-2 (cyclooxygenase-2) to decrease its expression to reduce 5-LOX (arachidonate 5-lipoxygenase) activity and leukotriene synthesis. These effects collectively contribute to its anti-inflammatory activity in inhibiting mitogen-activated protein kinases (MAPKs) to disrupt the inflammation-promoting transcription factor, SMAD3,[17,18] or reducing inducible nitric oxide synthase (iNOS), another pro-inflammatory mediator.[19] CCM is also known as an anticancer agent, interfering with angiogenesis and tumorigenesis by inhibiting Egr-1 induction, the MAPK pathway, and the protein tyrosine kinase (PTK) cascades. The exact mechanisms, however, vary depending on the type of cancer cells.[3] Furthermore, studies have highlighted CCM's antibacterial,[20] antiviral,[21] hepatoprotective,[22] and cardioprotective properties.[23] Recently, CCM has been shown to exert a neuroprotection effect by securing the mitochondria of neurons against damage caused by β-amyloid.[24]

Despite its therapeutic potential, CCM faces challenges common to naturally derived drugs in their low water solubility and permeability,

resulting in poor bioavailability. For this reason, CCM is classified as a Class IV drug in the Biopharmaceutics Classification System (BCS).[25] A clinical study investigating the pharmacokinetic profile of CCM revealed that the drug could not be detected in blood plasma following an oral administration of a high dose of 12 g.[26] This highlights the extremely poor plasma concentration of pure CCM, which is due to poor solubility. In addition, CCM taken orally has to undergo significant metabolic reduction and conjugation reactions, which limit its absorption and bioavailability.[27,28] Having mentioned the challenges of the delivery of CCM, there have been well-established reviews focusing on improving the oral bioavailability of CCM,[29-31] nanoformulations,[32-34], and effective CCM delivery systems against various diseases.[35-37] The purpose of this review is to summarise recent achievements in improving the solubility of CCM using a wide range of formulation strategies, including particle size reduction, solid dispersion, co-crystalization, complexation, bioconjugation, eutectic solvents, and nanoparticles, as graphically demonstrated in Figure 1. The underlying principle and mechanism of each method, together with their merits and demerits, are also covered. The review offered insights into the choice of techniques for designing the CCM-based delivery system based on the level of solubility enhancement, the complexity of the process and the feasibility of large-scale production.

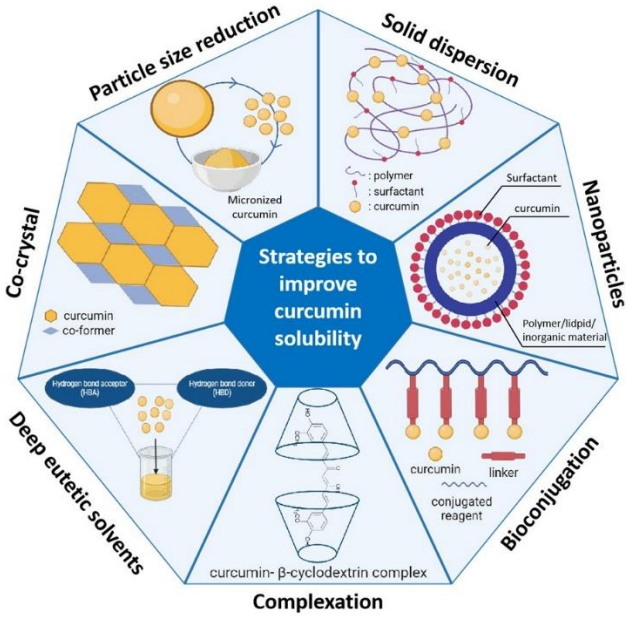


Figure 1: Strategies for improving the solubility of poorly water-soluble curcumin

Methodology

A comprehensive literature search was conducted using the databases: PubMed (https://pubmed.ncbi.nlm.nih.gov, accessed on 05 January 2023), ScienceDirect (https://www.sciencedirect.com, accessed on 05 January 2023), and Google Scholar (https://scholar.google.com, accessed on 05 January 2023). All relevant publication records were collectively searched and selected on the keywords based on the study aim, including: ("curcumin"), ("solubility enhancement" or "dissolution enhancement") and ("formulation" or "nanoparticles" or "solid dispersion" or "complexation" or "co-crystallization" or "eutectic solvents" or "bioconjugation" or "drug delivery systems"). The review included peer-reviewed articles published between 2015 and 2025 that focused on formulation strategies to enhance CCM's solubility and/or dissolution. Eligible studies described experimental or theoretical approaches such as particle size reduction, solid dispersion, co-crystallization, complexation, bioconjugation, eutectic solvents, and nanoparticle-based systems.

Strategies to enhance the solubility and dissolution of curcumin

Particle size reduction

Particle size reduction is among the most recognized conventional methods to modulate the physicochemical and biological properties of hydrophobic drugs.[38] Reducing particle size increases surface area of solid particles, resulting in solubility enhancement.[39] Particle size reduction can be obtained through different techniques, such as co-grinding, homogenization, spray drying, freeze drying, spray cooling, ball milling, or jet milling. [40] For instance, Al-Akayleh *et al.* sought to enhance the solubility of CCM by simply co-grinding it with the solubilizing polymer, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) at a CCM-to-Soluplus weight ratio of 2:1. The water solubility of the CCM-Soluplus co-ground mixture was found to be 2.5 times higher than that of the corresponding physical mixture.[41] Another study by He *et al.* examined the impact of particle size on CCM absorption after reducing its size to the nanoscale using the wet milling method. The results revealed that CCM crystals with small particle sizes of approximately 200 nm demonstrated a faster dissolution rate and higher plasma concentration compared to the pure drug.[42]

Recent innovations have shifted focus from conventional methods to more advanced techniques, such as the supercritical solvent approach. This novel strategy is considered promising, as it provides higher uniformity in particle size distribution compared to traditional milling methods. In this process, supercritical fluids, often carbon dioxide, are utilized as solvents due to their unique properties that lie between liquids and gases. The supercritical state is achieved when the substance is subjected to temperatures and pressures above its critical point, endowing it with enhanced diffusivity, low viscosity, and high solvating power.[43,44] The supercritical solvent approach, with its ability to fine-tune operating conditions, including temperature, pressure, and co-solvent concentration, enables the dissolution and precise control over particle size and morphology of poorly water-soluble drugs. The simple, solvent-free preparation method also makes this a potent strategy for improving the solubility and bioavailability of poorly water-soluble drugs.[45] Adapting this technique, Xue *et al.* reduced the size of CCM to approximately 300 nm in diameter using a supercritical carbon dioxide system, which is graphically illustrated in Figure 2, for enhanced solubility of CCM.[46] The resulting nanosized CCM showed a five-fold improvement in solubility in PBS buffer (pH 7.4) as compared to the free CCM. This enhancement further translated into the improved anti-bacterial activity *in vitro* and *in vivo*. Particularly, the survival rate of *P. aeruginosa*-infected mice treated with nanonized CCM was higher than that of those treated with pure CCM, 7 days compared to 4 days. To further develop the supercritical carbon dioxide system, Matos *et al.* combined a supercritical antisolvent system with a tapered fluidized bed configuration (Figure 3) to successfully coprecipitate CCM and polyvinylpyrrolidone (PVP) and coat the resulting coprecipitate onto microcrystalline cellulose (MCC) (175 µm) as host particles.[47] This approach significantly improved CCM's solubility by reducing its size and generating amorphous particles.

Electrospraying, an alternative size reduction technique, transforms viscous liquids into charged droplets, which are subsequently broken down into particles ranging from micrometers to nanometers. Operated by electrical forces, electrospraying provides the modulation over particle size distribution through various settings, including flow rate, applied voltage, and distance between the spraying nozzle and the collector plate.[48] Chhouk *et al.* utilized this method to reduce the size of CCM using ethanol as the solvent, which was followed by being encapsulated into the PVP matrix.[49]

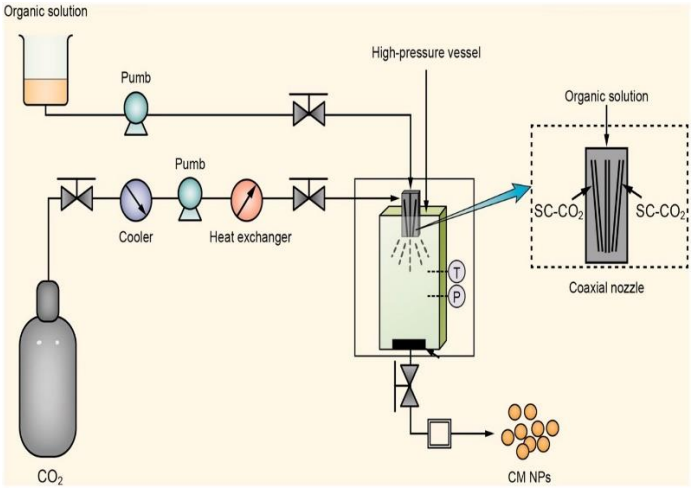


Figure 2: Illustration of the size reduction process of curcumin using supercritical carbon dioxide. Reprinted and adapted from Xue *et al*.[46] with permission

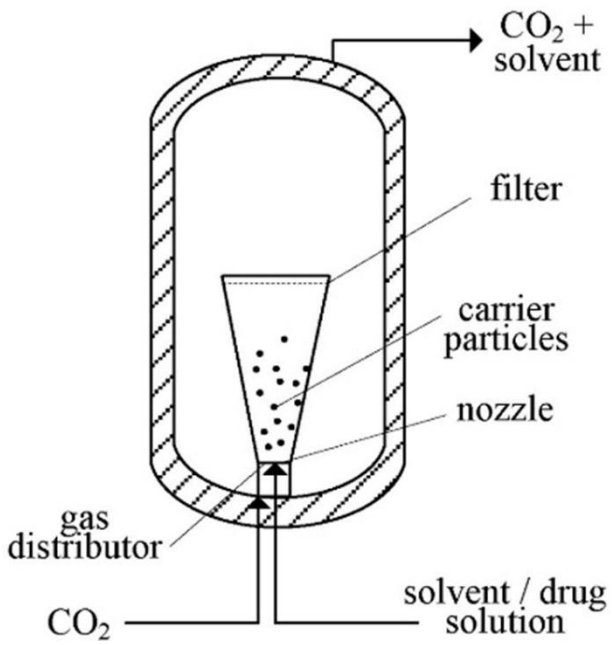


Figure 3: Illustration of supercritical carbon dioxide system with a tapered fluidized bed configuration. Reprinted and adapted from Matos *et al*.[47] with permission

A 12.5-fold increase in aqueous solubility was achieved after this size reduction process, from 0.09 to 1.13 mg/mL. Further incorporation of the micronized CCM into the PVP matrix enhanced the solubility by approximately 19 times, which could be attributed to the hydrophilicity of PVP.

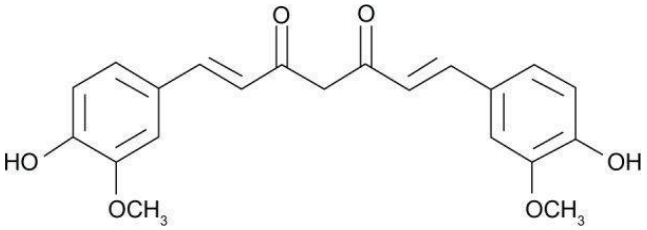
Solid dispersion

Solid dispersion is a promising strategy for enhancing the solubility and dissolution rate of poorly water-soluble compounds. By definition, solid dispersion is the dispersion of a drug in a solid inert carrier or matrix to attain modified physicochemical properties.[50] When the solid dispersion is exposed to water, the drug is released from the carrier and is subsequently dissolved in the media. The most significant benefit of the method is the transformation of CCM from the crystalline to amorphous state, resulting in enhanced solubility and dissolution. The system can be further formulated into solid dosage forms, such as tablets or capsules. However, a critical challenge lies in the propensity of drug recrystallization during storage of the amorphous CCM in the solid dispersion, necessitating stabilization**.** Some of the strategies include the incorporation of carriers that exhibit crystal growth inhibition property, modulation of the drug-to-carrier ratio, and selection of solid dispersion preparation method.[51]

A wide variety of methods have been used to prepare solid dispersions, which include solvent evaporation, hot-melt extrusion, and co-precipitation.[52-54] Wet grinding is also a method that can be used to prepare CCM solid dispersions, such as CCM-arginine,[55] or CCM-nicotinamide.[56] This method helps reduce the amount of solvent used in the process, as only the active compound is dissolved in the solvent. In contrast, the solvent evaporation method requires both the drug and the carrier to be dissolved. This makes the wet grinding method more cost-effective and environmentally friendly compared to the solvent evaporation method.[57] Recently, Patil *et al.* also used this technique to prepare CCM-lysine acetate co-amorphous solid dispersion and subsequently formulate it into tablets.[58] This system significantly increased the water solubility of CCM by approximately 476 times. The other eco-friendly methods, such as physical milling or co-grinding, have also been applied to produce solid dispersions to avoid the use of organic solvents.[59] For example, the planetary ball milling method was utilized to prepare the CCM-arabinogalactan solid dispersion system.[60] The ball miller utilised kinetic energy generated by the rotation of a cylinder filled with stainless steel around its axis to break drug crystals into smaller particles.[61] This mechanochemical treatment resulted in the solubility enhancement for the two-hour milled CCM-arabinogalactan solid dispersion by 10.6 times compared to the pure CCM and the physical mixture. *In vivo* pharmacokinetic studies in mice consistently showed the improved oral bioavailability of the prepared solid dispersion, which was demonstrated by an eight-fold increase in AUC and approximately a five-fold increase in C_{max} compared to the pure drug.[60] Different materials have been employed as carriers to prepare CCM-loaded solid dispersions, such as betaine,[62] polyethylene glycol (PEG),[63] hydroxypropyl methylcellulose (HPMC),[64] or PVP.[65] Of these carriers, HPMC is the most commonly used due to its ability to prevent recrystallization upon formation of the solid dispersion, which is attributed to the interaction between its methoxy moieties with the hydrophobic parts of drug molecules.[66] Yu *et al.* developed a CCM-HPMC solid dispersion formulation utilizing spray drying for solvent evaporation, which demonstrated a 20,000-fold increase in water solubility and improved dissolution of 50.7% CCM release after 8 hours compared to only 15.7% from pure drug.[67] Mohamed *et al.* prepared the CCM-loaded solid dispersions prepared using different carriers, including poloxamer 407, poloxamer 188, Gelucire 50/13, and mannitol. Of these systems, the Poloxamer 407-based solid dispersion was most effective in improving CCM's water solubility, which was 300-fold higher than the pure CCM. The *in vitro* cytotoxicity studies on colorectal adenocarcinoma cells showed a significantly higher level of cell death obtained when treated with the CCM-Poloxamer 407 solid dispersion compared to pure CCM. This result can be explained by the increased solubility of the CCM-loaded solid dispersion, which can facilitate effective cellular uptake and subsequently enhance anticancer activity *in vitro*.[68]

In addition to the use of a single carrier, a potential strategy for further enhancing the solubility and dissolution of solid dispersions involves combining different solid dispersion carriers. For instance, Zhang *et al.* employed the mixture of Eudragit EPO and HPMC E50 as the carriers for the amorphous solid dispersion of CCM.[64] *In vitro* studies demonstrated that the solubility and dissolution of CCM were significantly enhanced when CCM was incorporated into the Eudragit: HPMC (3:1, w/w) solid dispersion compared to that of using Eudragit or HPMC alone. The enhanced anti-inflammatory effect was exerted *in vivo* on mice, which was evidenced by a significantly higher swelling inhibition rate of 52.83% than only 12.77% of the pure CCM.

Table 1: Physicochemical properties of curcumin

Factor	Property	References
Molecular structure		3
Chemical formula	$C_{21}H_{20}O_6$	3
Molecular weight	368.38 g/mol	3
Appearance	Yellow-orange crystalline powder	3
Solubility	0.6 µg/mL in water	11
logP	3.29	12
pKa	$pKa_1 = 7.56$ $pKa_2 = 8.72$ $pKa_3 = 10.17$	10
Melting point	183 °C	2
Density	0.9348 g/cm^3	13

Alternatively, Wang *et al.* utilized a mixture of HPMC and carboxymethyl cellulose (CMC) as carriers for the solid dispersion loaded with CCM, which was shown to have a higher level of dissolution in PBS (pH 7.4) compared to CCM or the solid dispersion using HPMC only.[69] The observed synergistic effect could be due to the hydrogen bonding interactions between the hydroxyl groups of CMC and the hydroxypropyl moieties of HPMC, which strengthened the solid dispersion matrix. The addition of CMC also increased the wettability of the solid dispersion that further contributed to the enhanced drug dissolution. Another study by Xi *et al.* compared the effectiveness of HPMC and tocopheryl polyethylene glycol succinate (TPGS) as the stabilizer in preventing drug recrystallization in Kollidon CLSF-based solid dispersions of CCM.[70] While the solid dispersion with Kollidon CLSF® alone resulted in only a 2-fold increase in solubility, a 135-fold increase was achieved when combined with HPLC, and a higher 297-fold increase was observed with the addition of TPGS to Kollidon® CLSF-based solid dispersion. The TPGS-added formulation inhibited CCM recrystallization in the *in vitro* dissolution testing, which showed no significant changes in the dissolution profile after two-month storage in the ambient condition (25 °C and 60% RH). This formulation was also shown to enhance the *in vivo* bioavailability by 1.6-fold in rats. These results highlight the effectiveness of surfactants, in combination with the solid dispersion carrier, in preventing drug recrystalisation, leading to improved water solubility and oral bioavailability of poorly water-soluble CCM.

Cocrystals

Cocrystals are structurally homogeneous crystalline materials that consist of two or more solid neutral molecular reactants in stoichiometric amounts. To form a cocrystal, the API and coformers must have functional groups capable of forming either homo or hetero supermolecular synthons. This involves the formation of non-covalent bonds, mainly hydrogen bonds, between the API and coformers to generate the crystal lattice.[71] The other interactions, including Van der Waals force, halogen bonding, and π–π interaction, can also contribute to the generation of cocrystals.[72] Upon dissolving the cocrystal into gastrointestinal fluid, the cocrystal separates into its original individual components, which can be either molecular or ionic compounds.[73] Cocrystals and solid dispersions differ primarily in their structural composition. Cocrystals form a new crystal lattice via intermolecular interactions between the drug and coformer, while solid dispersions consist of the drug molecularly dispersed in the carrier matrix, often in an amorphous state.[72,73]

The formation of cocrystals can be achieved through a wide variety of processes, with some of the most common methods including solid-state grinding, solution-based crystallization, solvent evaporation, slurry conversion, and hot melt extrusion.[74-78] A wide range of coformers, such as amino acids, vitamins, and natural extracts, are available for the preparation of cocrystals.[74,79] Pantwalawalkar *et al.* used ascorbic acid as the co-former to fabricate the CCM-loaded co-crystal by solid-state grinding followed by solvent evaporation.[80] The crystalline state was confirmed by the thermal and diffractometric data, while the infrared (IR) spectra provided evidence of the formation of hydrogen bonding interactions. Compared to the pure CCM, the formed co-crystal showed an enhancement in both the solubility and dissolution of CCM. The strong intermolecular hydrogen bonds between CCM and ascorbic acid were postulated to be the main attribution to the improved solubility. The observed hydrogen bonding also contributes to the enhanced solubility of many other CCM-containing cocrystal systems. For example, Zhang *et al.* utilised 4,4'-bipyridine (BPY) as the coformer to prepare the CCM-loaded co-crystal.[81] The BPY molecule, containing two nitrogen atoms at the ends of its pyridyl rings, serves as the hydrogen bond acceptor that interacts with CCM, the hydrogen bond donor through its phenolic groups. The authors further postulated that the basic nature of BPY also augmented the solubility of CCM owing to the pH-dependent solubility characteristics of CCM, which exhibits enhanced solubility at alkaline pH. These factors collectively

contributed to a seven-fold increase in solubility compared to the pure CCM. However, reprecipitation of CCM occurred after six hours of dissolution testing, possibly due to the rapid dissolution of BPY in water, which could disrupt the cocrystal structure. Another research by Paulazzi *et al.* enhanced CCM's solubility by preparing a cocrystal with *N*-acetylcysteine using supercritical solvent technology.[82] The cocrystal exhibited significantly improved solubility, with 4.07, 2.29, and 2.59-fold increases in 40% ethanol, phosphate buffer (pH 6.8), and acidic media (0.1 M HCl), respectively, compared to pure CCM. The enhanced solubility of the cocrystal translated to improved pharmacological activity, demonstrating superior antinociceptive and anti-inflammatory effects in preclinical rat models compared to both pure CCM and the physical mixture. Cocrystals have also been prepared between CCM and another API. In addition to the enhancement in solubility, cocrystallization can also induce synergistic pharmacological effects, which may result in fewer side effects, reduced prescriptions, and improved patient adherence.[83] For instance, the preparation of CCM-resveratrol co-crystal showed the 1.5-fold solubility improvement in water, from 0.31 µg/mL of pure CCM to 0.47 µg/mL of co-crystal.[84] Moreover, this formulation, when administered orally to mice, resulted in a significant reduction in abdominal contortions in the abdominal writhing-induced model, at a concentration 100 times lower than that of pure CCM.

Complexation

Complexation is a widely studied approach for solubility enhancement, involving the formation of non-covalent interactions between the drug and carrier molecules. This method leverages carriers with hydrophilic properties and specific structural features to encapsulate hydrophobic drug molecules, thereby increasing the solubility in water.[85] Cyclodextrins (CDs), proteins, and other compounds with similar characteristics have been commonly used as carriers due to their ability to form stable inclusion complexes with hydrophobic drugs.[86-88] These complexes not only improve solubility but also enhance the drug's stability, absorption, and overall bioavailability, enabling better therapeutic outcomes.[89-92]

Complexation with β-cyclodextrin

The inclusion of CCM into cyclodextrins has been reported to improve its bioavailability,[93,94] and therefore, the research relating to this topic have been continuingly published. CDs are oligosaccharides formed by the enzymatic degradation of starch and usually present as the pristine hexameric α-, heptameric β- and octameric γ-CD forms. These cyclodextrin types differ in the number of glucose units in their ring structure, with α-CD containing 6 units, β-CD containing 7 units, and γ-CD containing 8 units.[95] The most commonly used forms are β-CD, γ-CD, and their derivatives, such as hydroxypropyl-β-CD (HP-βCD) or methyl-β-CD (M-βCD).[96-98] The solubilization mechanism, in general, is the incorporation of the hydrophobic groups of CCM into the central niche of the CD structure via either the electrostatic, Van der Waals force, hydrophobic, charge-transfer, or hydrogen bonding interactions.[99] The outer surface owing to the hydrophilic property ensures the entire structure to be readily dissolved in water, resulting in a more water-soluble complex **(**Figure 4**).**[100] An inclusion complex with β-cyclodextrin formed by simple planetary ball milling can enhance the solubility of CCM, increasing it by up to 10 times.[101] The solubility enhancement achieved through the complexation of CCM with CDs has been shown to translate into improved biological effects both *in vitro* and *in vivo***.** For instance, Zhang *et al.* developed a CCM-CD complex that effectively inhibited the proliferation and migration of HepG2 hepatoma carcinoma cells. This complex offers the combined benefits of sustained drug release for the long-term treatment of malignant tumors and minimization of unwanted side effects without compromising anticancer activity of CCM. Recently, Zeng *et al.* prepared CCM-HP-βCD complex for epilepsy treatment by the solvent evaporation method, in which the solid morphology of CCM was transformed from the crystalline to amorphous state.[102] An increase in the water solubility of CCM of approximately 64 times resulted in the enhancement in *in vivo* bioavailability, which was demonstrated by a 23-fold increase in C_{max} and tripled value in $AUC_{0\text{-}3h}$. The antiepileptic efficacy of the CCM-HP-β-CD inclusion complex was confirmed in the two pentylenetetrazol-induced seizure models using zebrafish and mice. In the zebrafish model, the complex demonstrated a stronger anti-seizure effect than free CCM at both concentrations of 5 mg/mL and 10 mg/mL. Similarly, in the mouse model, significant reductions in seizure frequency were observed at dosages of 80 mg/kg and 100 mg/kg. The stronger antiepileptic effect observed in two animal models could be explained by the increased oral bioavailability upon complexation. Another derivative of CD that has been used to improve the solubility of CCM is sulfobutyl-ether βCD (SBE-βCD). The natural four-carbon butyl chain combined with the repulsion of negative charges create a highly hydrophilic outer surface and an extended hydrophobic inner cavity for immobilizing hydrophobic therapeutic agents.[103] The complex of this type of CD and CCM was formed via the hydrogen bonding interactions and was used for the treatment of urinary tract infections.[104] This complex demonstrated improved solubility, antimicrobial activity and safety profiles *in vitro* due to its improved hydrophilicity.

Complexation with other compounds

While CDs have become the most popular complexation agents, other compounds with similar properties can also be used as carriers for delivering poorly water-soluble drugs. For instance, Lang *et al.* modified the structure of isomaltomegalosaccharides to create a novel carrier capable of solubilizing various flavonoids, including CCM, which resulted in a 15-fold increase in the water solubility of CCM.[105] Another promising material is protein fibrils, composed of β-sheet, which have gained achievements in improving the solubility of CCM. Using this complexation method, whey protein fibrils have successfully boosted the solubility of CCM by 1200-fold.[106] Another research by Jin *et al.* utilized soy protein isolate (SPI), a protein known to promote fibril formation, to develop soy protein fibrils (SPF) aimed at improving the solubility of CCM. The resulting CCM-SPF complex achieved a fourfold increase in solubility and a bioavailability ten times higher than that of pure CCM.[107] *In vitro* digestion studies showed the high retention of CCM within the complex, highlighting its potential as an effective method to enhance the absorption of hydrophobic drugs in the gastrointestinal tract. Further developing on this approach, Ji *et al.* applied ultrasonication treatment to SPF, a process that exposed additional hydrophobic and hydrogen-bonding sites, thereby strengthening the interactions between CCM and SPF.[108] As a result, the solubility of CCM in the ultrasound-treated SPF (USPF)-based complex doubled compared to the SPF-based complex. Additionally, the USPF-based complex exhibited a smaller and more uniform size distribution, which increased the surface area without altering fibril morphology.

Alternatively, cyclic β-1,2-glucans (Cys), a family of circular oligosaccharides biosynthesized by *Agrobacterium* and *Rhizobium* species, was utilized as a complexation carrier to encapsulate CCM, offering a larger inner cavity radius and superior water solubility compared to CDs.[109] This study confirmed its potential, demonstrating that the CCM-Cys complex exhibited a significantly higher level of dissolution of CCM and a greater complexation efficiency with lower binding energy compared to the CCM-CD complex. Another protein used to prepare complexation with CCM lately was protein Z (PZ).[110] As a member of the serine protease inhibitor family, PZ can potentially withstand gastrointestinal digestion, making it a promising carrier for the delivery of therapeutic agents through its hydrophobic cavity.[111] The CCM-PZ complex was formed via hydrogen bonds between specific amino acids (Pro-287, Asn-340, and Tyr-234) of PZ and the moieties of CCM. *In vitro* studies demonstrated the complex's stability during digestion, preventing CCM leakage. *In vivo* studies on mice confirmed enhanced CCM bioavailability, shown by higher plasma concentration, prolonged half-life, and lower clearance. An increase by nearly 305% in oral bioavailability was achieved for the complex compared to the CCM suspension, demonstrating the effectiveness of PZ as an effective complexation agent for the solubilization of CCM.

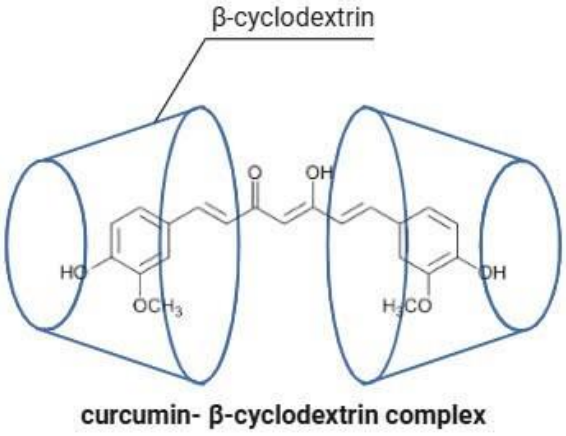


Figure 4: Graphical illustration of curcumin-β-cyclodextrin complexation

Bioconjugation

Among various strategies to improve the solubility of hydrophobic drugs, modifications to their chemical structures without compromising therapeutic effects have proved to be highly applicable.[112-115] Polymer-drug conjugates offer valuable features such as improvement in aqueous solubility, stability, therapeutic efficacy, and controlled drug release.[115] Polymers are linked to poorly water-soluble drugs by covalent bonds, which are essential for the stable formation of polymer-drug conjugates. Bioconjugation of drugs to polymers enhances their solubility and dissolution by increasing the drug's hydrophilicity and preventing aggregation. CCM has been successfully conjugated to a wide range of natural and synthetic polymers to enhance its bioavailability. For instance, Chen *et al.* conjugated CCM to hydroxyethyl starch, achieving a 3984-fold increase in water solubility compared to the free CCM, along with improved protection against UV light and heat degradation. The formulation also provided the acid-responsive manner to release drug, concluded by the cumulative release reaching more than 60% after 24 hours at pH 5.0 compared to only 25% at pH 7.4.[116] These enhancements were translated to increased antioxidant and anticancer activity of this poorly water-soluble drug *in vitro*. Similarly, Zhao *et al.* reported that CCM covalently linked to carboxylated chitosan exhibited 30 times higher solubility than pure CCM, which was associated with its effective free radical scavenging ability and photodynamic antibacterial activity (Figure 5).[117] Pan *et al.* conjugated CCM to a phenylboronic acid-containing copolymer via covalent linkages between the PBA groups of the polymer and the 1,3-diketone groups of CCM. This conjugation significantly improved CCM's water solubility, as evidenced by the formation of stable nanoparticles at pH ~ 7.4, which remained dispersed in solution, unlike free CCM, which precipitated out. The CCM-polymer conjugate demonstrated selective cytotoxicity against various cancer cell lines, including MCF-7, HepG2, and A549 cells, surpassing the efficacy of free CCM.[118] In addition to drug-polymer conjugates, drug-drug conjugates, in which two APIs are linked to each other, offer potential benefits, such as eliciting synergistic pharmacological effects, enhanced solubility, or lowered toxicity.[119] Utilising this concept, Dash *et al.* prepared the CCM-atorvastatin conjugate to achieve a synergistic anti-inflammatory effect.[119] This conjugation strategy was shown to enhance the solubility of CCM by four times, which subsequently promoted absorption in an *in vivo* mouse model.

Deep eutectic solvents

Deep eutectic solvent (DES) is the combination of two specific chemicals, either solid or liquid, in a defined molar ratio with a melting point lower than that of each original component. DES comprises hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs), which can be prepared by continuous mixing at high temperature without solvents.[120] While choline chloride has been the most popular and frequently used HBA,[121-123] a variety of compounds can be used as HBD, mostly alcohols, organic acids, and sugars.[124,125] DES not only provides good stability, low toxicity, high biodegradability, but it is also an affordable and environmentally-friendly method.[126] Therefore, DES has been used for extraction, stabilization, and solubility enhancement for hydrophobic drugs. However, its high viscosity limits the efficiency of substance extraction from plant cells, as the DES encounters difficulty permeating plant materials.[127] Positive results were obtained by Jun Cao *et al.* on improving the solubility of four phytochemicals, including CCM, baicalin, andrographolide, and oleanolic acid.[128] In specific, CCM exhibited a 4,453-fold increase in solubility using a DES system composed of choline chloride as the HBA and levulinic acid as the HBD in a 1:2 molar ratio. This enhanced solubility may be attributed to the enhanced interactions between CCM and the DES, including dipole-dipole interactions and hydrogen bonding. More recently, the preparation of CCM-loaded choline chloride (ChCl)-based DESs and the impact of the type of DESs on aqueous solubility were investigated by Yu *et al.*[129] Four HBDs were studied, i.e., 1,3-propanediol (1,3-PDO), 1,2-propanediol (1,2-PDO), ethylene glycol (EG), and glycerol (G). The solubility of CCM was significantly enhanced in these DESs, with the highest increase—a 1,700-fold improvement—observed for the ChCl/1,2-PDO system, compared to free CCM. This enhancement can be attributed to the relatively weak internal interactions among the hydroxyl groups in 1,2-PDO, which allow for stronger interactions with CCM compared to the other DESs. Conversely, DESs with a higher number of hydroxyl groups exhibit dominant internal interactions, thereby limiting the ability to interact and solubilize CCM. Hydrogen bonding and Van der Waals forces have been identified as the interactions between the DES molecules and CCM.

The solubility enhancement of CCM through DES systems can be further optimized by incorporating ultrasonication techniques. For example, Patil *et al.* utilized choline chloride as HBA and lactic acid as the HBD to form the DES capable of dissolving CCM with an extraction efficiency of 66.12 mg/g curcuminoids from turmeric in 75 minutes **(**Figure 6).[130] Following the application of ultrasound, the curcuminoid yield increased significantly to 77.13 mg/g within a notably shorter duration of 20 minutes, while also reducing the required solvent volume. Compared to ethanol, DESs exhibited higher efficiency in dissolving curcuminoids, attributed to the acidic component (HBD), which degrades the cellulosic structure of cell walls, enhancing the solvent's penetration into the cellular interior. Consequently, higher curcuminoid yields are obtained in less time. The authors also compared this new technology to conventional Soxhlet extraction, which demonstrated that DES offered a superior efficiency in CCM extraction by reducing processing time and production costs while maintaining comparable energy input and product yield.

Furthermore, DES has been combined with other techniques for an effective solubilisation of CCM. For instance, Dhingra *et al.* fabricated a water-in-oil emulsion system comprising the hydrophobic DES oil phase constituted of tetra-n-butylammonium chloride and n-decanoic acid in a molar ratio of 1:2, aiming to improve the solubility and stability of CCM. The solubility of CCM in the prepared emulsion was approximately 51 mg/mL, which was 6-fold higher than using DES only, without compromising its structural integrity.[131] Bashkeran *et al.* reported that using the natural DES containing betaine and glucose can enhance the solubility of CCM in water by more than 10,000 times. The authors later incorporated this DES into CCM-loaded niosomes, which showed improved encapsulation efficiency and stability compared to CCM-loaded niosomes formulated without DES.[132] Hirpara *et al.* prepared the ChCl-water DES system with the existence of salt and the cationic surfactant, dodecyl trimethyl ammonium bromide (DTAB) for solubilisation of CCM.[133] The formation of micelles with counter-ion binding significantly enhanced the solubility of CCM, resulting in a 200-fold increase compared to its intrinsic solubility.

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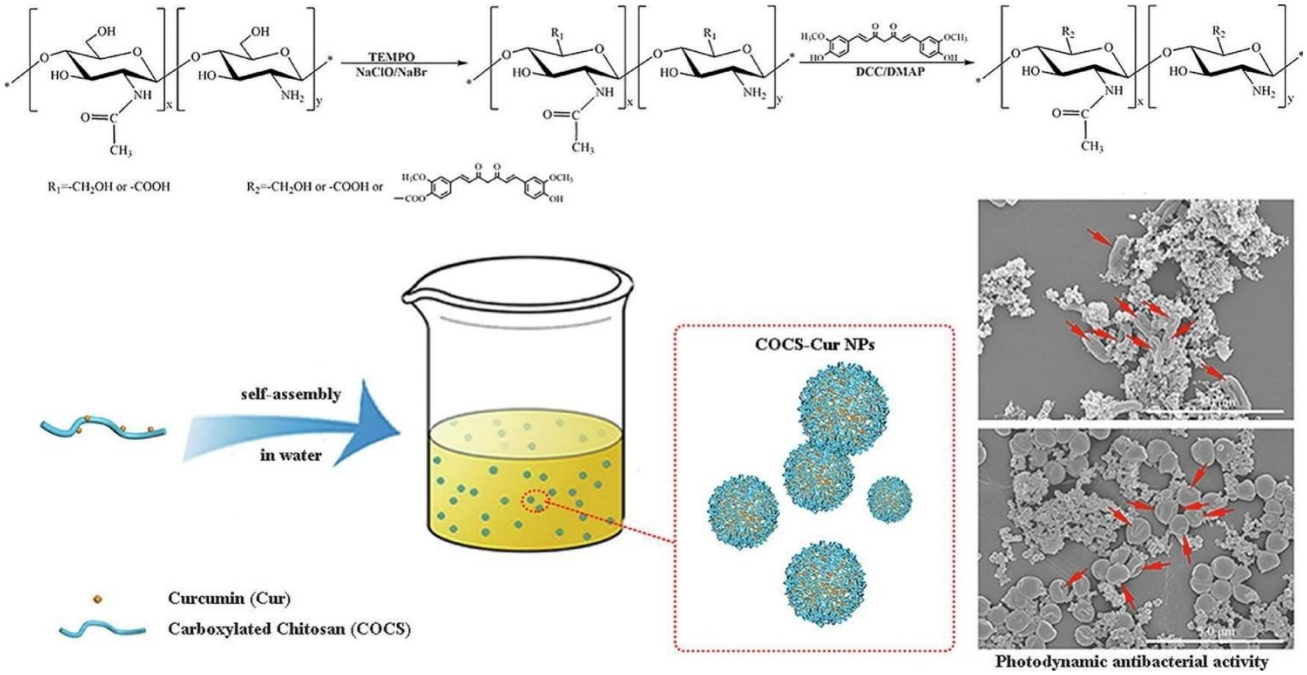

Figure 5: Fabrication of self-assembled curcumin-carboxylated chitosan micelles for enhanced free radical scavenging and photodynamic antibacterial activity. Reprinted and adapted from Zhao *et al.*[117] with permission

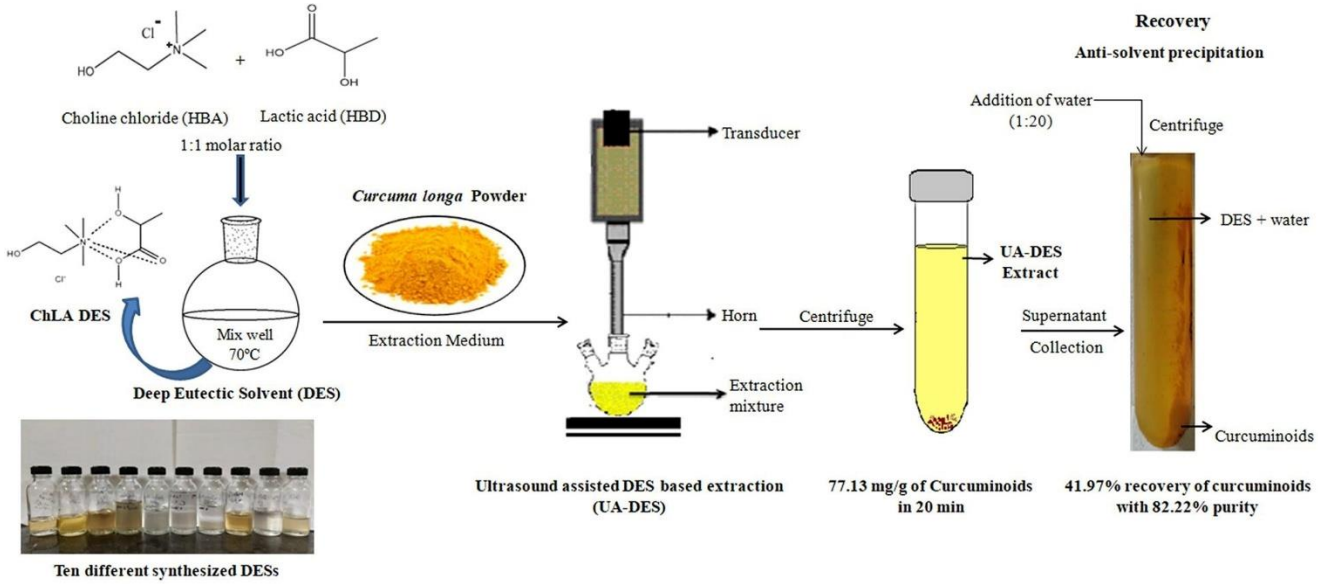

Figure 6: Utilisation of the lactic acid/choline chloride DES for extraction of curcumin from the tumeric powder. Reprinted and adapted from Patil *et al.*[130] with permission

Nanoparticles

Nanoparticles are defined as systems or structures with particle sizes smaller than 1000 nm.[134] This technology represents a significant advancement in enhancing the physicochemical properties of drugs and facilitating their delivery into the human body for therapeutic applications. The nano size provides an increased surface area-to-volume ratio, enabling molecular interactions that yield desirable properties such as improved solubility or reduced stability, which results in enhanced bioavailability. Additionally, nanosizing enhances drug bioavailability by modulating drug distribution and evading macrophage-mediated clearance.[135] A diverse range of CCM-loaded nanoparticles has been developed using polymers, lipids, and inorganic materials.[136-139] CCM-loaded nanoparticulate delivery systems not only promote solubility and protect CCM from degradation but also enhance its bioavailability,[140] the antioxidant,[141-144] and anti-inflammatory activities.[145-147] Furthermore, numerous studies have highlighted the potent antitumor effects of CCM-loaded nanoparticles, which can target the tumor sites and respond to pH changes at the tumor microenvironment for triggered release of CCM.[148-156]

The significant research interest in polymeric nanoparticles stems from their tunable physico-chemical properties. This flexibility allows for the development of nanoparticles with high biocompatibility, biodegradability, and the potential for diverse surface modifications.[137,157] A wide range of polymers, including poly(vinyl

alcohol) (PVA), poly(lactic-co-glycolic acid) (PLGA), silk fibroin, chitosan, and N-isopropylacrylamide (NIPAAM), have been employed to fabricate polymeric nanoparticles aimed at improving the dissolution rate and bioavailability of CCM. [136,158-161] For instance, a recent study incorporating CCM into chitosan-sodium tripolyphosphate nanoparticles achieved a 2100-fold increase in CCM solubility, from 0.017 to 35.92 µg/mL at 25 °C, with an encapsulation efficiency of 93.79%.[162] Another research by Ren *et al.* demonstrated that encapsulating CCM into the pea protein-based nanoparticles improved both its solubility and antitumor activity *in vitro*.[163] Eskandari *et al.* combined PLGA with levan, a natural fructose homopolymer, to form the micelle structure for CCM delivery to overcome chemoresistance of gemcitabine (GMC) in breast cancer therapy (Figure 7).

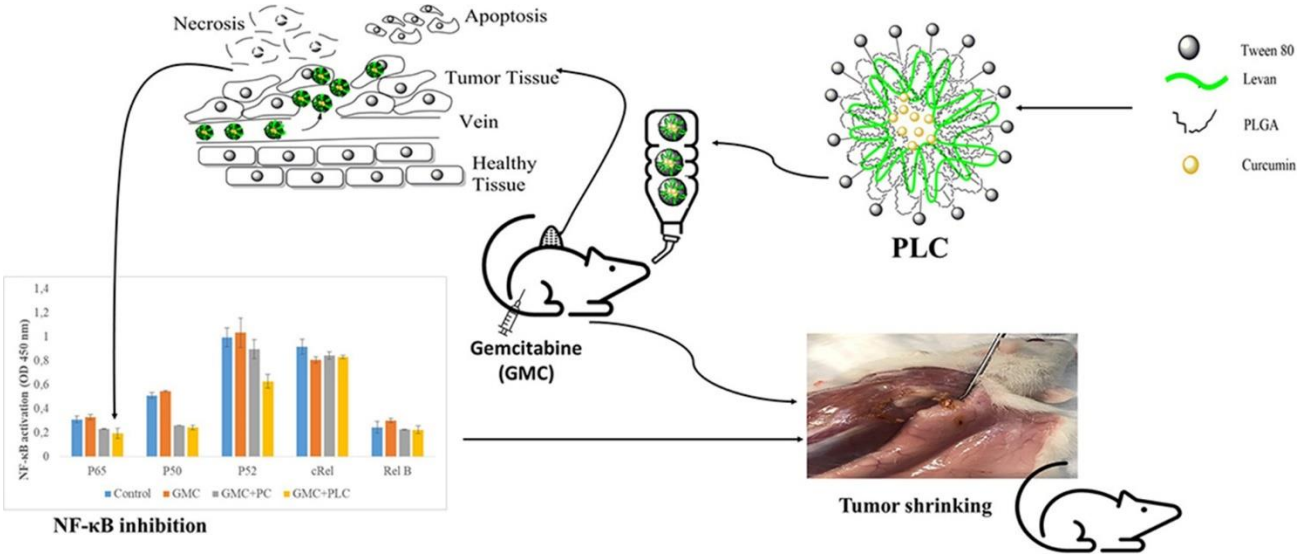

Figure 7: Curcumin-loaded PLGA-levan micelles for breast cancer treatment. Reprinted and adapted from Eskandari *et al.*[164] with permission

This approach not only enhanced the stability of micelles for three months at room temperature but also significantly increased CCM's solubility by 10,000 times, while reducing the production of NF-κB in both *in vitro* and *in vivo* models.[164] This system showed improved efficacy, evidenced by tumor size shrinking capability, compared to the group that received CCM and GMC alone. Lipid nanoparticles have emerged as a highly promising class of drug delivery systems due to their inherent biocompatibility and biodegradability, as lipids are naturally occurring components of biological membranes. These nanoparticles combine the advantages of stability with the ability to encapsulate a wide range of therapeutic agents, including both hydrophilic and lipophilic drugs.[165,166] Liposomes, a phospholipid bilayer structure encapsulating drugs in the core, is the first generation of lipid-based nanoparticles.[167] Tai *et al.* prepared the CCM-encapsulated liposome system that enhanced the bioavailability of CCM while reducing phospholipid oxidation, addressing key challenges in liposomal delivery.[168] The development of solid lipid nanoparticles (SLNs) formulated by biocompatible solid lipids stabilized with surfactants, demonstrating the potential of lipid-based drug delivery systems.[169] Gupta *et al.* successfully incorporated CCM into glyceryl monostearate-compritol 888®ATO SLNs stabilized with PEG 600, Tween 80, and Phospholipon 90G. This formulation strategy showed a remarkable increase in CCM solubility of about 1.4×10^6 times while maintaining a high drug loading capacity and enhanced stability. *In vivo* pharmacokinetic studies conducted on rats demonstrated a 70-fold enhancement in CCM's bioavailability.[170] Supporting the potential of SLNs for targeted therapy, Rahman *et al.* showed that CCM-loaded glyceryl monostearate-based SLNs hold promise as a lung cancer therapy while enhancing the *in vitro* solubility and dissolution of CCM compared to the pure drug.[171] SLNs offer several advantages, but limitations such as low drug loading, drug leakage during storage, morphology transition, and high water residues can hinder their effectiveness. To address these drawbacks, nanostructured lipid carriers (NLC) were introduced, incorporating liquid lipids within the internal core to form structural anomalies, thereby disrupting the highly-ordered crystalline arrangement to mitigate drug leakage and enable a higher drug loading.[172] In addition to the solubility improvement obtained by encapsulating CCM into NLCs, numerous studies have focused on improving the intestinal stability and absorption of this formulation. Won *et al.* combined an enteric coating strategy to NLC to protect CCM from the harsh acidic environment of the stomach and to promote the drug release in the intestine.[173] This pH-responsive nanosystem exhibited a 2.5-fold increase in drug dissolution from less than 10% to about 28% after 24 hours in simulated intestinal fluid (pH 6.8) and deionized water compared to the corresponding CCM-loaded NLCs.

Inorganic nanoparticles also present a compelling nanocarrier for the delivery of CCM. They possess several advantages, including the potential to enhance drug loading capacity, improve bioavailability, and enable controlled release. Additionally, inorganic nanoparticles exhibit superior stability, and low toxicity, albeit being non-biodegradable.[139,174] Both metals and metal oxides have been used to prepare inorganic nanoparticles. While zinc oxide, titanium oxide, iron oxide, and silicon dioxide are preferred metal oxides; silver, gold, and copper have been employed as metallic materials for the fabrication of inorganic nanoparticles.[175-181] A diverse range of inorganic nanoparticles have been explored as carriers for the delivery of CCM. One of which was to form nanocomposite with silver ions by ultrasonic synthetic method.[182] The enhanced hydrophilicity of CCM-Ag, demonstrated by its strong binding interaction with bovine serum albumin (BSA), resulted in higher CCM solubility compared to the pure drug in various media, including 0.1 N HCl (pH 1.2), sodium acetate buffer (pH 4.5), potassium phosphate buffer (pH 6.8), and water. Utilizing a similar concept, Gao *et al.* developed a CCM-Cu material and subsequently complexed it with hyaluronic acid to enhance CCM's water solubility and bioavailability.[183] The product successfully increased the solubility of CCM by 35 folds while promoting the anti-prostatitis effects *in vivo* in rats. CCM was also combined with ferric ions to form Fe-CCM complex nanoparticles for enhanced solubility and antibacterial efficacy against food-borne pathogens.[184] In addition to conventional inorganic materials, mesoporous silica nanoparticles

(MSN) have emerged as an effective delivery system due to tunable pore structure, good biocompatibility, chemical structural stability, convenient surface modification, and stimulus-response.[185-187] Jiao *et al.* loaded CCM into the nanopores of nano-silica by the solvent evaporation method, which exhibited significantly higher solubility of 1510 ± 50.33 µg/mL compared to 80.00 ± 34.64 µg/mL of the pure CCM.[188] Recent studies on the utilization of CCM-loaded nanoparticles for solubility enhancement are summarized in Table 2.

Table 2: Summary of recent studies on the use of nanoparticles for the delivery of curcumin

Type of nanoparticles	Components	Encapsulation Efficiency (%)	Size (nm)	Outcomes	References
Polymeric nanoparticles	Sunflower seed protein isolate (SFPI)	83	194	Enhanced curcumin solubility (8.1 µg/mL compared to ~11 ng/mL of the pure CCM)	[189]
Polymeric nanoparticles	Human serum albumin (HSA)	7	220	- Enhanced curcumin solubility (68.29 µg/mL compared to 4.03 µg/mL of the pure CCM) - Promoted apoptosis of cancer cells while maintaining the viability of normal cells	[190]
Polymeric nanoparticles	- Foxtail millet prolamin - Sodium caseinate	71.3	235	- Solubility in water: 12400-fold higher than CCM -Anticancer property: enhanced free radical scavenging activity and superior tumor suppression.	[191]
Polymeric nanoparticles	- Bovine serum albumin (BSA) - Dextran	73.5	50–80	- Solubility in water: 25,454-fold enhancement compared to the pure curcumin - Improved stability at both low and high temperatures. - Improved antioxidant activity	[192]
Polymeric nanoparticles	- Modified starch - Cinnamic acid	26.73	271.30	- Solubility: 18-fold improvement - Stability: enhanced thermal and photostability	[193]
Lipid nanoparticles	- PLGA, - PEG 6000 - PVA - 1,2-distearoyl-sn-glycero-3-phosphatidylcholine (DSPC) - 1,2-distearoyl-sn-glycero-3-phosphoethanola-mine-N-[methoxy (polyethylene glycol)-	88.23	436	- Solubility: 2620-fold improvement than pure CCM -Targeted delivery to the brain including deep-seated brain regions .	[194]

	2000] (DSPE-PEG2000)				
Lipid nanoparticles	- Zein - Sophorolipid (Spl)	94.08	124.7	- Solubility: 246-fold increase - Enhanced antioxidant activity	[195]
Lipid nanoparticles	- PEG 400 - PVA	_	284-295	-Solubility: increased the water solubility by 60 folds - Enhanced membrane permeation	[196]
Lipid nanoparticles	- 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC) - Tween 80	87.7	116.4	- Enhanced solubility by 700 folds - *In vivo* bioavailability: 10-fold higher C_{max} and 7.8-fold higher in AUC compared to the curcumin suspension.	[197]
Lipid nanoparticles	- Shea butter - Capmul MCM - Cellulose	_	~500	- Enhanced solubility by 4 times	[198]
Lipid nanoparticles	Phosphotidylcho-line - Cholesterol - Olive oil - PEG 2000 - Tween 80	76.3	~52	- Enhanced solubility by 1000 folds - Enhanced antibacterial activity	[199]
Lipid nanoparticles	- Modified maize starch - Sunflower oil	_	81.23	- Enhanced CCM solubility in water by ~22.5 folds - Enhanced physical and chemical stability	[200]
Inorganic nanoparticles	Mesoporous calcium silicate	Drug loading: 9.09%	463.80	- Enhanced solubility by 3410 times	[201]
Inorganic nanoparticles	Mesoporous silica SBA-15	_	Pore diameter: 6.040 nm	- Enhanced solubility by 2201 times	[202]

Challenges and future perspectives

Over the years, numerous commercial CCM products have entered the market, leveraging innovative strategies to enhance its poor aqueous solubility and low bioavailability. These commercial CCM products, summarized in Table 3, have employed various solubility-enhancing approaches such as phytosomes, complexation with CDs, nanoemulsions, and solid lipid nanoparticles. Despite these advancements in enhancing CCM solubility and its therapeutic potential, several significant challenges remain in the large-scale commercialization of CCM-based products. A major obstacle is the difficulty in scaling up production due to the complex processes involved in the formulation preparation.[203] Transitioning CCM-loaded delivery systems from the laboratory scale to successful industrial-scale production requires meticulous optimization of formulations and processing parameters to maintain consistent product standards.[204] Additionally, CCM's inherent sensitivity to pH, temperature, and light complicates large-scale production, often compromising formulation stability compared to controlled laboratory conditions. The reliance on specialized equipment, such as microfluidic devices commonly used for preparing nanoscale drug delivery systems, presents further barriers as these devices are costly and may not be readily accessible to many businesses.[205] Furthermore, the commercialization process of transforming delivery systems into dosage forms like tablets or capsules can lead to unforeseen component interactions, potentially reducing the efficacy of the final product. Challenges related to packaging, storage, and transportation of CCM products also threaten product integrity.[206] Addressing these challenges requires innovative approaches that integrate advancements in materials science and scalable manufacturing technologies to ensure product efficacy. Another critical concern is the toxicity associated with current formulations. Many production methods rely on hazardous chemicals to dissolve CCM, posing health risks and complicating the verification of product biosafety.[216,217] Additionally, the evaporation of these toxic chemicals harms the environment, contributing to climate change, ozone depletion, and pollution of soil, air, and water.[218]

Table 3: Commercial products of curcumin and their solubility enhancement strategies

Commercial product	Solubility enhancement strategy	References
Meriva®	Phytosomes (soy lecithin)	207
BCM95® CG	Synergistic effect of sesquiterpenoids in turmeric essential oil and curcuminoids.	208
Carvacumin®	Complexation with γ-cyclodextrin	209
Theracumin®	Curcumin dispersed with colloidal submicron-particles (dextrin, maltose, cornstarch, silicon dioxide, calcium stearate)	210
Novasol®	Liquid micelle (Tween 80)	211
BioCurc®	Liquid droplet nano-micelles (Gelucire® and polysorbate 20)	212
LongVida®	Solid lipid nanoparticles (stearic acid and soy lecithin)	213
curcuRouge™	Solid dispersion (Modified starch, Cornstarch)	210
CurQfen	Complexation with galactomannoside	214
CuroWhite™	Complexation with β-cyclodextrin	215

To address these issues, green manufacturing strategies are essential for producing eco-friendly pharmaceutical products. Recent advances in green production methods, which integrate green chemistry and engineering principles, have focused on minimizing environmental impact.[219,220] For instance, innovative technologies, such as hot-melt extrusion, offer solvent-free manufacturing processes that address the excessive use of organic solvents. [221] Notably, several approved pharmaceutical products have been commercialized in the market using this method for large-scale production, such as Eucreas™ (Metformin HCl) and Covera-HS® (Verapamil HCl).[222,223] However, this approach faces challenges such as potential drug degradation and recrystallization of amorphous drugs due to the high temperatures employed and the absence of solvents in the process. Overcoming these obstacles will be crucial for the widespread adoption of CCM-based therapeutics and their successful translation into commercial products. Addressing the challenges in scaling up production, maintaining formulation stability, and developing eco-friendly manufacturing processes will be key to realizing the full potential of CCM-based therapies and enabling their successful commercialization.

Conclusion

CCM has demonstrated significant therapeutic potential and biosafety in the prevention and treatment of various diseases. However, its poor aqueous solubility and low bioavailability continue to impede its clinical approval as a therapeutic agent. Recent advancements in solubility and dissolution enhancement have introduced innovative strategies, including solid dispersions, co-crystals, bioconjugation, deep eutectic solvents, and nanoparticle-based systems, in addition to traditional methods like micronization. Each approach offers distinct advantages and limitations, emphasizing the need for careful evaluation of their feasibility and practical application. Despite substantial progress, further research is crucial to develop formulations that are not only efficient and biocompatible but also cost-effective, scalable, and environmentally sustainable. Continued innovation in this field holds the promise of transforming CCM-based therapeutics, paving the way for broader clinical applications, and providing a framework for addressing challenges associated with poorly water-soluble drugs.

Conflict of interest

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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