

Research Progress on Solubilization Techniques of Crocetin

Guigui Luo^{1*}

¹ School of Pharmacy, Fuzhou Medical College of Nanchang University, Fuzhou, China

*Correspondence: Guigui Luo

Received: 30 March 2026; Accepted: 24 April 2026; Published: 9 May 2026

Abstract:

Saffron (*Crocus sativus* Linnaeus) possesses both medicinal and spice value and is highly regarded in traditional medicine and modern health care. The core active ingredient of saffron is crocetin, a carotenoid derivative with various pharmacological effects, including protective effects on the heart, liver, and nervous system, as well as anti-tumor, antidepressant, anti-diabetic, and anti-atherosclerotic activities. However, crocetin suffers from poor water solubility and low bioavailability in vivo, which severely limits its clinical application. Therefore, research on solubilization techniques for crocetin is of great importance. Currently, technologies such as structural modification, microencapsulation, nanoparticles, liposomes, emulsions, and solid dispersions have been employed to improve the water solubility of crocetin, achieving remarkable results. This paper reviews the recent research progress on solubilization techniques for crocetin and proposes future development directions in this field, providing references for subsequent research and the development of crocetin formulations.

Keywords:

Crocetin, Water Solubility, Absorption, Nanoparticles, Emulsion

1. Introduction

Saffron is a perennial herbaceous plant belonging to the genus *Crocus* in the Iridaceae family. Its dried red stigmas have practical value, serving as both a natural pigment and a medicinal material. One of its main active components, crocetin (CRT), also known as crocetin acid or saffron acid, is also a primary active substance in the dried mature fruits of *Gardenia jasminoides* Ellis. In terms of chemical structure, CRT exists in both cis and trans isomers, with the trans isomer responsible for most of its pharmacological effects [1]. It features a 20-carbon chain containing seven carbon-carbon double bonds and two carboxyl groups [2] (as shown in Figure 1). Its octanol-water partition coefficient (logP) is 4.50, with a molecular weight of 328.40 g/mol. Crocetin belongs to the large family of carotenoids. These unique chemical structural characteristics render CRT a hydrophobic compound that is insoluble in water and most organic solvents [3].

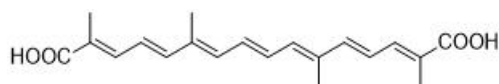


Figure 1. Chemical structure of Crocetin.

As shown in Figure 2, CRT has the ability to directly penetrate the intestinal wall. After entering the body, it can be widely distributed in various organ tissues such as the brain, heart, liver, kidneys, and lungs. According to the literature, CRT exhibits pharmacological activities including antidepressant [4,5], anti-tumor [6], anti-atherosclerotic [7,8], neuroprotective [9], anti-fatigue, and anti-altitude sickness effects [2]. Although CRT demonstrates multiple pharmacological effects, its poor water solubility (only 0.72 µg/mL [10]) and suboptimal stability result in extremely low bioavailability in vivo. Studies have shown that the bioavailability of CRT at a dose of 100 mg/kg in rat plasma is only 5.63% [11]. The drug cannot be effectively absorbed and utilized, which greatly limits the clinical application and therapeutic efficacy of CRT.

To address this issue, researchers have attempted to increase its water solubility and stability through structural modification and dosage form optimization. Structural modification of CRT primarily involves altering the -COOH groups on both ends of the molecule, thereby changing its physicochemical properties and biological activity. For example, structural modifications have produced sodium crocetin, crocetin glucuronide (CM), and a series of CRT derivatives, which improve the water solubility and biological activity of CRT. In terms of dosage forms, different formulations differ in drug-loading patterns, drug release pathways, and release rates. Consequently, the bioavailability and pharmacological effects of the drug often vary when administered in different dosage forms. Some scholars have prepared CRT into cyclodextrin inclusion complexes, nanoliposomes, or nanoparticles to enhance its pharmacological activity and water solubility. This paper systematically reviews and summarizes the recent research progress on solubilization techniques for CRT, providing a reference for further clinical research and formulation development.

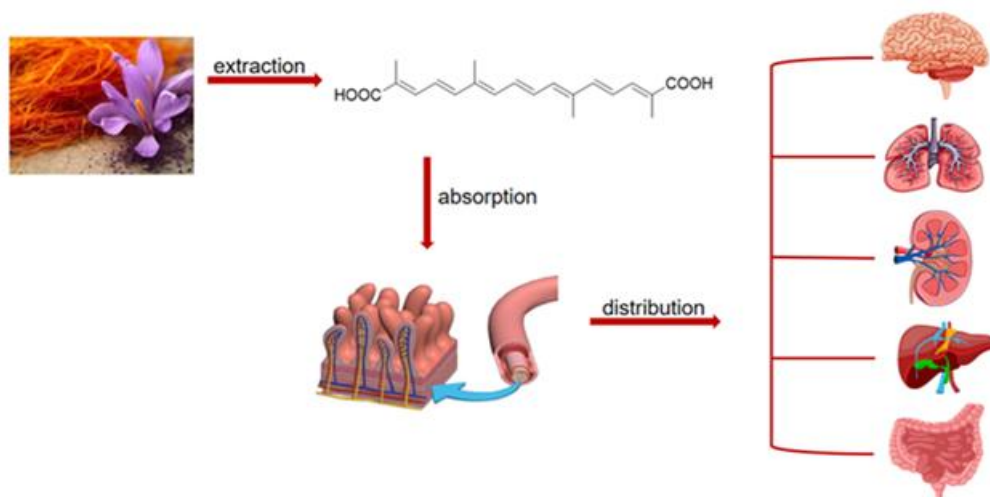


Figure 2. Schematic diagram of the *in vivo* metabolic pathway of Crocetin.

2. Solubilization Techniques for Crocetin

2.1. Structural Modification

Structural modification refers to the purposeful alteration of the local structure of a drug molecule through chemical methods to improve its physicochemical properties, pharmacodynamic characteristics, pharmacokinetic behavior, or to reduce toxic side effects, thereby enhancing the overall value of the drug. Structural modification can overcome the poor water solubility of crocetin (CRT), thereby unlocking its

substantial medicinal potential. Current structural modifications of CRT mainly involve the synthesis of organic ammonium salts, inorganic salts, and their derivatives.

Zhang Wei et al. [11] reacted CRT with sodium hydroxide to form sodium crocetin, increasing its solubility from the original 10 µg/mL to 10 mg/mL — a 1000-fold improvement. Further validation through rat bioavailability experiments showed that the oral bioavailability of sodium crocetin at doses of 25 mg/kg and 100 mg/kg reached 54.56% and 43.77%, respectively, which was significantly higher than that of CRT (11.25% and 5.63%). After intragastric administration of 25 mg/kg CRT, the plasma concentration peaked at 3.56 mg/mL after 1.7 hours, whereas sodium crocetin reached a peak concentration of 33.70 mg/mL after only 1.4 hours.

Zhu Anyun et al. [12] converted CRT into crocetin monoglucuronide (CM). Pharmacokinetic data showed that the in vivo concentration of CM was significantly higher than that of the prototype crocin-1, with a half-life ($t_{1/2}$) of 11.26 h for CM compared to 0.34 h for crocin-1, indicating a longer retention time for CM and suggesting improved bioavailability. However, CM exhibits poor stability under light and heat conditions and is prone to decomposition.

Yang Yong'an et al. [13] reacted CRT with diethylamine, n-propylamine, tert-butylamine, 2-aminopropylmorpholine, and benzylamine to generate corresponding organic ammonium salt derivatives, which improved water solubility and therapeutic efficacy and were suitable for industrial production. Wang et al. [14] modified CRT by coupling it with ethylamine and 4-fluorobenzylamine. Compared with CRT, the derivatives exhibited higher solubility. In this study, the water solubility of CRT was measured as 1.238 µg/mL, while the synthesized derivatives showed at least 10 times higher solubility in water. Moreover, the derivatives enhanced anti-tumor and anti-inflammatory effects without obvious cytotoxicity to normal cells.

Chu et al. [15] modified CRT by coupling it with piperoyl, diethylamine, and benzylamine to obtain CRT derivatives. The presence of nitrogen atoms in these derivatives enabled the formation of more stable hydrogen bonds, thereby improving the water solubility of CRT. The results showed that the water solubility of the derivatives was significantly higher than that of CRT, with the highest increase reaching 57.95 times.

2.2. Microencapsulation

Microcapsules are miniature containers formed by physically or chemically encapsulating active substances within small carriers, typically with diameters ranging from 2 to 250 µm [16]. They can improve the stability and solubility of active substances. Microcapsules generally consist of a polymeric wall material and a core material (the active substance to be protected). Depending on the properties of the wall material, the physical or chemical properties of the active substance are correspondingly altered.

2.2.1. Cyclodextrin Inclusion Complexes

Cyclodextrins (CDs) are a series of cyclic oligosaccharides and semi-synthetic derivatives produced from starch by cyclodextrin glucosyltransferase from *Bacillus* species; they are essentially starch derivatives [17,18]. As shown in Figure 3, CDs possess a unique cavity structure that can form inclusion complexes with specific molecules — a special supramolecular structure in which one molecule is embedded within the cavity of the CD [19]. Commonly used CDs include α -cyclodextrin (α -CD),

β -cyclodextrin (β -CD), γ -cyclodextrin (γ -CD), and their derivatives. Among them, β -CD is widely applied due to its high encapsulation efficiency, suitable cavity size, and low cost [19]. β -CD is a cone-shaped polysaccharide composed of seven α -D-glucopyranose units linked by β -glycosidic bonds, forming an appropriate cavity size capable of forming stable inclusion complexes with various organic molecules through hydrogen bonding and other interactions [20]. It features a hydrophobic internal cavity and a hydrophilic exterior due to the presence of hydroxyl groups. CDs play important roles in the pharmaceutical and food industries. In particular, in drug formulation, CDs are often used as drug carriers to enhance drug solubility and stability, and to provide functions such as taste masking, sustained release, and targeted delivery [21], making them an ideal choice for drug development and application.

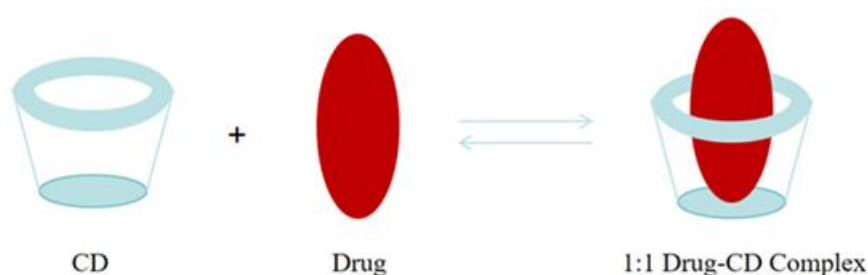


Figure 3. Host-guest inclusion interaction between cyclodextrin and drug.

Liu Xuecheng et al. [10] compared the solubilization effects of α -CD, β -CD, γ -CD, methyl- β -cyclodextrin (M- β -CD), and hydroxypropyl- β -cyclodextrin (HP- β -CD) on CRT. They found that M- β -CD exhibited the most significant solubilization effect, increasing the water solubility of CRT by 17 times. The inclusion process parameters were optimized using single-factor experiments and the Box-Behnken response surface method. The optimal parameters were determined as a material-to-liquid ratio of 33%, stirring temperature of 60°C, and stirring time of 120 min. The inclusion complex also demonstrated good release performance in a medium containing 0.1% polysorbate 80 at pH 6.8, conforming to the first-order release model and exhibiting a sustained-release effect.

Liu et al. [21] compared inclusion complexes formed with α -CD, HP- β -CD, and γ -CD, finding that their bioavailability was increased by 3.68-, 3.94-, and 3.77-fold, respectively, compared with free CRT. All inclusion complexes showed approximately 90% drug encapsulation efficiency. NMR analysis, phase solubility studies, and solubility tests indicated that HP- β -CD had the highest inclusion efficiency, with a stability constant of 7912 M⁻¹ (2 times and 20 times higher than those of α -CD and γ -CD, respectively). Its solubility (12429.04 $\pm$ 20.33 mg/L) and relative bioavailability were also superior to the other two complexes.

Wong et al. [22] developed a water-soluble, injectable CRT formulation using γ -CD to maximize the therapeutic effect of CRT against Alzheimer's disease (AD). The encapsulation efficiency of the inclusion complex exceeded 95%. After intravenous injection of the CRT- γ -CD complex, the concentration of CRT in the brain increased significantly, reaching the highest concentration (5 mg/kg) 30 minutes after administration. This study provided new insights for CRT treatment of AD and improved its solubility, bioavailability, and applicability.

Liu Dongchun et al. [23] prepared CRT-CD inclusion complexes using various CDs, including HP- β -CD, sulfobutylether- β -cyclodextrin (SBE- β -CD), β -CD, γ -CD, and α -

CD. Infrared spectroscopy and in vitro dissolution experiments demonstrated that the inclusion complexes significantly improved the water solubility and dissolution rate of CRT. In a pH 6.8 medium, the cumulative dissolution of CRT reached 98.57% within 5 minutes, which was markedly higher than that of the raw drug.

2.2.2. Others

Microencapsulation can enhance both the stability and water solubility of CRT. Zhou et al. [24] used spray drying with β -CD, gum arabic, and maltodextrin as wall materials to encapsulate CRT, achieving encapsulation efficiencies of 77.91%–85.03% at 210°C. When gum arabic was used as the wall material, the oxygen pressure was lowest (0.03 ± 0.01 atm), resulting in the highest stability of CRT. Kyriakoudi et al. [25] employed maltodextrin for inclusion, obtaining encapsulation efficiencies of approximately 54%–81% and improving bioavailability to 72%.

2.3. Nanoparticles

Nanoparticles (NPs) are ultra-fine solid colloidal drug-carrying particles with sizes ranging from 1 to 100 nm, using natural or synthetic polymeric materials as carriers [26]. NPs include nanospheres and nanocapsules. Nanocapsules are mainly used to encapsulate lipophilic drugs, while nanospheres adsorb drugs on their surface or encapsulate/dissolve them internally. Due to their small particle size, NPs facilitate retention at mucosal and corneal sites, thereby enhancing drug absorption and bioavailability [27]. Preparing CRT into NPs can improve its pharmacokinetic profile and poor solubility, thereby increasing delivery efficiency.

2.3.1. Poly (lactic-co-glycolic acid) (PLGA)

PLGA is commonly used in the development of various nanoparticle-based drug delivery systems and has been approved by the U.S. Food and Drug Administration (FDA) [28]. PLGA-NPs offer improved stability and make a significant contribution to drug solubility. PLGA is a highly biocompatible polymer with biodegradable properties, ultimately degrading in vivo into water and carbon dioxide [29]. The degradation time of PLGA can be precisely controlled by adjusting the ratio of glycolic acid to lactic acid monomers, enabling controlled release from polymeric microspheres [30]. Studies have shown that polymeric NPs can also enhance drug targeting efficiency and bioavailability [31].

Yang et al. [32] prepared CRT-loaded PLGA nanoparticles (CRT-PLGA-NPs) using a double emulsion evaporation technique and evaluated multiple parameters. The prepared CRT-PLGA-NPs exhibited a drug loading of $6.51 \pm 0.14\%$ and an encapsulation efficiency of $75.39 \pm 1.62\%$, with an average particle size of 218 nm and a polydispersity index (PDI) of 0.25, indicating monodispersity. In vitro release experiments showed an initial burst release in the first 4 hours, followed by a sustained release pattern, with approximately 75% of the drug released within 48 hours. In vivo experiments demonstrated that CRT-PLGA-NPs significantly reduced blood glucose levels in diabetic rats and decreased the expression of renal inflammation and fibrosis markers.

Hafezi Ghahestani et al. [33] encapsulated CRT using a single emulsion/solvent evaporation method to address its poor water solubility. By optimizing preparation conditions, the best results were achieved with 5% polyvinyl alcohol as stabilizer, dichloromethane as organic solvent, and a CRT-to-polymer ratio of 1:20. The

resulting NPs had a particle size of approximately 288 nm and an encapsulation efficiency as high as 97.20%. In vitro release showed approximately 44.49% release within 24 hours, reaching maximum release within 4 days. MTT assays revealed that the encapsulated CRT significantly reduced the IC_{50} value against MCF-7 breast cancer cells to $84.73 \pm 12.14 \mu\text{M}$, far lower than that of free CRT ($589.65 \pm 5.72 \mu\text{M}$), indicating a markedly enhanced anti-proliferative effect.

Neyshaburinezhad et al. [34] encapsulated CRT into PLGA-NPs using an improved single emulsion-solvent evaporation method, yielding particles with a size of approximately 239.8 ± 9.0 nm, an encapsulation efficiency of $79 \pm 3.0\%$, and a drug loading of $4.9 \pm 0.2\%$. Langroodi et al. [35] prepared PLGA nanoparticles containing both CRT and doxorubicin using a W/O/W double emulsion/solvent evaporation method, resulting in particle sizes of 100–300 nm. After optimization (5% polyvinyl alcohol, dichloromethane:acetone = 4:1 as organic solvent, and drug-to-polymer ratio of 1:20 with overnight stirring to remove solvent), the NPs had an average size of approximately 178 nm, with drug loading and encapsulation efficiency of 3% and 65%, respectively. Approximately 80% of the drug was cumulatively released within 48 hours. Compared with Hafezi Ghahestani's study, the cumulative release under these optimized conditions reached a higher level. This study provides strong evidence for the application of CRT-PLGA-NPs.

2.3.2. Chitosan Nanoparticles

Chitosan (CS) is a non-toxic, biodegradable, biocompatible, antibacterial, and mucoadhesive biopolymer obtained by deacetylation of chitin. It is a cationic amino polysaccharide [36-37]. As a novel drug carrier, it can improve drug stability [36].

Wu Jian et al. [38] increased the solubility of CRT by combining low-molecular-weight amphiphilic extracts with modified nanoliposomes. First, low-molecular-weight amphiphilic extracts efficiently captured oil-soluble components such as CRT from saffron at low temperature through dynamic equilibrium with short-chain molecular clusters and lysine, significantly improving the extraction rate. The resulting extract was rich in CRT. Subsequently, the oil-soluble extract was encapsulated within the lipid bilayer of nanoliposomes using modified chitosan to protect its structure. This multi-layer protection mechanism not only enhanced the stability of CRT but also significantly improved its dispersibility in the medium. Experimental data showed that the modified nanoliposomes retained 85% of CRT and 90% of safranal after 90 days of storage at 50°C, demonstrating the effectiveness of this solubilization technique.

Rahaiee et al. [39] prepared chitosan-sodium alginate (CS-Alg) biodegradable nanoparticles to improve the stability of CRT. Atomic force microscopy imaging showed uniform particle size distribution with an average size of 140 ± 20 nm. Using an improved ionic gelation method and response surface methodology to optimize key variables (particle size, Zeta potential, and encapsulation efficiency), the optimal formulation was obtained with 0.08% CS, 0.10% Alg, and pH 4.7. Under these conditions, the NPs had an average particle size of 236 nm, a Zeta potential of -33.52 mV, an encapsulation efficiency of 38.16%, a drug loading of 30.96%, and a yield of 48.33%. This study significantly improved the stability of CRT, with optimal storage stability at 4°C and pH 4. Although the encapsulation efficiency was relatively low compared with other techniques, it provides a reference for encapsulating other active substances. Rahaiee et al. [40] also found that the swelling of the prepared NPs was

pH-dependent, with greater swelling in acidic media. Under simulated gastrointestinal conditions, CRT exhibited controlled release.

2.3.3. Inorganic Nanoparticles

Inorganic nanoparticles are composed of inorganic materials such as metals, metal oxides, or minerals. They possess unique magnetic, optical, or electrical properties and high chemical stability, including magnetite nanoparticles, gold nanoparticles, and silver nanoparticles. Magnetic nanoparticles (MNPs), a type of iron oxide, exhibit unique chemical and physical properties as well as superparamagnetism and have been widely used in magnetic resonance imaging, magnetic hyperthermia, and drug delivery. Since MNPs tend to aggregate spontaneously, their surfaces need to be modified with biodegradable and biocompatible substances such as polymers, ligands, and surfactants to prevent this [41].

Ibrahim et al. [42] increased the stability of MNPs and reduced their toxicity by adding a polyethylene glycol (PEG) coating. The dense PEG layer also enhanced the hydrophilicity of the MNP surface, thereby increasing water solubility. By optimizing the PEG coating concentration, the stability and dispersibility of the NPs were improved. Under optimal conditions, the CRT loading in 5×, 10×, and 20× CRT-PEG-MNPs reached 96%, 87%, and 90% of the initial added amount, respectively. In vitro release experiments showed that 20× CRT-PEG-MNPs released 70% of CRT within 72 hours at pH 7.4, demonstrating good drug release performance. MTT assay results also indicated significant growth inhibition of these NPs against the HepG2 liver cancer cell line. Studies have shown that selenium nanoparticles (SeNPs) possess better biocompatibility, biological efficacy, and lower toxicity [43]. Mary et al. [44] used PEG-functionalized selenium nanoparticles (PEG-SeNPs) as carriers and covalently conjugated CRT, the active component of saffron, to enhance its anticancer effect and solubility. The drug loading of CRT-conjugated PEG-SeNPs was 8.77%. CRT release within 48 hours reached 91.0% at pH 5.3 and 34.5% at pH 7.4. Although the release rate was higher under acidic conditions, the drug loading was relatively low.

2.3.4. Others

To increase the solubility of CRT, Bari et al. [45] used CRT as a cross-linking agent to form stable nanoparticles through chemical cross-linking with silk fibroin, effectively solving the solubility problem of CRT in water. The NPs were then converted into microparticles by drying. The diameter before drying was 250 nm, while the average diameter of the dried microparticles was approximately 1.7–2.3 μm, significantly improving the stability of CRT. Similarly, Perteghella et al. [46] successfully prepared stable silk fibroin nanoparticles with an average diameter of approximately 248 nm using an ethanol precipitation method combined with CRT hydrolysis. The nanoparticles remained stable for 28 days at 4°C, and the addition of 0.1% trehalose during freeze-drying effectively prevented particle aggregation.

2.4. Liposomes

Liposomes are miniature vesicular structures composed of phospholipid bilayers, morphologically similar to cell membranes. They can encapsulate both hydrophilic and lipophilic substances, with phospholipids as the main component. Liposomal encapsulation technology is a delivery method that protects drugs, nutrients, or other active ingredients from degradation, enhances targeting and solubility, and is widely

used in medicine, cosmetics, and food. Liposomes can encapsulate CRT within the hydrophobic region to form stable complexes, protect CRT from gastrointestinal degradation, and improve oral absorption efficiency. Nano-liposomes (NL) can further increase the specific surface area of CRT, thereby enhancing its contact with water and improving water solubility.

Puglia et al. [47] prepared solid lipid nanoparticles (SLNs) using hydrogenated coco-glycerides as solid lipid and surfactants, followed by quasi-emulsion solvent diffusion and solvent diffusion methods to obtain CRT-SLNs. The average particle size was 278.1 ± 22.20 nm, with a PDI of 0.305 ± 0.02 and an encapsulation efficiency of 94%. Mousavi et al. [48] prepared three types of crocetin nano-liposomes (CRT-NL) with different raw material ratios using dioleoylphosphatidylethanolamine (DOPE), dipalmitoylphosphatidylcholine (DPPC), egg phosphatidylcholine (EPC), and distearoylphosphatidylglycerol (DSPG) via dehydration-rehydration. The resulting particle sizes ranged from 148.74 to 220.68 nm, with encapsulation efficiencies of 3.5%–9.4%. The IC_{50} of CRT-NL against HeLa cells was 0.61, lower than that of free CRT, indicating stronger cytotoxicity and significant induction of cancer cell apoptosis. However, the relatively low encapsulation efficiency limits the application of this technique.

Mertes et al. [49] used NL to encapsulate trans-crocetin to improve oxygenation in patients with COVID-19-related acute respiratory distress syndrome (ARDS). Preliminary Phase I/II clinical trial results showed that 45% of patients experienced more than a 25% improvement in oxygenation index within 24 hours after treatment with the NL formulation. The half-life of trans-crocetin in healthy mice was also increased six-fold. Nan Jian [2] prepared NL using medium-purity (70%) soybean lecithin via the ethanol injection method and developed chitosan-coated CRT-NL (CS-CRT-NL) to control CRT release during simulated digestion. The study significantly improved bioavailability. The storage stability of NL, CRT-NL, and CS-CRT-NL was compared over 21 days. CS-CRT-NL maintained stable particle size, reduced Zeta potential, and nearly unchanged PDI after 21 days, showing high storage stability. Under ultraviolet irradiation, the retention rate of CRT-NL solution increased by 4% in the first 24 hours. Compared with free CRT, NL encapsulation significantly enhanced the antioxidant and anti-inflammatory activities of CRT and extended its shelf life.

Nan Jian et al. [50] used the same preparation method in a study on anti-alcoholic hepatitis and obtained CRT-NL with an average particle size of 76.29 ± 0.20 nm, PDI of 0.28 ± 0.03 , and Zeta potential of -41.23 ± 3.80 mV. This NL not only significantly improved the dispersibility of CRT in water but also achieved an average encapsulation efficiency of 55.63% and a drug loading of 2.71 $\mu\text{g}/\text{mg}$, providing a solid material basis for subsequent studies on the anti-alcoholic liver injury activity of CRT.

Hu Yaya et al. [51] prepared CRT-NL using the thin-film hydration combined with ultrasonication method. When the octadecylamine dosage was 40/100 mg/mL, ultrasonication time was 40 min, hydration time was approximately 2 h, hydration temperature was 40°C, and the ratio of soybean lecithin:cholesterol:CRT was 6:1:1, the resulting CRT-NL had an average particle size of 240 ± 8.60 nm, PDI of 0.216 ± 0.03 , Zeta potential of 24.1 ± 3.30 mV, encapsulation efficiency of $95.5 \pm 3.20\%$, and drug loading of $26.1 \pm 1.20\%$. This significantly improved the solubility of CRT, providing strong support for its subsequent pharmacological research and clinical

application, and further enhancing its oral bioavailability.

2.5. Emulsions

An emulsion is a multiphase dispersion system composed of two immiscible liquids, in which one liquid is uniformly dispersed as fine droplets in the other, forming a stable emulsion system [52]. Emulsions are mainly classified into oil-in-water (O/W), water-in-oil (W/O), and complex emulsions such as O/W/O and W/O/W. Emulsions can improve the bioavailability of active substances, mask unpleasant tastes and odors, and increase solubility. Compared with conventional emulsions, nanoemulsions (NE) have much smaller particles (average radius between 100 and 1000 nm) and can enhance the bioavailability and water solubility of the encapsulated substance.

Mehrnia et al. [53] prepared NE using Span 80 and polyglycerol ester as surfactants. The microemulsion prepared with polyglycerol ester had smaller droplet sizes, while Span 80 could hardly cover all droplets, leading to CRT precipitation. Using 10% PGPR and 0.1% CRT, the average droplet size of the resulting NE was 9.7 ± 3 nm. Atefi et al. [54] prepared beverage emulsions by adding different concentrations of gum arabic and a fixed concentration of xanthan gum, combined with sunflower oil or sesame oil containing 0.1% CRT. When the gum arabic content was 4%, the emulsion exhibited the best long-term storage stability. Sunflower oil, due to its smaller average particle size and lower size index, was more favorable than sesame oil for preparing stable CRT beverage emulsions.

2.6. Solid Dispersions

Solid dispersion (SD) is a pharmaceutical technology that mixes a drug with an inert carrier to form a solid solution or dispersion, thereby improving drug solubility, bioavailability, and stability (as shown in Figure 4). CRT can be uniformly dispersed in the carrier in molecular, colloidal, or particulate form, significantly reducing drug particle size and markedly increasing surface area, thus enhancing water solubility. Zhong Hui et al. [55] used polyvinylpyrrolidone 30 (PVP K30), PEG 6000, and poloxamer 188 as carrier materials to prepare CRT-SD by solvent and melting methods. The results showed that when PVP K30 was used as the carrier, the SD prepared by the solvent method exhibited the best solubilization effect. At a drug-to-carrier ratio of 1:4, the cumulative release rate reached approximately 60% within 2 hours, increasing the solubility of CRT from 30.5 $\mu\text{g/mL}$ to 735.3 $\mu\text{g/mL}$, demonstrating the effectiveness of the solubilization technique.

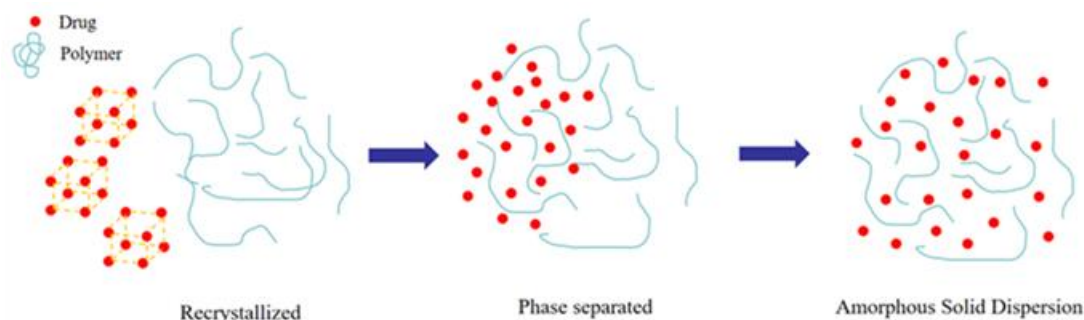


Figure 4. Mechanism of action of solid dispersions.

Table 1. *Solubilization Techniques and Effects of Crocetin.*

Technique	Water Solubility / Release Rate	Reference
Structural Modification	10 mg/mL	[11]
Microencapsulation	12.449 mg/mL	[21]
Nanoparticles	44.49%	[33]
Liposomes	/	/
Emulsions	/	/
Solid Dispersions	0.735 mg/mL	[55]

3. Conclusion and Prospects

Crocetin (CRT) possesses a wide range of pharmacological activities. However, its poor water solubility, instability, and low bioavailability severely limit its clinical application. In recent years, researchers have achieved remarkable results in improving the water solubility of CRT through various techniques, including structural modification, microencapsulation, nanoparticles, liposomes, emulsions, and solid dispersions. The water solubility of CRT has been increased from the initial 0.72 µg/mL to as high as 12.449 mg/mL.

In the area of structural modification, some derivatives obtained after modification may suffer from issues such as poor stability, altered biological activity, and difficulties in industrial-scale production. In the future, computer-aided drug design (CADD) technologies can be employed to predict and optimize the structures and activities of derivatives, thereby reducing production costs and improving production efficiency. Regarding microencapsulation, the preparation process is complex, and the drug loading capacity is limited by the wall materials. Therefore, it is necessary to explore new wall materials and preparation techniques, which are expected to further increase the drug loading of microcapsules.

In the field of nanoparticles, certain techniques suffer from limited drug loading and encapsulation efficiency, making it difficult to meet the requirements for high-dose drugs. In the future, novel carrier materials with higher specific surface area and better biocompatibility can be adopted to enhance the interaction between the drug and the carrier. For liposomes, problems such as low encapsulation efficiency and poor stability still exist. In future research, new carrier materials can be explored and combined with liposomes to further improve the solubility and stability of crocetin.

With the advancement of science and technology, CRT can also be combined with other solubilization techniques, such as co-crystals, lipid nanocrystals, and polymeric micelles, to explore more efficient and optimized drug solubilization strategies.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

- [1] José Bagur, M.; Alonso Salinas, G.L.; Jiménez-Monreal, A.M., et al. Saffron: An old medicinal plant and a potential novel functional food. *Molecules*, 2017, 23(1), 30.
- [2] Nan, J. Preparation, characterization and bioactivity study of crocetin nanoliposomes [Doctoral dissertation, Hefei University of Technology]. 2023.
- [3] Mehri, S.; Abnous, K.; Khooei, A., et al. Crocin reduced acrylamide-induced neurotoxicity in Wistar rat through inhibition of oxidative stress. *Iranian Journal of Basic Medical Sciences*, 2015, 18(9), 902.
- [4] Lin, S.; Li, Q.; Jiang, S., et al. Crocetin ameliorates chronic restraint stress-induced depression-like behaviors in mice by regulating MEK/ERK pathways and gut microbiota. *Journal of Ethnopharmacology*, 2021, 268, Article 113608.
- [5] Talaei, A.; Moghadam, M.H.; Tabassi, S.A.S., et al. Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial. *Journal of Affective Disorders*, 2015, 174, 51-56.
- [6] Sun, Y.; Xu, H.J.; Zhao, Y.X., et al. Crocin exhibits antitumor effects on human leukemia HL-60 cells in vitro and in vivo. *Evidence-Based Complementary and Alternative Medicine*, 2013, 1, Article 690164.
- [7] Liu, W.; Hou, Y.; Jin, Y., et al. (2020). Research progress on liposomes: Application in food, digestion behavior and absorption mechanism. *Trends in Food Science & Technology*, 104, 177-189.
- [8] Cai, H.L.; Liu, Y.H.; Liu, N.N. Effects of crocetin on blood lipids and LOX-1 expression in atherosclerotic rats. *Chinese Journal of Modern Medicine*, 2011, 13(10), 3-5.
- [9] Cerda-Bernad, D.; Valero-Cases, E.; Pastor, J. J., et al. Saffron bioactives crocin, crocetin and safranal: Effect on oxidative stress and mechanisms of action. *Critical Reviews in Food Science and Nutrition*, 2022, 62(12), 3232-3249.
- [10] Liu, X.C.; Ding, P.G.; Jin, H.J., et al. Preparation, characterization, safety and antitumor evaluation of trans-crocetin-cyclodextrin inclusion complexes. *Chinese Traditional and Herbal Drugs*, 2022, 53(15), 4663-4672.
- [11] Zhang, W. Preparation and bioavailability study of high-purity sodium crocetin [Doctoral dissertation, Zhejiang Chinese Medical University]. 2017.
- [12] Zhu, A.Y. Synthesis, metabolism and anti-Alzheimer's disease efficacy study of crocetin glucuronide [Doctoral dissertation, Zunyi Medical University]. 2019.
- [13] Yang, Y.A.; Zhu, H.L.; Ji, H., et al. Crocetin organic amine salts and their preparation method: CN201110451408.7 [P]. 2013-07-03.
- [14] Wang, M.Z.; Gao, J.; Chu, Y., et al. Synthesis of crocetin derivatives and their potent inhibition in multiple tumor cells proliferation and inflammatory property of macrophage. *BMC Complementary Medicine and Therapies*, 2020, 20(1), 29.
- [15] Chu, Y.; Gao, J.; Niu, J., et al. Synthesis, characterization and inhibitory effects of crocetin derivative compounds in cancer and inflammation. *Biomedicine & Pharmacotherapy*, 2018, 98, 157-164.

- [16]Zhang, C.F.; Liu, Y.H.; Wang, Y.R., et al. Research progress on pharmacokinetics and pharmaceuticals of crocin and crocetin. *Chinese Traditional and Herbal Drugs*, 2019, 50(01), 234-242.
- [17]Morin-Crini, N.; Fourmentin, S.; Fenyvesi, É., et al. 130 years of cyclodextrin discovery for health, food, agriculture, and the industry: A review. *Environmental Chemistry Letters*, 2021, 19(3), 2581-2617.
- [18]Li, H.F. Synthesis, supramolecular assembly and application of novel cyclodextrin derivatives. *Synthetic Materials Aging and Application*, 2019, 48(05), 141-145.
- [19]Ren, M.; Sun, X.Y., He, F.Y., et al. Research progress on β -cyclodextrin inclusion complexes. *Shandong Chemical Industry*, 2020, 49(18), 77-78.
- [20]Aloisio, C.; Gomes de Oliveira, A.; Longhi, M. Characterization, inclusion mode, phase-solubility and in vitro release studies of inclusion binary complexes with cyclodextrins and meglumine using sulfamerazine as model drug. *Drug Development and Industrial Pharmacy*, 2014, 40(7), 919-928.
- [21]Liu, N.; Xiao, J.; Zang, L.H., et al. Preparation of trans-crocetin with high solubility, stability, and oral bioavailability by incorporation into three types of cyclodextrins. *Pharmaceutics*, 2023, 15(12), 2790.
- [22]Wong, K.H.; Xie, Y.; Huang, X., et al. Delivering crocetin across the blood-brain barrier by using γ -cyclodextrin to treat Alzheimer's disease. *Scientific Reports*, 2020, 10(1), 3654.
- [23]Liu, D.C.; Song, R.; Wu, P., et al. Application of crocetin and its cyclodextrin inclusion complexes in assisting anti-tumor therapy and alleviating toxic side effects of tumor treatment: CN202511281584.9 [P]. 2025-11-18.
- [24]Zhou, H.; Yuan, X.; Zhao, Q., et al. Determination of oxygen transmission barrier of microcapsule wall by crocetin deterioration kinetics. *European Food Research and Technology*, 2013, 237(4), 639-646.
- [25]Kyriakoudi, A.; Tsimidou, M.Z. Properties of encapsulated saffron extracts in maltodextrin using the Büchi B-90 nano spray-dryer. *Food Chemistry*, 2018, 266, 458-465.
- [26]Liu, X.Y.; Luo, Y.Y.; Deng, S.Q., et al. Preparation and evaluation of human serum albumin-modified irinotecan hydrochloride PLGA nanoparticles. *Chinese Pharmaceutical Journal*, 2021, 56(21), 1740-1748.
- [27]Dudhani, A.R.; Kosaraju, S.L. Bioadhesive chitosan nanoparticles: Preparation and characterization. *Carbohydrate Polymers*, 2010, 81(2), 243-251.
- [28]Xu, Y.; Kim, C.S.; Saylor, D.M., et al. Polymer degradation and drug delivery in PLGA-based drug-polymer applications: A review of experiments and theories. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 2017, 105(6), 1692-1716.
- [29]Bala, I.; Hariharan, S.; Kumar, M.N.V.R. PLGA nanoparticles in drug delivery: The state of the art. *Critical Reviews in Therapeutic Drug Carrier Systems*, 2004, 21(5).
- [30]Freiberg, S.; Zhu, X.X. Polymer microspheres for controlled drug release. *International Journal of Pharmaceutics*, 2004, 282(1-2), 1-18.

- [31] Pirooznia, N.; Hasannia, S.; Lotfi, A. S., et al. Encapsulation of alpha-1 antitrypsin in PLGA nanoparticles: In vitro characterization as an effective aerosol formulation in pulmonary diseases. *Journal of Nanobiotechnology*, 2012, 10(1), 20.
- [32] Yang, X. Design and optimization of crocetin loaded PLGA nanoparticles against diabetic nephropathy via suppression of inflammatory biomarkers: A formulation approach to preclinical study. *Drug Delivery*, 2019, 26(1), 849-859.
- [33] Hafezi Ghahestani, Z.; Alebooye Langroodi, F.; Mokhtarzadeh, A., et al. Evaluation of anti-cancer activity of PLGA nanoparticles containing crocetin. *Artificial Cells, Nanomedicine, and Biotechnology*, 2017, 45(5), 955-960.
- [34] Neyshaburinezhad, N.; Kalalinia, F.; Hashemi, M. Encapsulation of crocetin into poly (lactic-co-glycolic acid) nanoparticles overcomes drug resistance in human ovarian cisplatin-resistant carcinoma cell line (A2780-RCIS). *Molecular Biology Reports*, 2019, 46(6), 6525-6532.
- [35] Langroodi, F.A.; Hafezi Ghahestani, Z.; Alibolandi, M., et al. Improvement of antitumor activity of doxorubicin by co-formulation of crocetin and doxorubicin in PLGA nanoparticles. *Journal of Cellular Immunotherapy*, 2017, 3(2e30), 8.
- [36] Martins, A.F.; Oliveira, D.M.; Pereira, A.G.B., et al. Chitosan/TPP microparticles obtained by microemulsion method applied in controlled release of heparin. *International Journal of Biological Macromolecules*, 2012, 51(5), 1127-1133.
- [37] Martins, A.F.; Piai, J.F.; Schuquel, I.T.A., et al. Polyelectrolyte complexes of chitosan/heparin and N,N,N-trimethyl chitosan/heparin obtained at different pH: I. Preparation, characterization, and controlled release of heparin. *Colloid and Polymer Science*, 2011, 289(10), 1133-1144.
- [38] Wu, J.; Wu, Y.X. A preparation method of oil-soluble extract of safflower and its application in soothing cream: CN202510103688.4 [P]. 2025-05-02.
- [39] Rahaiee, S.; Shojaosadati, S.A.; Hashemi, M., et al. Improvement of crocin stability by biodegradable nanoparticles of chitosan-alginate. *International Journal of Biological Macromolecules*, 2015, 79, 423-432.
- [40] Rahaiee, S.; Hashemi, M.; Shojaosadati, S.A., et al. Nanoparticles based on crocin loaded chitosan-alginate biopolymers: Antioxidant activities, bioavailability and anticancer properties. *International Journal of Biological Macromolecules*, 2017, 99, 401-408.
- [41] Rahdar, A.; Hajinezhad, M.R.; Sargazi, S., et al. Pluronic F127/carfilzomib-based nanomicelles as promising nanocarriers: Synthesis, characterization, biological, and in silico evaluations. *Journal of Molecular Liquids*, 2022, 346, Article 118271.
- [42] Ibrahim, S.; Baig, B.; Hisaindee, S., et al. Development and evaluation of crocetin-functionalized pegylated magnetite nanoparticles for hepatocellular carcinoma. *Molecules*, 2023, 28(7), 2882.
- [43] Tran, P.A.; Sarin, L.; Hurt, R.H., et al. Differential effects of nanoselenium doping on healthy and cancerous osteoblasts in coculture on titanium. *International Journal of Nanomedicine*, 2010, 351-358.

- [44] Mary, T.A.; Shanthi, K.; Vimala, K., et al. PEG functionalized selenium nanoparticles as a carrier of crocin to achieve anticancer synergism. *RSC Advances*, 2016, 6(27), 22936-22949.
- [45] Bari, E.; Perteghella, S.; Rassu, G., et al. Sericin/crocetin micro/nanoparticles for nucleus pulposus cells regeneration: An “active” drug delivery system. *Frontiers in Pharmacology*, 2023, 14, Article 1129882.
- [46] Perteghella, S., Rassu, G., Gavini, E., et al. Crocetin as new cross-linker for bioactive sericin nanoparticles. *Pharmaceutics*, 2021, 13(5), 680.
- [47] Puglia, C.; Santonocito, D.; Musumeci, T., et al. Nanotechnological approach to increase the antioxidant and cytotoxic efficacy of crocin and crocetin. *Planta Medica*, 2019, 85(03), 258-265.
- [48] Mousavi, S.H.; Moallem, S.A.; Mehri, S., et al. Improvement of cytotoxic and apoptogenic properties of crocin in cancer cell lines by its nanoliposomal form. *Pharmaceutical Biology*, 2011, 49(10), 1039-1045.
- [49] Mertes, P.M.; Collange, O.; Coliat, P., et al. Liposomal encapsulation of trans-crocetin enhances oxygenation in patients with COVID-19-related ARDS receiving mechanical ventilation. *Journal of Controlled Release*, 2021, 336, 252-261.
- [50] Nan, J.; Si, G.R.; Cheng, H.R., et al. Study on the activity of crocetin nanoliposomes against alcoholic liver injury. *Journal of Hefei University of Technology (Natural Science Edition)*, 2025, 48(03), 376-380.
- [51] Hu, Y.Y. Pharmacological activity of Gardenia and Aconitum on arthritic rats and preparation study of crocetin liposomes [Doctoral dissertation, Zunyi Medical College]. 2018.
- [52] Tang, F.Y. Development of compound oregano oil oral emulsion [Master's thesis, Henan Agricultural University]. 2010.
- [53] Mehrnia, M.A.; Jafari, S.M.; Makhmal-Zadeh, B.S., et al. Crocin loaded nano-emulsions: Factors affecting emulsion properties in spontaneous emulsification. *International Journal of Biological Macromolecules*, 2016, 84, 261-267.
- [54] Atefi, M.; Zargaraan, A.; Nayebzadeh, K., et al. Physicochemical characteristics of beverage emulsions containing crocetin as a functional ingredient of saffron. *Food Science and Biotechnology*, 2022, 31(12), 1537-1546.
- [55] Zhong, H. Study on crocetin solid dispersion sustained-release tablets [Master's thesis, Jiangsu University]. 2014.



© 2026 by the author(s); licensee International Technology and Science Publications (ITS), this work for open access publication is under the Creative Commons Attribution International License (CC BY 4.0). (<http://creativecommons.org/licenses/by/4.0/>)