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REVIEW ARTICLE

Enhancing Curcumin Oral Bioavailability Through Nanoformulations

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Abstract
Curcumin is a promising therapeutic agent that exhibits manifold therapeutic activities. However, it is challenging to study curcumin as it exhibits poor aqueous solubility and low permeability and it is a substrate for P-glycoprotein (P-gp). It is readily metabolized in the body, but many active metabolites of curcumin have been identified that could also be exploited for therapy. Strategies for the oral bioenhancement of curcumin to leverage the potential of curcumin as a therapeutic molecule are discussed here in light of these challenges. A brief discussion of conventional bioenhancement strategies using cyclodextrin complexes, solid dispersions, and solid self-emulsifying drug delivery systems is given. However, the major focus of this review is the application of nano-based approaches to the bioenhancement of curcumin. A description of the main advantages of nanosystems is followed by a detailed review of various nanosystems of curcumin, including nanosuspensions and various carrier-based nanosystems. Each nanosystem considered here is first briefly introduced, and then studies of the nanosystem containing curcumin are discussed. Lipid-based systems including liposomes and solid lipid nanoparticles, microemulsions, self-microemulsifying drug-delivery systems, nanoemulsions, and polymeric nanoparticles—which are widely explored—are dealt with in detail. Other miscellaneous systems discussed include inorganic nanoparticles, micelles, solid nanodispersions, phytosomes, and dendrimers. The possibility of using intact nanoparticles to achieve the targeted oral delivery of curcumin and thus harness the benefits of this wonder nutraceutical is an exciting prospect.

Key Points

Curcumin, a hydrophobic nutraceutical pigment, has various therapeutic activities

Curcumin, a BCS class IV agent, exhibits poor bioavailability due to low solubility and permeation

Nano-based approaches can improve the oral bioavailability of curcumin

1 Introduction

Curcumin, a bioactive hydrophobic polyphenolic nutraceutical pigment, has attracted significant global attention due to its range of therapeutic activities [1]. Pharmacological studies have demonstrated the potential of curcumin in the prevention and treatment of various diseases [2]. Curcumin is widely accepted to be a holistic nutraceutical that can improve the general health of those who consume it. The United States Food and Drug Administration (USFDA) categorizes curcumin as a generally recognized as safe (GRAS) substance [3, 4]. Moreover, it has been proven that a dose of curcumin of up to 12 g/day is safe for human consumption without incurring any side effects [3, 5–7]. Curcumin contains approximately 77% of the active constituent diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin as the major components [2, 8, 9]. The multifarious activities of curcumin have triggered considerable research aimed at identifying therapeutic applications of this substance in several preclinical animal models [10, 11]. Some of this research has evolved into phase I [12, 13] and phase II [14] clinical trials. The various applications of curcumin as a therapeutic agent are summarized succinctly in Fig. 1. Despite its versatility, safety, and promising therapeutic potential, the exploitation of curcumin as a therapeutic agent has been severely limited by a number of challenges. The present review provides a comprehensive discussion of strategies for the oral bioenhancement of curcumin, focusing in particular on nano-based approaches for the improved oral delivery of curcumin.

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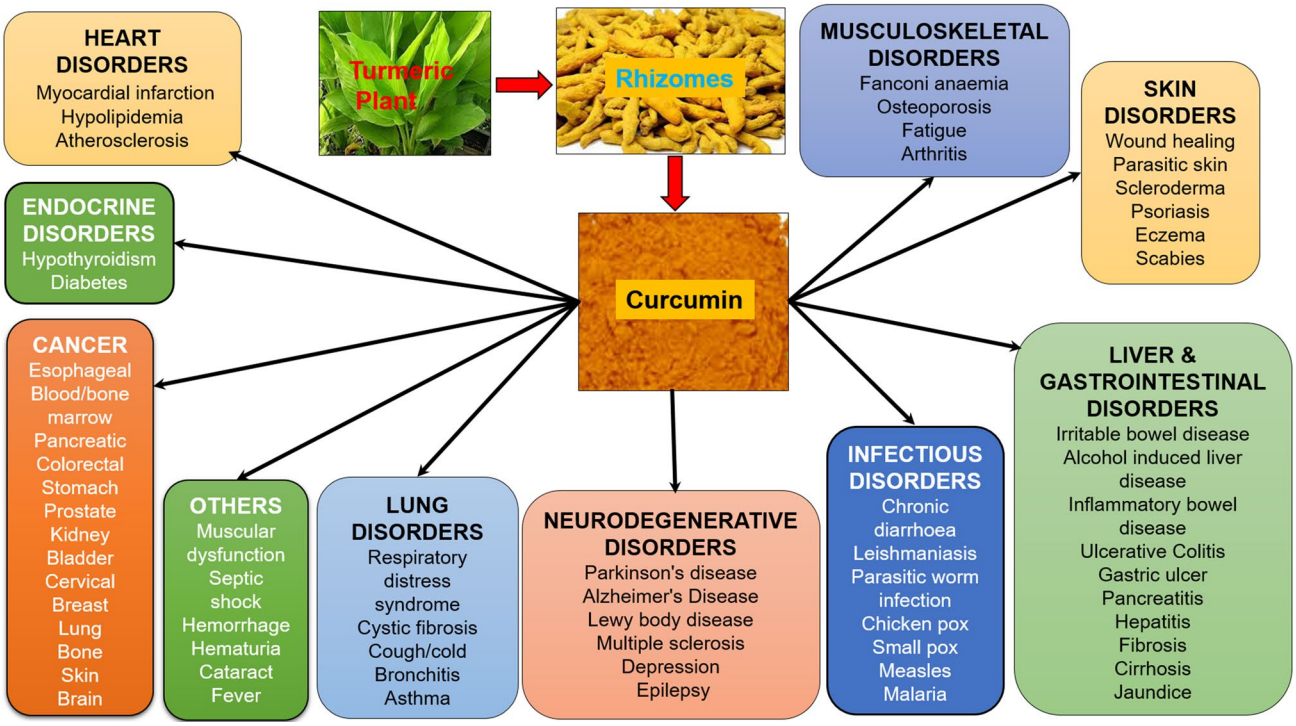

Fig. 1 Curcumin as a therapeutic agent

2 Challenges Involved in the Efficacious Delivery of Curcumin

Curcumin is a class IV drug in the Biopharmaceutics Classification System (BCS), which indicates that it exhibits poor aqueous solubility and negligible permeability through the gastrointestinal epithelium. In addition, curcumin is a substrate for P-glycoprotein (P-gp), a transmembrane ATP-dependent drug efflux pump which expels curcumin from the intestinal membrane, thereby limiting its permeability [15, 16]. Curcumin has a log*P* value of ~ 3 and is practically insoluble in water (~ 10–20 µg/mL), even at acidic and neutral pH [17–20]. This, in conjunction with its poor permeability, limits the absorption of curcumin [21]. Although the permeability of curcumin is higher under acidic conditions, it is significantly below the permeabilities associated with the USFDA-approved BCS class of highly permeable substances.

Curcumin conjugates are water soluble [22] and can therefore be detected in the urine of curcumin-treated mice [23]. Following intraperitoneal or intravenous administration, curcumin is excreted primarily in bile as tetrahydrocurcumin and hexahydrocurcumin glucuronides (the major metabolites) and dihydroferulic acid along with ferulic acid (minor biliary metabolites) [24]. Figure 2 depicts the metabolic pathways of curcumin. Some of its metabolites are as active as or even more active than curcumin. Hexahydrocurcumin, a major metabolite, is reported to be just as or even more potent in vitro and in vivo than curcumin [25] in terms of arresting the cell cycle in SW480 cells (a human colorectal cancer cell line) [26]. In vitro study showed that tetrahydrocurcumin inhibits radiation-induced lipid peroxidation [27] and increases antioxidant enzyme levels [28]. Tetrahydrocurcumin decreased the development of polyps and aberrant crypt foci in azoxymethane-induced colon carcinogenesis in rats [29] and significantly attenuated chloroquine-mediated oxidative kidney damage [30]. Tetrahydrocurcumin also showed superior antioxidant and antidiabetic activities compared to curcumin in type-2 diabetic rats [31]. Octahydrocurcumin exhibited stronger free-radical scavenging activity than curcumin [32]. As well as being a substrate of P-gp, curcumin binds to multidrug resistance-associated protein (MRP) transporters, which is yet another reason for its low bioavailability [33, 34]. All of these factors synergistically limit the bioavailability of curcumin.

3 Bioenhancement Strategies for Curcumin

Strategies for the bioenhancement of curcumin must necessarily address the issues that limit its bioavailability, as discussed above. Various strategies have been explored for

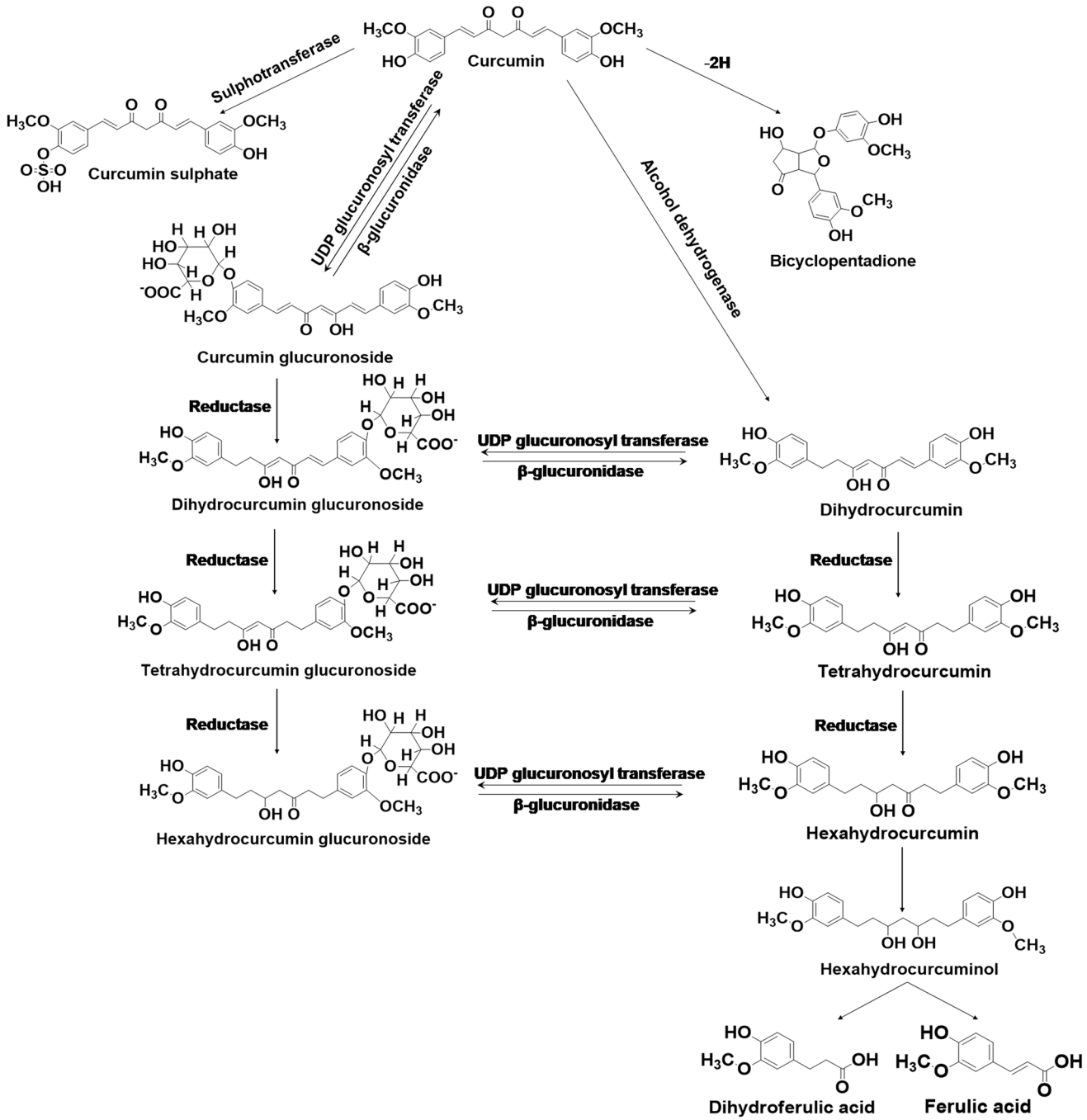

Fig. 2 Metabolic pathways of curcumin, as adapted from Pan et al. [22]. *UDP* uridine 5′-diphospho-glucuronosyltransferase, *-2H* oxidation

oral curcumin bioenhancement. Enhancing the solubility and dissolution rate is a major area of investigation, and that research has already been discussed in a review [35]. Solubility enhancement approaches include cyclodextrin inclusion complexes, solid dispersions (SDs), and solid self-emulsifying drug-delivery systems (S-SEDDs) using surfactants as solubilizers. Increasing the surface area by micronization, manipulating solid-state crystallinity, and synthesizing prodrugs are other well-reported techniques for improving the aqueous solubility of curcumin [36].

Cyclodextrins (CDs) entrap hydrophobic drugs such as curcumin in their lipophilic cavities, facilitating solubilization and possibly stabilization, and often even masking the taste of the drug. All of these properties are relevant for curcumin [37, 38]. Complexation significantly enhances the solubility of curcumin. For instance, a 31-fold increase in

solubility was seen using the coprecipitation technique, a 19-fold increase using the solvent evaporation technique, an 18-fold increase using the freeze-drying technique [39], and a 190-fold increase was observed with the kneading method using methyl-β-cyclodextrin (MβCD) [40]. The solubilities of various cyclodextrin complexes also increased at pH 5 and pH 6 by up to an order of 10^4 [41, 42] and 0.73 mg/mL, respectively [43]. Curcumin exhibited greater affinity for 2-hydroxypropyl-β-CD (HPβCD) than other cyclodextrin derivatives when prepared by solvent and kneading techniques. The capacities of various cyclodextrins to enhance curcumin solubility decrease in the following order: HPβCD > MβCD > βCD > γCD (gamma-cyclodextrin) [40]. These complexes also enhance curcumin's anticancer and anti-inflammatory activities [39]. A 202-fold increase in the solubility of curcumin was observed when it was complexed with HPβCD; this complex significantly inhibited angiogenesis in chick embryos compared to uncomplexed curcumin [40].

Solid dispersions of hydrophobic drugs in a hydrophilic inert carrier in the solid state have been found to improve the solubility and dissolution rate of the drug and to decrease presystemic metabolism, thereby increasing the bioavailability of the drug [44]. Solid dispersions are usually prepared by a solvent/fusion solvent method, solvent evaporation, and a melting (fusion) method [45, 46]. A solid dispersion of curcumin with Solutol® HS15 showed higher solubility and a fivefold improvement in bioavailability compared to those of free curcumin [47]. Meanwhile, solid dispersions of curcumin with cellulose acetate and mannitol presented enhanced aqueous solubility compared to curcumin, as well as a sevenfold improvement in oral bioavailability [48]. A curcumin Gelucire®50/13-Aerosil solid dispersion showed a 3600-fold improvement in aqueous solubility, a 7.3-fold improvement in dissolution rate, and greater stability (up to 9 months). In addition, an improvement in curcumin gastrointestinal absorption was indicated by a 5.5-fold increase in systemic bioavailability and enhanced anti-inflammatory activity in rats [49].

A heat-treatment-based approach showed that upon heating curcumin, a 12-fold enhancement in curcumin solubility was achievable. Heating did not degrade the curcumin [50]. S-SEDDS, wherein the self-emulsifying liquid is converted into a solid form, improved curcumin solubility, dissolution, and absorption. The transformation of curcumin to an amorphous or partially amorphous state led to increases in solubility and dissolution rate [51, 52]. Different solidification techniques, such as spray drying, adsorption to solid carriers, melt granulation, and melt extrusion techniques were used to prepare the S-SEDDS [53–55]. Curcumin formulated in S-SEDDS dissolved rapidly and completely within 5 min at a gastric pH of 1.2 and an intestinal pH of 6.8 (phosphate buffer) [51]. Administration of S-SEDDS containing curcumin enhanced defensive action against chronic heart failure by improving ventricular pump function and decreasing myocardial lipid peroxidation damage, infarction, fibrosis, and pachynsis as compared to a curcumin suspension administered in rats [56].

3.1 Curcumin as a P-gp Substrate

Curcumin is reportedly a P-gp substrate. Hence, P-gp inhibition as a strategy to enhance curcumin bioavailability has also been explored. Piperine inhibited the metabolism of curcumin as well as the flux of glucuronide in the secretory direction. It also inhibited ABC transporters on the apical side of Caco-2 cells along with MRP-1 and MRP-2 associated with enteroenteric and hepatic pre-systemic metabolism [57, 58]. P-gp function and the expression of P-gp at the protein and mRNA levels were also inhibited [59] in a concentration-dependent manner [60, 61]. Quercetin, a flavonoid, improved curcumin bioavailability by inhibiting the P-gp efflux pump as well as the metabolizing enzyme CYP3A4 in the intestinal mucosa, leading to improved uptake of curcumin by human colon carcinoma WiDr cells [62–64]. Combinations of curcumin with piperine and quercetin have been employed successfully for the bioenhancement of curcumin [65–67].

4 Nano-Based Approaches to Enhancing Oral Bioavailability

Nanoparticles offer substantial benefits over conventional drug-delivery systems due to their small size and consequently large surface area. While enhancing solubility is one way to improve bioavailability, transporting intact nanoparticles though the gastrointestinal mucosa is another mechanism that could permit significant bioenhancement. Enhanced permeation through mucosal tissues is also feasible using appropriate nanostrategies. Furthermore, nanoformulations can be tailored to ensure sustained and controlled release, contributing to bioenhanced drug delivery. Targeted delivery through an increased circulation half-life as well as altered drug disposition due to drug localization and cell-specific uptake in vivo are other important benefits of nanoformulations. Nanostrategies are therefore specifically attractive for BCS class IV drugs such as curcumin that require solubilization and permeation enhancement [68].

Among the various nutraceuticals that have been investigated for possible bioenhancement using nano-based strategies, curcumin has been relatively well studied. Efforts have been directed primarily towards the design of curcumin nanosystems for cancer treatment [69–72]. Another important therapeutic lead is the application of curcumin nanosystems for the treatment of infectious diseases such

as tuberculosis [73], hepatitis B [74], malaria [75], influenza [76], and the Zika and chikungunya viruses [77], as well as for other conditions such as rheumatoid arthritis [78]. Most of those studies reported parenteral administration and are therefore not discussed here. As the most popular route—and the one that is most convenient for the patient—is the oral route, and it is recommended that nutraceuticals should be administered for long periods, this review primarily focuses on nanostrategies that have been employed for the bioenhancement of curcumin following oral administration.

When reviewing various reported nanotechnologies for oral curcumin delivery below, we provide a brief description of each nanosystem and how it facilitates bioenhancement in order to aid reader understanding. Figure 3 provides a pictorial representation of the various nanosystems discussed here.

4.1 Nanosuspensions

Nanosuspensions are carrier-free dispersions of water-insoluble drugs in aqueous media [79]. The colloidal size range of the drugs is less than 1 μm, and the nanosuspensions are stabilized by surfactants and other agents [80, 81]. The small particle size (PS) and correspondingly high surface area, coupled with high thermodynamic energy, favor rapid dissolution of the drug. Two major approaches are reported for the preparation of drug nanosuspensions: top-down and bottom-up [82, 83]. The first relies on sizing down large micron-sized particles to nanosize, which in most cases requires high shear/pressure homogenizers. On the other hand, the bottom-up technique involves the generation of nanosuspensions with desired size distributions from solutions by crystallization, precipitation, etc., which inherently requires organic solvents that are removed after the process is complete. Other techniques such as spray drying and supercritical processes using carbon dioxide may also be employed [84]. The limited stability of high-energy nanosuspensions is

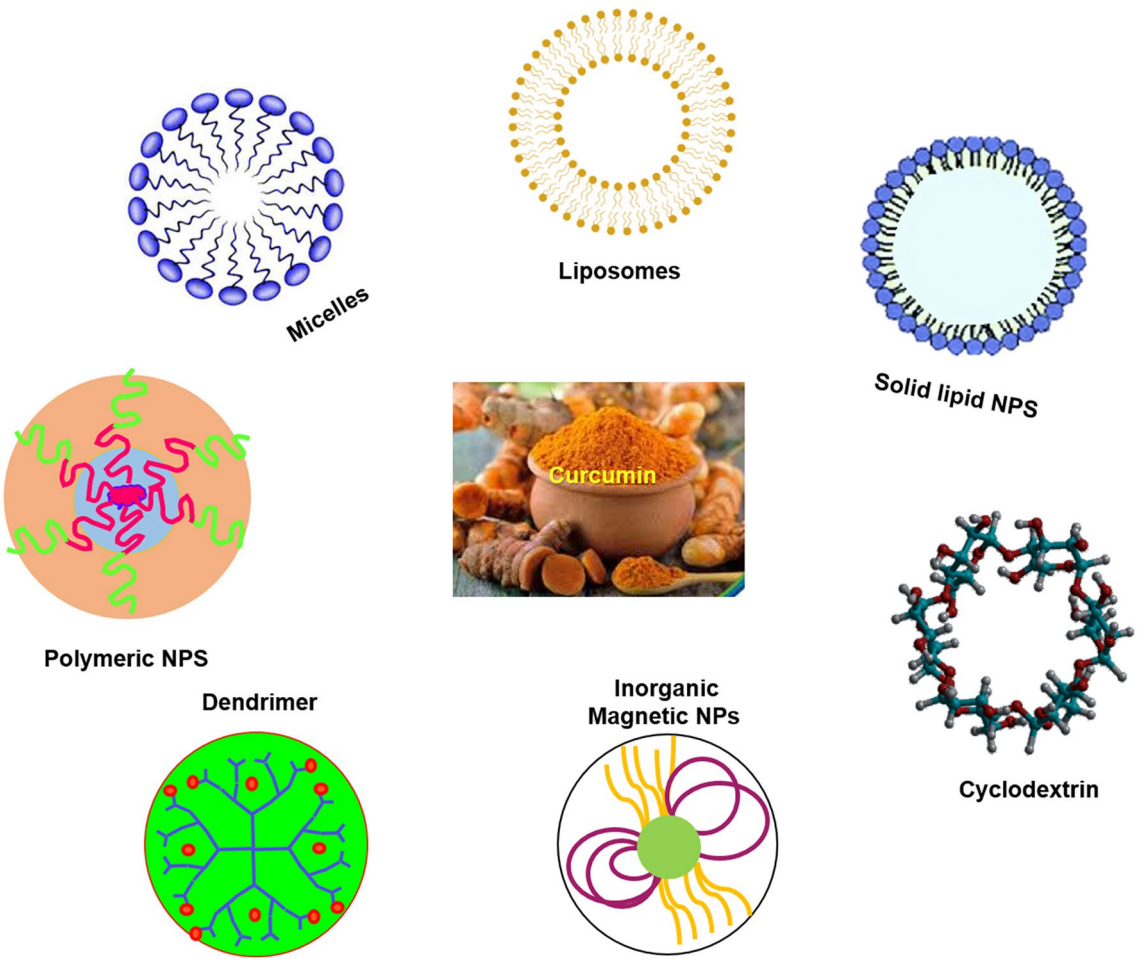

Fig. 3 Nano-based delivery systems of curcumin. *NPs* nanoparticles

yet another challenge, and one that necessitates approaches for stabilizing nanodispersions [85]. Conversion to the solid state through processes such as freeze drying and vacuum drying is utilized. While this demands sophisticated drying equipment such as freeze dryers and vacuum dryers, another problem is the possible agglomeration of the nanosized particles, resulting in larger particles [86]. One advantage of this approach, however, is the possibility of converting the nanosuspension into a bioenhanced yet convenient solid dosage form such as a tablet or capsule for oral administration.

Studies on curcumin nanosuspensions are scarce. Curcumin nanosuspensions created by a solvent–antisolvent precipitation method using sodium lauryl sulfate and polyvinylpyrrolidone K-60 presented threefold-increased aqueous solubility, increased stability, and an improved dissolution rate compared to free curcumin [87]. Curcumin–TPGS nanosuspensions and curcumin–Brij78 nanosuspensions prepared by a CO_2-assisted in-situ nanoamorphization method yielded enhanced dissolution rates, with a sustained release period in vitro of over 32 h. The three- to fourfold bioenhancement achieved following oral administration was also attributed to P-gp inhibition by Brij78 and tocopheryl polyethylene glycol succinate (TPGS) as well as to their ability to inhibit curcumin metabolism [88]. A curcumin nanosuspension prepared by high-pressure homogenization followed by lyophilization using TPGS as stabilizer exhibited spherical curcumin nanoparticles ~200 nm in size. A sevenfold bioenhancement following oral administration was attributed to the increased fluidity of the intestinal mucosal membrane, which loosened the conformation of the membrane protein [89]. A curcumin nanosuspension obtained by a solvent–antisolvent technique and stabilized by Poloxamer 188 and TPGS generated larger particles 596.5 ± 5 nm in size. Nevertheless, a tenfold bioenhancement was observed [90]. It is therefore apparent that nanosuspension bioenhancement is influenced by not only the stabilizer and size but also significantly by the particular nanosuspension preparation process employed.

4.2 Lipid-Based Nanoparticles

4.2.1 Liposomes

Liposomes are phospholipid-based vesicular systems. They comprise one or more aqueous layers surrounded by phospholipid membrane bilayers that exhibit high biocompatibility and low toxicity. They may be prepared from natural or synthetic phospholipids. Liposomes are flexible vesicles whose rigidity is often modulated through the inclusion of cholesterol in the lipid membrane. They are usually 0.025 µm (small) to 2.5 µm (large) in diameter and can be unilamellar, multilamellar, or even multivesicular. Multilamellar liposomes exhibit an onion structure wherein the unilamellar phospholipid vesicles form concentric spheres, each separated by an aqueous phase [91, 92].

Liposomes may be prepared by various techniques, including solvent dispersion methods, mechanical dispersion methods, and detergent removal methods. Among these, the most popular are the lipid film hydration and ether/ethanol injection methods. The drug may be loaded before or after the formation of the liposomes by active or passive techniques, respectively [93]. Both hydrophobic and hydrophilic drugs may be incorporated into liposomes. While hydrophobic drugs are entrapped by the lipid bilayer, hydrophilic drugs are incorporated into the aqueous core of the liposome. Due to their high biocompatibility, liposomes are the most extensively investigated nanosystems. Comparisons of the oral bioenhancement of a number of hydrophobic drugs using liposomes to conventional oral dosage forms such as tablets and suspensions is reported [94, 95].

Different approaches have been investigated for the preparation of liposomal curcumin formulations. A combination of thin film evaporation and dynamic high-pressure microfluidization was studied for the preparation of curcumin Pluronic liposomes [96], while liposomal curcumin was made from lecithin by a mechanochemical method of homogenization and microfluidization [97]. A curcumin–βCD complex loaded into nanomagnetoliposomes was prepared by a simple and rapid coencapsulation method [98], while silica-coated curcumin-loaded flexible liposomes were generated by a dry-film dispersion technique [99]. Curcumin liposomes comprising soya phosphatidylcholine and TPGS coated with *N*-trimethyl chitosan chloride are also reported [100]. The liposomes were evaluated for size, bioenhancement, and in some cases for efficacy based on their plasma antioxidant activity. In vitro anticancer efficacy in cell lines is also reported. Details of these studies are summarized in Table 1.

4.2.2 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal lipid carriers (50–1000 nm) made up of biocompatible and biodegradable physiological lipids. Although lipidic in nature (unlike liposomes), SLNs are rigid particles that are only suitable for loading hydrophobic drugs. Important facets of SLNs are their capacity for high drug loading, good stability, excellent biocompatibility, and enhanced bioavailability. Being hydrophobic, they are excellent nanocarriers for controlled release and for targeted drug delivery to the reticuloendothelial system [101]. SLNs can be prepared by various methods, including high-pressure homogenization, ultrasonication, high-speed homogenization, solvent evaporation, a microemulsion-based method, a double emulsion method, solvent emulsification-diffusion, a supercritical fluid technique, film-ultrasound dispersion, a solvent injection technique, a precipitation technique, and a spray drying method [102]. All of

Table 1 Summary of liposomal nanosystems of curcumin

Liposomal carrier	Method of preparation	Dose	Outcomes	Reference
Based on Pluronic	Thin-film evaporation	–	PS 50–100 nm, spherical. Bioavailability was strongly influenced by the composition of Pluronic and decreased in the order F127 > P85-Lps > F87 and curcumin-Lps	[96]
Lecithin	Mechanochemical homogenization and microfluidization	100 mg/kg to rats	PS 263 nm. 4.96-fold enhancement in $AUC_{(0-120)}$ (26,502.8 μg × min/L), higher C_{max} (319.2 ± 70.4 μg/L), and higher plasma antioxidant activity	[97]
Based on a βCD complex	Simple and rapid encapsulation method	–	PS 67 nm. Low IC_{50} value (64.7791 μg/mL). Synergistically enhanced radical scavenging activity	[98]
Based on silica coating	Thin-film method with homogenization	50 mg/kg to rats	PS 157 nm. Exhibited 7.76-fold and 3.31-fold improvements in curcumin bioavailability compared to curcumin suspension and curcumin-loaded flexible liposomes, respectively	[99]
Coated with *N*-trimethyl chitosan chloride	Thin-film dispersion method	40 mg/kg to rats	PS 657.7 nm, zeta potential + 15.64 mV, improved systemic bioavailability with a 1.6-fold increase in AUC (416.58 μg × h/L) and a 1.5-fold increase in C_{max} (46.13 μg/L) compared to uncoated curcumin liposomes and curcumin suspension	[100]

PS particle size, *Lps* liposomes, *AUC* area under the concentration–time curve, C_{max} maximum plasma concentration, IC_{50} half-maximal inhibitory concentration, *βCD* β-cyclodextrin

these methods employ solvents. A green method for preparing SLNs is the melt homogenization method. In SLNs, the drug is generally dispersed in the lipid matrix. A limitation of SLN is the expulsion of the drug from the SLNs over time; this issue led to the development of nanostructured lipid carriers (NLCs).

A number of lipids have been evaluated as candidates for the preparation of SLNs. Gelucire®50/13 SLNs were prepared by a microemulsion template method followed by freeze drying [103], while soya lecithin SLNs were prepared by hot homogenization followed by freeze drying [104] and an emulsion/evaporation method [105]. Glycerol monostearate (GMS)-soya lecithin SLNs were also studied [106]. Apart from their physicochemical properties, stability [107], and bioenhancement [108], the curcumin SLNs were evaluated for cytotoxicity, in vitro cell uptake, and in vitro and in vivo anticancer efficacies [109]. The effect of the dose of curcumin on bioavailability was also reported. NLCs of curcumin revealed good permeation and particularly enhanced efficacy in colitis [110]. Details of various studies are summarized in Table 2.

4.2.3 Liposomes Versus SLNs for Curcumin

Liposomes are among the most biocompatible nanoformulations developed thus far, due to the high biocompatibility, safety, and biodegradability of the phospholipids. Nevertheless, SLNs are far more straightforward to manufacture than liposomes, and the lipids used in SLNs are biocompatible and biodegradable. While curcumin liposomes are preferable for parenteral delivery, curcumin SLNs are the practical choice for oral delivery, based also on cost.

4.3 Microemulsions and SMEDDSs

Microemulsions (MEs) are transparent or slightly opalescent optically isotropic emulsions with nanosized globules. They comprise oil, water, and surfactant, most often in combination with a cosurfactant [111, 112], and can be o/w, w/o, or even bicontinuous. Unlike emulsions, microemulsions form spontaneously with minimal energy input. Their high solubilization capabilities for hydrophilic and lipophilic drugs, good thermodynamic stability, and ability to protect drugs from degradation [113–115] are some of their major advantages. Furthermore, the ability of microemulsions to enhance bioavailability, especially of hydrophobic drugs, is well demonstrated [116–119]. They are generally prepared by simply gently mixing all of the components. The drug is either dissolved in the most soluble component prior to mixing or added to the microemulsion under stirring. A phase inversion temperature method has also been reported for the preparation of microemulsions [120]. A microemulsion of curcumin with various oils, surfactants, and cosurfactants was reported. While high concentrations of monoglycerides (MG) and diglycerides (DI-G) were readily incorporated into the ME, long-chain triglycerides such as vegetable oils

Table 2 Summary of SLNs and NLCs of curcumin

SLN carrier	Method of preparation	Dose	Outcomes	Reference
Gelucire®50/13	Microemulsion template and freeze-drying method	100 mg/kg to rats	PS 375 nm. A 2.7-fold increase in $AUC_{(0–5h)}$ (75.5 ng×h/mL) and a 1.2-fold increase in C_{max} (31.3 ng/mL) within 1 h of administration compared to 250 mg/kg of curcumin aqueous suspension. Oral bioavailability significantly increased to 647% compared to curcumin aqueous suspension	[103]
Soya lecithin	Modified hot homogenization and freeze drying	50 mg/kg to rats	PS 245.1 ± 5.4 nm. Zeta potential was − 10.4 ± 3.9 mV. A 6.3-fold greater lymphatic uptake and 9.5-fold greater oral bioavailability. Improved intestinal delivery and antitumor effects, superior dose-dependent cytotoxicity and cellular uptake in MCF-7 cells	[104]
Soya lecithin	Emulsion/evaporation method	100 mg/kg for 5 days in mice	PS 125.2 nm. Zeta potential was − 19.4 ± 2.2 mV. Higher curcumin plasma levels and significant reduction of growth in Hodgkin's lymphoma xenograft compared to controls. Reduced cell proliferative protein expression and apoptosis in HL tumor extracts, and decreased IL-6 and TNF-α levels	[105]
GMS soya lecithin	Emulsification and low-temperature solidification	50 mg/kg to rats	PS 135.3 ± 1.5 nm, zeta potential was 24.7 ± 2.1 mV. A 12.27-fold higher $AUC_{(0–t)}$ and 942.53% improved oral bioavailability compared to curcumin suspension. Enhanced water solubility, increased curcumin absorption by enhancing intestinal permeability and Pgp-mediated efflux inhibition	[106]
Soya lecithin	Microemulsification method	1 mg /kg, 12.5 mg/kg, 25 mg/kg, 50 mg/kg to rats	PS 134.6 nm. Useful in neurodegenerative and cancerous disorders. 155-fold, 59-fold, 32-fold, and 39-fold increases in bioavailability	[107]
Smoothex (glycerol stearate)	High shear homogenization and ultrasonication	50 mg/kg to mice	PS 739.26 ± 53.12 nm. Zeta potential 18.83 ± 1.03 mV. $AUC_{(0–8h)}$ 2.34 ± 0.26 µg×h/L, C_{max} 1.04 ± 0.28 µg/mL, and bioavailability improved 6.88-fold as compared to curcumin suspension. Applied in foods and nutraceuticals	[108]
Palmitic acid and cholesterol	High-shear homogenization and ultrasonication technique	50 mg/kg to mice	PS 138.8 ± 7.6 nm. Zeta potential 35.70 ± 1.03 mV. Higher $AUC_{(0–8h)}$ (6.23 ± 0.75 mg×h/mL) and C_{max} (1.21 ± 0.12 µg/mL), longer $t_{1/2}$ (12.26 ± 4.77 h), longer absorption, higher oral bioavailability (23.07%), and enhanced brain distribution. Time-dependent cytotoxic effects on MCF-7 and B16F10 cells	[109]
Miglyol 812N/F	High-pressure homogenization technique	15 mg/kg/day for 5 days in mice	Enhanced curcumin permeation and anti-inflammatory activity. Decreased the intensity of colitis in a murine dextran sodium sulfate induced colitis model	[110]

PS particle size, *HL* Hodgkin's lymphoma, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor-alpha, $t_{1/2}$ elimination half-life, *GMS* glycerol monostearate, *SLN* solid lipid nanoparticles, *NLC* nanostructured lipid carriers, *AUC* area under the concentration–time curve, C_{max} maximum plasma concentration

were incorporated in lower quantities [121, 122]. The nature of the surfactant and cosurfactant significantly influenced the solubilization capacity [123] of the ME for oils and the drug, with ethanol enabling greater oil incorporation, a globule size of less than 30 nm, and significantly enhanced drug solubility [124]. The challenge is to overcome the issues that limit the use of ethanol in formulations. Bioenhancement also varies based on the composition of the ME, and special functionalized MEs have been reported that are tailored to specific end uses. Various curcumin MEs that have been evaluated for oral delivery are compiled in Table 3 [121, 122, 124–126]. Although MEs for use as drug-delivery systems are simple to manufacture and exhibit high physical stability, the large amount of surfactant needed continues to represent a serious limitation [113–115].

Self-microemulsifying drug-delivery systems (SMEDDSs) are dry microemulsions without an aqueous phase that are advantageous for the incorporation of hydrolytically unstable drugs [127]. They provide all the advantages of microemulsions, as they spontaneously form microemulsions in aqueous media. SMEDDSs can be inserted into capsules or converted into solid dosage forms by spray drying, adsorbed onto highly adsorptive solids, and even coated onto pellets or tablets [128, 129]. SMEDDSs of curcumin that were coated onto inert tablet cores as a polymeric advanced third-generation solid dispersion revealed in situ film formation with enhanced solubility and bioavailability of curcumin, and showed promising efficacy in a preclinical model of rheumatoid arthritis [78]. Other studies of curcumin SMEDDSs [51, 78, 130–132] are listed in Table 3.

4.4 Nanoemulsions

Nanoemulsions (NEs) are kinetically stable transparent or translucent dispersions of oil, emulsifier, and water with a globule size of less than 100 nm [133, 134]. Unlike microemulsions, NEs do not form spontaneously; considerable energy is required to generate NEs as the surfactant concentration in them is low. They are also called mini emulsions or ultrafine emulsions [135, 136]. Being emulsions, they also permit the incorporation of hydrophobic and hydrophilic drugs, and, due to the small globule size, they facilitate the bioenhancement of hydrophobic drugs [137, 138]. A number of methods of preparing nanoemulsions have been reported, which differ from ME preparation methods by the substantial energy required. Reported methods of preparing NEs include high-energy emulsification, ultrasonication, high-pressure homogenization, low-energy emulsification, a phase inversion temperature method, a phase inversion composition method, a solvent displacement method, microfluidization, spontaneous emulsification, a solvent evaporation technique, and a hydrogel method [139].

Due to their limited stability and the energy needed to prepare them, relatively few studies on curcumin nanoemulsions have been reported; these are discussed in Table 3 [140–144].

4.5 Polymeric Nanoparticles

Polymeric NPs are solid colloids up to 1000 nm in size that are prepared using either natural or synthetic polymers that may or may not be biodegradable [145, 146]. Based on the distribution of the drug within the polymer, they are referred to as either nanocapsules (wherein the drug is within the cavity surrounded by a polymer coating) or nanospheres (where the drug is dispersed homogeneously in a polymeric matrix) [147, 148]. NPs show increased reactivity, surface area, sensitivity, and stability compared to liposomes [149]. Their high membrane permeability (due to their tiny size) as well their ability to target specific organs make them attractive drug carriers [150].

Among the approaches used to prepare drug-loaded NPs, nanoprecipitation is the simplest. This method is based on the precipitation of drug-loaded polymeric particles from an organic solution in aqueous media. Other methods include solvent evaporation, emulsion solvent diffusion, emulsion solvent evaporation, electrospraying, and nano spray drying [151–153]. Green techniques based on ultrasonication and microwaves are also reported [154, 155]. Polymeric NPs favor the attachment of ligands for targeted drug delivery [1, 156].

Polymeric NPs are the most studied nanosystems for curcumin bioenhancement. They are made from natural or synthetic polymers that may also be biodegradable [157]. Various methods of preparation are reported, which generally depend on the polymer used. Such polymers include bovine serum albumin–dextran [158], caseinate-zein polysaccharide [159], chitosan-zein [160], chitosan [161–164], *Enteromorpha prolifera*-based chitosan [165]. Eudragit® RLPO [166], genipin-crosslinked caseinate [167], Gantrez™ [1, 156], lysozyme *Artemisia sphaerocephala* Krasch-seed polysaccharide [168], poly(lactic-*co*-glycolic acid) (PLGA) [34, 73, 169–173], rice bran albumin [174], saponin coating [175], serratiopeptidase [176], sodium alginate and cationized gelatin [177], and Soluthin MD® [178].

These curcumin NPs have been evaluated not only for bioenhancement but also for various therapeutic activities in vitro and in vivo. A brief summary of the large number of published studies on curcumin NPs is provided in Table 4.

4.6 Miscellaneous Nanosystems

Other nanosystems have also been explored for oral curcumin delivery, albeit to a limited extent. They are discussed in this section.

Table 3 Summary of emulsion-based lipidic nanosystems of curcumin

Type of formulation	Method of preparation	Dose	Outcomes	Reference(s)
Microemulsions	Oil titration method	1 mg/kg to rats	Globule sizes < 20 nm, with improved stability. Faster and higher ex vivo curcumin permeation through nasal mucosa of sheep. A 3.24-fold enhancement of curcumin AUC in the brain compared to intravenous curcumin, $AUC_{(0–24h)}$ (4953.11 ± 194.8 ng × h/g) and C_{max} (400.982 ± 27.8 ng/g), with a 1553.18% increase in brain bioavailability. Intranasal administration revealed a 5.1-fold enhancement of $AUC_{0–24}$ and relative bioavailability for curcumin in brain with curcumin–docosahexaenoic acid ME compared to curcumin solution	[121, 122]
	Pseudo-ternary phase diagrams	–	Globule size < 30 nm. 10,000-fold increase in aqueous solubility compared to an aqueous solution of curcumin. Increases in curcumin permeation of 10% after 6 h and around 70% after 24 h	[124]
	Water titration	200 mg/kg to rats	Droplet size 27.3 nm. A 4.5-fold higher AUC (690.49±150.05 mg × min/mL), 4.3-fold greater C_{max} (3570 ± 1180 ng/mL), and 22.6-fold increase in bioavailability compared to curcumin suspension	[125]
	Water titration	24 mg/kg to rats	Droplet size 51.24±1.45 nm with zeta potential −4.17 ± 0.53 mV. A 9.6-fold enhancement in bioavailability with an approximately tenfold increase in $AUC_{(0–t)}$ (180.97 ± 2.71 ng × h/mL) and a 12.3-fold greater C_{max} (66.19 ± 4.43 ng/mL) compared to curcumin suspension	[126]
SMEDDSs	Spray drying	25–100 mg/kg to rats	Droplet size 147 ± 5.8 nm. AUC increased by 7.6 times (282.54 ± 61.37 ng × h/mL) and C_{max} 4.6 times (155.56 ± 18.34 ng/mL)	[51]
	Simplex lattice	50 mg/kg to mice	PS 21 nm. Absorption via passive transfer diffusion across the lipid membranes of rat intestine. 3.86 times higher oral absorption of curcumin compared with its suspension	[130]
	Water titration method	50 mg/kg to rats	Enhanced solubility, absorption, and 16-fold higher bioavailability. 14-fold higher absorption with a 13.93 times greater AUC and a 17.52-fold higher C_{max} than free curcumin	[131]
	Water titration method	200 mg/kg to mice	Droplet size 32.9 ± 19.3 nm. Approximately 12.7-fold higher $AUC_{(0–\infty)}$ (277.06 µg × h/L), 3.1-fold increased C_{max} (196.56 µg/L), and 12.73-fold higher bioavailability than curcumin suspension	[132]

Table 3 (continued)

Type of formulation	Method of preparation	Dose	Outcomes	Reference(s)
Advanced third-generation Cur-SMEC-SD	Water titration method	50 mg/kg to rats	Globule size ~ 100 nm. $AUC_{(0-t)}$ 19.05 μg × h/mL, $AUC_{(0-\infty)}$ 22.21 μg × h/mL, C_{max} 5.02 μg/mL, with a 413.82% bioenhancement compared to free curcumin and a twofold increase compared to curcumin SD without SMEC. Enhanced stability for 6 months. Inhibition of paw volume compared to plain curcumin and curcumin SD, demonstrating enhanced efficacy. High efficacy of ~ 80% compared to standard treatment with indomethacin in rheumatoid arthritis	[78]
Nanoemulsions	Phase inversion temperature technique	–	An improved 2-month storage stability and high solubility for curcuminoids. Droplet size decreased as the concentration of surfactant increased	[140]
	Precipitation	197 mg/kg to mice	PS 218 nm, with classic digestion-diffusion permeation mechanism by Caco-2 cell monolayers. $AUC_{(0-\infty)}$ 210 μg × min/mL) C_{max} 29.9 ± 5.1 μg/mL, and a ninefold increase in oral bioavailability	[141]
	–	1800 mg/kg to mice	A 40-fold increase in C_{max} and a 10.5-fold improvement in oral bioavailability. Decreased toll-like receptor-4 and receptor advanced glycation end-product protein expression, decreased blood monocytes, inhibited secretion of monocyte chemoattractant protein-1, and suppressed inflammation	[142, 143]
	High-pressure homogenization	–	Droplet size 106.1 nm. TNF-α and IL-6 gene expression was downregulated in lipopolysaccharide-stimulated Caco-2 cells at 4.2 mg/mL. Transforming growth factor-beta 1 was upregulated and there were no changes in the mRNA levels of IL-10 and IL-8 compared to untreated cells	[144]

PS particle size, *ME* microemulsion, *Cur-SMEC-SD* curcumin self-microemulsifying composition solid dispersion, *SMEC* self-microemulsifying composition, *IL-6* interleukin 6, *IL-8* interleukin 8, *IL-10* interleukin 10, *TNF-α* tumor necrosis factor-alpha, *mRNA* messenger RNA, *SMEDDSs* self-microemulsifying drug-delivery systems, *TPP* tripolyphosphate, *AUC* area under the concentration–time curve, C_{max} maximum plasma concentration

4.6.1 Inorganic Nanoparticles

In recent years, inorganic nanoparticles have gained considerable attention in relation to diagnostic and therapeutic applications, mainly for cancer. Inorganic nanoparticles include, for example, nanometer-sized quantum dots, manganese phosphate nanoparticles, noble metals, carbon nanotubes, silica nanoparticles, and magnetic nanoparticles [179, 180], and they possess unique size-dependent physical properties such as optical and electrical effects, an efficient contrasting effect, and magnetism. They also have good microbial resistance and good storage properties [181, 182]. However, even though curcumin inorganic NPs have the potential to be used in various important applications, no study of their possible utilization for oral bioenhancement has been reported.

4.6.2 Micelles

Micelles are aqueous dispersions of self-assembled aggregates of surfactant or block copolymer molecules in the size range 5–100 nm [183, 184]. They are formed when the concentration of block copolymer is above the critical micellar concentration in aqueous solution [185, 186]. Micelles can form through simple dissolution, dialysis, o\w emulsion, solvent evaporation, and lyophilization [187]. Adequate loading of hydrophobic drugs such as curcumin into micelles is a challenge, as is ensuring that the resulting micelles are safe,

Table 4 Summary of polymeric nanosystems of curcumin

Polymer	Method of preparation	Dose	Outcomes	Reference(s)
Bovine serum albumin–dextran	Lyophilization method	–	PS < 200 nm with a spherical structure. Resistant to pH change. A low EC_{50} of 3.27 µg/mL in Caco-2 cells and high cellular antioxidant activity compared to curcumin	[158]
Caseinate-zein polysaccharide	Electrostatic adsorption	–	Excellent water redispersibility with significantly higher antioxidant activity than curcumin	[159]
Chitosan-zein	Electrospraying process	–	PS 550 nm, approximately 50% reduction in neuroblastoma cell viability at 10–25 mg/mL. Concentration-dependent cytotoxicity towards SH-SY5Y neuroblastoma cells	[160]
Chitosan	Ionotropic-gelation method	–	Enhanced uptake and fourfold enhancement in cytotoxic activity at 3.12 µg/mL in HeLa cells. DNA damage, cell-cycle blockage, and higher reactive oxygen species levels suggest that anticancer activity is induced through apoptotic pathways	[161]
	Ionic gelation method	–	PS 214 ± 1.0 nm. Slowest release observed at a chitosan:TPP weight ratio of 3:1, with 36% retention at the end of 6 h. Capacity for mucoadhesion and can deliver curcumin at the colon site	[162]
	Emulsion	–	PS 98.8 nm. Higher biocompatibility towards healthy VERO (African green monkey kidney) cells at 158 ± 7 µg/mL, minor cytotoxicity towards SiHa human cervical tumor cells	[163]
	Ionic gelation	10 mg/kg and 50 mg/kg to rats	PS 629.5 ± 20.5 nm with zeta potential − 6.06 ± 1.22 mV. 13-fold enhancement in aqueous solubility (56.6639 µg/mL). 48.79 times higher pharmacological availability in blood. Also enhanced antiproliferative action towards the C6 cell line, with potent antioxidant activity	[164]
Enteromorpha prolifera-based chitosan	Electrostatic complexation	–	PS 230–330 nm. Enhanced solubility, stability and bioavailability, higher cellular uptake, anticancer activity at 10 and 20 µg/mL against B16F10 cells. Exhibited concentration-dependent cytotoxicity	[165]
Eudragit® RLPO	Emulsion-solvent evaporation and freeze drying	–	Good aqueous redispersibility, compatible with intestinal Caco-2 cells. Rapid curcumin release over 60 min, improved oral bioavailability of curcumin	[166]
Genipin-crosslinked caseinate	Mixing	–	PS 272.9 ± 13.1 nm. Released by passive diffusion. Good stability over a wide pH range. Enhanced cellular uptake in a human cervical cancer HeLa cell line. Enhanced anticancer activity at 10 mg/mL in HeLa cells	[167]

Table 4 (continued)

Polymer	Method of preparation	Dose	Outcomes	Reference(s)
Gantrez™	Nanoprecipitation	200 mg/kg to rats	PS 532.2 ± 15.2 nm. $AUC_{(0–inf)}$ 4439.6 ± 92.5 ng × h/mL and C_{max} 61.3 ± 22.3 ng/mL with 117% higher bioavailability	[1, 156]
Lysozyme *Artemisia sphaerocephala* Krasch-seed polysaccharide	Electrostatic interaction	20 mg/kg to mice	PS 88.8 ± 22.3 nm. Excellent stability, biocompatibility, and biodegradability. High curcumin serum levels. Enhanced cytotoxicity towards HepG2 cells compared to free curcumin	[168]
PLGA	In situ method	–	PS 200 nm. Rapid and high uptake by the RAW 264.7 macrophage cell line, suggesting its suitability for treating intracellular infections	[73]
	Single emulsion solvent evaporation	5 mg/dose (350 µg) to mice	PS 495 nm. Three- to fourfold greater brain concentration and better bioavailability. Similar effect to native curcumin, even at a 15-fold lower concentration, in overcoming inflammation and neurological symptoms and avoiding blood–brain barrier breakdown. Showed greater inhibition of the sequestration of $CD8^+$ T cells in the brain and parasitized red blood cells and enhanced IFNγ levels compared to curcumin alone	[169]
	Emulsion technique	50 mg/kg	A ninefold improvement in oral bioavailability, reduced glucose levels in diabetic rats, significantly reduced inflammatory cytokine levels, and inhibited 8-oxo-2′-deoxyguanosine in pancreatic tissue	[170]
	Emulsion diffusion-evaporation technique	250 mg/kg to rats	PS 264 nm. Ninefold enhancement in oral bioavailability compared to curcumin-piperine suspension	[171]
	Emulsion solvent-evaporation method	50 mg/kg to rats	PS 155 nm. A 55.4-fold increase in oral bioavailability compared to curcumin aqueous suspension	[172]
	High-pressure emulsification Solvent evaporation	50 mg/kg to rats	PS 158 ± 10 nm. AUC 7.32 ± 0.8 µg × min/mL and C_{max} 0.044 ± 0.004 µg/mL. Higher absorption and 22-fold higher oral bioavailability than conventional curcumin	[173]
	Solvent evaporation	100 mg/kg	PS 200 nm. 640-fold higher aqueous solubility, enhanced permeation, inhibition of P-gp-mediated efflux, and increased intestinal residence time. $AUC_{(0–t)}$ 2066 ± 332 µg × min/mL and C_{max} 6.75 ± 1.54 µg/mL. 5.6-fold (563%) higher bioavailability and a longer half-life than plain curcumin	[34]

Table 4 (continued)

Polymer	Method of preparation	Dose	Outcomes	Reference(s)
Rice bran albumin	Antisolvent precipitation	20 mg/kg to rats	Greater than tenfold increase in oral bioavailability in vivo. 1.60, 1.42, 1.58, and 1.66 times greater antiproliferative activity towards Du145, HepG2, HCT-116, and MCF-7 tumor cell lines, respectively, compared to plain curcumin, as well as higher antioxidant and anti-inflammatory activities.	[174]
Saponin coating	pH-driven loading method	100 mg/kg to rats	PS 52 nm. Zeta potential − 30 mV. 8.9-fold greater bioavailability compared to curcumin. 3.3-fold higher in vitro bioaccessibility	[175]
Serratiopeptidase	Desolvation	–	PS 175 ± 1 nm. Exhibited anticancer properties in MCF-7 and HeLa cell lines through reactive oxygen species production and DNA damage at 156 mg/L concentration. Nanoparticles decreased the level of interleukin 6 (IL-6) but increased the tumor necrosis factor alpha (TNF-α) level in THP1 cell lines. Improved stability and produced a synergistic effect in cancer cells	[176]
Sodium alginate and gelatin	Electrostatic complexation	–	PS 533 nm, zeta potential of − 54 mV. Significantly increased intracellular uptake and anticancer activity towards MCF-7 cells. Nanometric size could favor accumulation in MCF-7 tumor cells through the EPR effect	[177]
Soluthin MD®	High-speed homogenization and lyophilization	50 mg/kg	PS 108 ± 3.4 nm. 55.22-fold higher AUC and 104.797-fold higher C_{max} along with a 130-fold improvement in oral bioavailability. ~ 23-fold reduction in 50% cell growth, significant increase in anticancer efficacy compared to pure curcumin	[178]

PS particle size, *PLGA* poly(lactic-*co*-glycolic acid), EC_{50} half-maximal effective concentration, $CD8^{+}T$ cytotoxic T cell, *IFNγ* interferon gamma, *Du145* human prostate cancer cell line, *HepG2* human liver cancer cell line, *HCT-116* human colon cancer cell line, *MCF-7* Michigan Cancer Foundation 7, *DNA* deoxyribonucleic acid, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor alpha, *THP1* human monocytic cell line, *EPR* enhanced permeation and retention, *P-gp* permeability glycoprotein, *AUC* area under the concentration–time curve, C_{max} maximum plasma concentration

given that they are surfactant-based carriers. Nevertheless, micellar curcumin formulations have been evaluated for oral delivery [188–191], and they are discussed in Table 5.

4.6.3 Solid Nanodispersions

Nanodispersions are nanosized dispersed drug particles that are less than 1 μm in size and generally comprise emulsifying components [192]. They can be self-microemulsifying or even self-micellizing. Nanodispersions are prepared by an emulsification-evaporation method [193], or by other techniques such as melt emulsification or even the solubilization of liquid components in a solid matrix. Their small size, rapid dissolution, and the possible formation of micelles or a ME enables bioenhancement. The few studies that have been reported on nanodispersions [194–196] are reported in Table 5. Despite numerous advantages, nanodispersions of curcumin have not been widely studied, probably because they rely on surfactants for bioenhancement and long-term surfactant toxicity is a concern.

4.6.4 Phytosomes

Phytosomes, also called phytolipids, are phyto-phospholipid complexes that are essentially composed of phosphatidylcholine with polyphenolic compounds [197]. Phytosomes are a patented technology intended for the creation of lipid-compatible molecular complexes with improved absorption and bioavailability of phytochemicals for enhanced therapeutic benefits [198] through enhanced pharmacokinetic and pharmacodynamic effects [199, 200]. The application of phytosomes for the oral delivery of curcumin [201–206] is also discussed in Table 5.

4.6.5 Dendrimers

Dendrimers are nanometric, hyperbranched, monodisperse polymeric materials that are also known as arborols [207, 208]. Dendrimers consist of an initiator core, interior layers of repeating units, and an outermost exterior layer that provides a multifunctional surface for surface chemistry modification and has the advantage of a narrow polydispersity index [209]. Their small size and ability to cross cell barriers via both paracellular and transcellular pathways have made them attractive carriers for nano drug delivery. Table 5 depicts studies of curcumin dendrimers for oral delivery [210–214].

5 Bioenhancement Through Targeting

Targeted delivery of curcumin nanosystems following oral delivery could be enabled by ensuring intact particle uptake through the Peyer's patches (PP) in the GIT. Hydrophobic particles are known to be readily taken up by the Peyer's patches, with particles < 1 μm in size easily transcytosed into the circulation [215, 216]. It has been suggested that to enable such targeting, intact nanoparticles should reach the PP in the intestine; this is a vital prerequisite. Balancing mucoadhesion and hydrophobicity was proposed as one of the strategies to achieve high PP uptake [217]. Other authors have also demonstrated lung targeting using this approach. Designing curcumin nanoparticles for intact uptake through the PP could open up the possibility of exploiting curcumin for targeted delivery to the lungs to act as an anticancer, anti-infective, and anti-inflammatory agent of great promise. This is a nascent field, and these results throw the door open to a myriad of research possibilities.

6 Future Perspective and Conclusion

Curcumin, a wonder nutraceutical, has manifold therapeutic activities and has been extensively studied. This review of the oral bioenhancement of curcumin, which presents the gamut of research efforts in this field, suggests that nanodelivery is a viable approach to overcoming the solubility and permeability challenges associated with BCS class IV drugs such as curcumin. This could provide a huge window of opportunity to harness the drug for various therapeutic needs. Indeed, harnessing safe phytoconstituents such as curcumin through intelligent drug-delivery strategies could open the door to the development of various patient-friendly and safe therapies of major afflictions that affect mankind. One major area that could be explored is the uptake of intact curcumin NPs for targeted delivery to various organs and even tumors.

Table 5 Summary of miscellaneous nanosystems of curcumin

Type of formulation	Method of preparation	Dose	Outcomes	Reference(s)
Micelles	Thin-film dispersed method	–	PS 46 nm. Absorbed through the intestine via passive diffusion. Relative bioavailability of curcumin in micelles compared to curcumin suspension was 927.3%	[188]
	Solvent evaporation method	–	PS 188 ± 3 nm. Threefold increase in cytotoxicity and 55-fold enhancement in oral bioavailability compared to curcumin alone	[189]
	Ultrasonic cavitation	–	PS 19.99 nm. Curcumin:water and surfactant:water weight ratios were 0.7 and 0.11, respectively	[190]
	–	–	More than 20,000-fold increase in water solubility and greater stability in basic pH and light. Improved dissolution and increase in permeation across everted sacs of rat small intestine. 117-fold improved oral bioavailability compared to curcumin suspension	[191]
Solid nanodispersions	Simple mixing method	340 mg/kg to rats	PS 158–610 nm. Improved oral bioavailability compared to suspension. Higher stability at physiological temperature	[194]
	–	150 mg/kg to rats	PS 85.40–135.3 nm. Enhanced membrane permeability. A 19-fold oral bioenhancement compared to free curcumin. Higher cytotoxic activity against glioblastoma U-87 MG cells compared to curcumin	[195]
	Solvent diffusion-evaporation method	–	Spherical particles with good storage stability under ambient conditions. Sustained release profile over 72 h with the Higuchi model	[196]
Phytosomes	–	360 mg/kg	5.6-fold higher AUC (26.7 μg × min/mL), 29-fold higher absorption, and higher curcumin accumulation in liver	[201–203]
	–	–	Curcumin naringenin combination exhibited higher antioxidant activity with an extended duration of action	[204–206]
Dendrimers	–	–	No cytotoxicity towards the T47D breast cancer cell line. Reduced cancer proliferation and increased telomerase inhibition	[210]
	–	–	Improved aqueous solubility and bioavailability with C_{max} 90 ng/mL, and showed tumor-targeting efficacy against different cancer cell lines such as human malignant glioma cell line U-251, breast cancer cell line MDA-MB-231, HNSCC cells, and HPV-negative and HPV-positive cervical carcinoma cell lines. G3-curcumin dendrimers were internalized by U-251 glioma cells, specifically within nuclei	[211]
	–	–	Exhibited both cytotoxic activity and improved water solubility. Induced cytotoxicity against SKBr3 and BT549 human breast cancer cells, and induced cellular apoptosis based on caspase-3 activation	[212]
	–	–	Polyamidoamine curcumin dendrimer downregulated and inactivated the activity of telomerase and induced apoptosis with dose-dependent cytotoxicity in a breast cancer cell line	[213]
	–	–	Treatment of MDA-MB231, MCF7, and SKBr3 breast cancer cells led to increased expression of tumor suppressor candidate 7 (RNA gene) and GAS5 (non-protein-coding RNA), significantly reduced apoptosis, and superior membrane penetration compared to dendrosomal curcumin. The antitumor properties of dendrosomal curcumin were enhanced in the presence of GAS5	[214]

PS particle size, *HNSCC* head and neck squamous cell carcinoma, *MDA-MB-231* epithelial human breast cancer cell line, *HPV* human papillomavirus, *SKBr3* breast cancer cell line, *BT549* human breast cancer cell line, *RNA* ribonucleic acid, *GAS5* growth arrest-specific 5, *AUC* area under the concentration–time curve, C_{max} maximum plasma concentration

Compliance with Ethical Standards

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