Review Article

Nanotechnologies for Curcumin: An Ancient Puzzler Meets Modern Solutions

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Curcumin, a low-molecular-weight natural polyphenol mainly found in the plant *Curcuma longa* (turmeric), is widely used as a food colorant and as a potential protective agent against several chronic diseases including cancer, HIV-infection, neurological, cardiovascular, and skin diseases. Moreover, evidences from long-term use process and preclinical trials have demonstrated low toxicity of curcumin, even at relatively high doses. However, it has been well known that the application of curcumin was limited owing to its water insolubility, instability, and poor bioavailability. For decades, many attempts have been made to compensate for these disadvantages, with the development of improved delivery platforms as the feasible approaches. The past ten years witnessed the encouraging progress in the use of nanoscale drug delivery systems on curcumin such as loading curcumin into liposomes or nanoparticles, forming self-microemulsifying drug delivery systems (SMEDDS), cyclodextrin inclusions, and solid dispersions, as well as the latest reported technologies such as nadodisks and nanotubes. This paper summarizes the recent works on the design and development of nanoscale delivery systems of curcumin, with the goal of harnessing the true difficulties of this multifunctional agent in the clinical arena.

1. Introduction

Curcumin (Figure 1), an active constituent mainly derived from *Curcuma longa* (turmeric), is a natural yellow-orange polyphenol which has been used for its medicinal benefits for centuries [1, 2]. Curcumin was firstly extracted in impure form in 1815, then in 1870 the pure crystalline state was prepared. Almost three decades later, its composition was finally elucidated as 1, 6-heptadiene-3, 5-dione-1, 7-*bis*-(4-hydroxy-3-methoxyphenyl)-(1E, 6E) [3–6]. In China, curcumin has been used as a part of herbal medicine for centuries to alleviate throbbing pain in the chest and hypochondriac region, mass in abdomen, and pain of the shoulder due to win-cold or traumatic injuries. The accumulating of experimental and clinical evidences indicates that curcumin has a variety of pharmacological activities, such as antitumor, antiinflammatory, antivirus, antioxidation, anti-HIV, and low toxicity [7–11].

However, good things never come easy. Applicational advancement of curcumin has been hindered by its water insolubility, degradation at alkaline pH, and photodegradation and thus extremely low bioavailability in both vascular and oral administration [12, 13]. Therefore, many approaches have been investigated, including synthetic analogues, chemical modification to prodrugs, combined with other dietary components and using nanoscale drug delivery systems to overcome deficiencies.

Among these methods, nanoscale drug delivery systems have become a source of concern for many researchers in the domain of tradional Chinese medicine (TCM). Many successful examples of the combination of nanotechnology and TCM have been reported. Due to the surface effect, small size effect, quantum size effect, and quantum tunnel effect of nanoparticles, nanoscaled TCM has produced some new outcomes. For instance, xionghuang (realgar), a famous TCM, has been identified as an effective antitumor agent. When
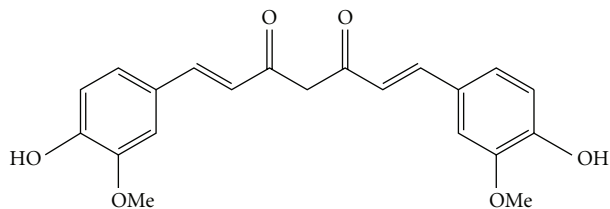
FIGURE 1: Chemical structure of curcumin.

fabricated into nanoscale, the apoptosis rate of the tumor cells was markedly increased [14]. Furthermore, nanotechnologies disrupt the cell membrane and thus release the trapped materials. Take Ganoderma lucidum (Lingzhi) for example, the immune function could be evidently enhanced after nanoscale processes [15].

Consequently, a good understanding of nanotechnologies is necessary for the advancement of curcumin with higher efficacy. To date, many studies have focused on loading curcumin into liposomes or nanoparticles, forming self-microemulsifying drug delivery systems (SMEDDS), cyclodextrin inclusions, and solid dispersions [16–18], and much progress has been made in the past ten years. The purpose of this paper is to provide an updated summary of the applications of novel delivery systems of curcumin.

2. Liposomes

Liposomes (Figure 2) are closed spherical vesicles consisting of a lipid bilayer that encapsulates an aqueous phase in which drugs can be stored [19]. Possessing the advantages of high biocompatibility, easy preparation, chemical versatility, and simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components, liposomes as a drug delivery system have been used to improve the therapeutic activity and safety of drugs for many years [20].

By the same token, liposomes have found wide application in ameliorating curcumin's bioavailability and efficacy; indeed, various modifications of liposomal curcumin have been developed such as polymeric conjugation on the liposome surface to acquire better clinical outcomes [4, 17–26]. The exploration disclosed an effective method for the preparation of curcumin-loaded liposomes using sonication at an average size of 100–150 nm [22]. Exclusion chromatography was used to remove the unentrapped curcumin. *In vitro* tests showed that treatment of liposomal curcumin (5–10 μM) for 24–48 h at 37°C resulted in at least a 70–80% inhibition of cellular proliferation without affecting their viability, which was approximately 10-fold higher versus free curcumin.

3. Nanoparticles

Nanoparticles (NPs), which are particles ranging in size from 1 to 100 nm, possess distinct physical and chemical properties that can be exploited for drug delivery [19]. Encapsulating drugs within NPs can improve the solubility and pharmacokinetics of drugs and sometimes enable targeting and

slow release. Generally, nanoparticles' carrier materials can be divided into synthetic biodegradable high molecular polymers (polyvinyl alcohol, polylactic acid, etc.) and natural polymers (proteins, polysaccharides, etc.) [27]. Among the various nanodrug systems, polymer NPs, solid lipid NPs, magnetic NPs, polymer micelles, and albumin NPS are the five ones that are widely applied and intensively studied on curcumin.

3.1. Polymer Nanoparticles. Due to the small size and excellent biocompatibility, nanosized polymer nanoparticles can circulate in the bloodstream for a longer time; thus, specific therapy can be achieved [28]. The widely researched synthetic polymers include chitosan [29, 30], poly(D,L-lactide-co-glycolide) (PLGA) [31–33], and PEG. In addition, other carrier materials such as poly(butyl)cyanoacrylate [34], silk fibroin [35], N-isopropylacrylamide (NIPAAM) [36], and hydrophobically modified starch [37] have also shown a high potential for solving the problems of curcumin.

PLGA and a stabilizer polyethylene glycol- (PEG-)5000 were employed to form a nanoparticulate curcumin formulation with 97.5% efficiency encapsulation and 80.9 nm particle diameter [32]. The result of an *in vitro* experiment demonstrated that curcumin-loaded PLGA NPs enhanced cellular uptake and increased bioactivity in inducing apoptosis and suppressing proliferation of tumor cells. The nanoparticulate formulation also showed better bioavailability and had a longer half-life than free curcumin in mice. Moreover, polymers can be combined to form copolymers, which could be a promising drug carrier. For example, the PLGA-PEG-PLGA triblock copolymers prepared using the solvent-dialysis method could encapsulate hydrophobic curcumin, which indicated good pharmacokinetic profiles [38].

3.2. Solid Lipid Nanoparticles (SLNs). SLNs are made of natural or synthetic lipid or lipoid, such as lecithin and triglycerides, which are solid at human physiological temperature [39]. SLNs present many potential advantages. For example, they protect labile compounds from chemical degradation, provide sustainedrelease to improve the availability of the drug, and target the effect to improve the efficiency of the drugs [40].

Kakkar et al. [41] prepared curcumin-loaded solid lipid nanoparticles (C-SLNs), with an average particle size of 134.6 nm and a total drug content of 92.33 ± 1.63%, using the microemulsification technique. *In vivo* studies demonstrated significant improvement in bioavailability after administration of C-SLNs at all the doses other than free solubilized curcumin. In another study, transferring-mediated solid lipid nanoparticles containing curcumin were recently fabricated [42], and the potential of enhancing the anticancer effect of curcumin in breast cancer cells *in vitro* was confirmed.

3.3. Magnetic Nanoparticles. Magnetic drug targeting, in which a drug is conjugating with a magnetic material under the action of the external magnetic field, is an important drug delivery system. Drug-loaded magnetic nanoparticles
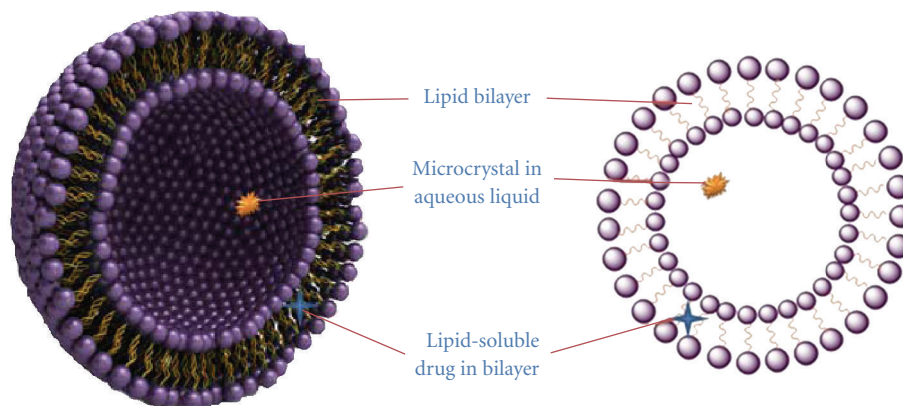
Figure 2: Structure of liposomes.

can accumulate in target tissue areas under the action of the external magnetic field; the drug then releases from the particles in a controllable way [43].

A nanosized magnetofluorescent water-dispersible Fe_3O_4-curcumin conjugate with chitosan or oleic acid as its outer shell and entrapped curcumin was designed [44]. The Fe_3O_4-curcumin conjugate exhibited a high-loading cellular uptake that was distinctly observed by magnetic and fluorescent methods and was also shown to be a good candidate for a dual (optical and magnetic) imaging probe.

3.4. Polymer Micelles. Another feasible approach to figuring out a way to solve the poor solubility, stability, and bioavailability of curcumin is to encapsulate it within micelles [45, 46]. Recently, polymeric micelles have gained attention as an excellent delivery system for poorly water-soluble drugs due to their high drug-loading capacity, high water-solubility, low toxicity, and appropriate size (<200 nm) for long circulation in the blood [45, 47, 48].

For example, Leung et al. [49] investigated encapsulation of curcumin in cationic micelles composed of surfactants cetyl trimethylammonium bromide (CTAB) or dodecyl trimethylammonium bromide (DTAB). Data showed that alkaline hydrolysis of curcumin is greatly curbed with the aid of either CTAB or DTAB micelles. Along the same lines, amphiphilic block copolymer micelles of poly(ethylene oxide)-b-poly(epsilon-caprolactone) (PEO-PCL) as vehicles for curcumin were also reported [50]. The author believed that PEO-PCL micelles as an injectable formulation can effectively solubilize, stabilize, and control the release of curcumin.

3.5. Albumin Nanoparticles. The possibility of loading a fair amount of active components of poor aqueous solubility is an issue of common concern. Albumin is the body's natural carrier of hydrophobic molecules, such as fatty acids, hormones, and fat-soluble vitamins [51]. Albumin has been extensively investigated as a drug carrier due to its nontoxicity and nonimmunogenicity [52]. Furthermore, albumin possesses good solubility in both water and ethanol, which provide a specific capacity for enhancing the solubility of curcumin. Novel curcumin-loaded human serum albumin nanoparticles (CCM-HSA-NPs) with a narrow size distribution in the 130–150 nm range were prepared [52].

The CCM-HSA-NPs showed a much greater water solubility (300-fold) than free curcumin and experienced negligible activity loss during storage [52]. The amounts of curcumin in tumors, vascular endothelial cell binding of curcumin, and transport of curcumin across a vascular endothelial cell monolayer after treatment with CCM-HSA-NPs were increased 14-, 5.5-, and 7.7-fold beyond that achieved by free curcumin. Furthermore, *in vivo* antitumor tests revealed that CCM-HSA-NPs had a better therapeutic effect than free curcumin without leading to toxicity.

4. Microsphere and Microcapsule

When a pharmaceutical agent is encapsulated within or dispersed in polymer materials, drug safety and efficacy can be greatly improved and new therapies are possible. Given the protection and selective permeation properties and organ-targeted release feasibility, microspheres and microcapsules are broadly applied not only in the food-making and cosmetics industry, but also in pharmaceutical fields such as drug delivery recently. Thus, a series of natural active ingredients, such as ptothecin, zedoary oil, rutin, and andrographolide, have been made into microspheres or microcapsules [28].

Many researchers have made some attempts to deliver curcumin by microspheres or microcapsules [53–57]. The fabrication of microcapsules using a layer-by-layer (LbL) approach with curcumin demonstrated that curcumin can be accumulated in hollow microcapsules with polyelectrolyte multilayer shells $(PSS/PEI)_6$ [55]. Bioactivity of the released drug is evaluated by cytotoxicity studies using L929 cell lines. The new formulation was found to be cytocompatible while the extract of capsules loaded with curcumin showed severe cytotoxicity on the mouse fibroblast cell, indicating that the released curcumin is active. In addition, the high stability of polyelectrolyte microcapsules in the aqueous medium indicates that these drug carriers are suitable for drug delivery applications.

5. Microemulsion

Microemulsions are isotropic dispersions consisting of oil and water stabilized by an interfacial film of surfactant molecules, typically in conjunction with a cosurfactant. Due to their extremely small emulsion droplet sizes in the range of 50 to 200 nm, which are much smaller than conventional emulsions ranging from 1 to 100 μm, microemulsions as a lipid-based delivery system possess many advantages, including high solubilization potential, thermodynamic stability, improved drug dissolution and surfactant-induced permeability enhancement [58, 59]. Among various drug delivery systems, the microemulsion system is considered to be an ideal alternative for hydrophobic drugs such as curcumin.

A number of studies have recently been published about the preparation methods, evaluation and pharmacokinetics profiles of curcumin microemulsions [16, 58, 60–62]. Using medium chain triacylglycerols as the oil and Tween 20 as emulsifier, O/W emulsions with mean droplet sizes ranging from 618.6 nm to 79.5 nm have been successfully prepared using high-speed homogenization at 24,000 rpm and high-pressure homogenization at 1500 bar [58]. A 12-O-tetradecanoylphorbol-13-acetate-induced [63] mouse ear inflammation model was built to estimate the activity of curcumin nanoemulsion. A 43% or 85% inhibition effect of edema of mouse ear exists for 618.6 nm and 79.5 nm 1% curcumin nanoemulsions, respectively, while the oral administration of 1% curcumin in Tween 20 water solution shows little or no inhibition effect.

Self-microemulsifying drug delivery systems (SMEDDS) have recently emerged as one of the most interesting approaches to improving the solubility, dissolution, and oral absorption for poorly water-soluble drugs [64]. Setthacheewakul et al. [60] successfully developed a new SMEDDS to improve the solubility and oral absorption of curcumin. A simplex lattice experiment design was used to optimize the formulation of SMEDDS: 57.5% surfactant (emulsifier OP: Cremophor EL = 1 : 1), 30.0% cosurfactant (PEG 400), and 12.5% oil (ethyl oleate), which showed a significant improvement of solubility of curcumin (21 mg/g). The results of an oral absorption experiment in mice demonstrated that SMEDDS could obviously increase the oral absorption of curcumin compared with its suspension.

6. Cyclodextrin Inclusion

Cyclodextrins (Figure 3) are cyclic oligosaccharides with a hydrophilic outer surface and lipophilic central cavity. Three types of cyclodextrins exist: α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin which are composed of six, seven, and eight α-(1,4)-linked glycosyl units, respectively [65]. Due to the advantages of accessibility and lowest-price, β-cyclodextrin is generally the most useful. Possessing a special ability of enabling drugs to increase water solubility, reduce bitterness, enhance stability, and improve bioavailability, cyclodextrins have been used extensively in pharmaceutical research and development [66, 67].
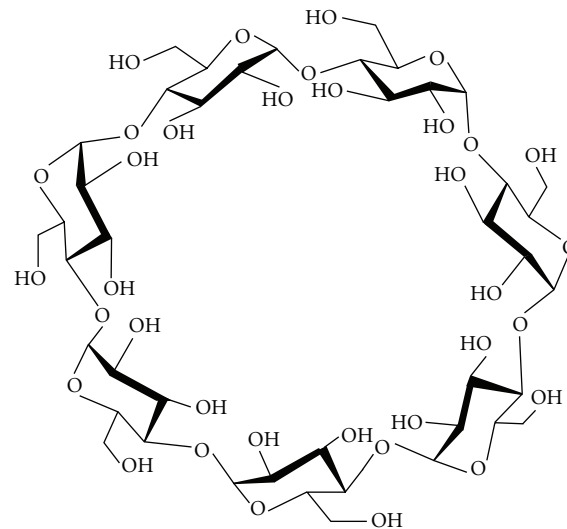

Figure 3: Chemical structure of β-cyclodextrin.

Recently, a growing body of experimental evidence has suggested potential significance in exploring the cyclodextrin carrier properties for the delivery of curcumin [68–72].

In order to explore the cyclodextrin carrier properties for the delivery of curcumin, a self-assembly of β-cyclodextrin and curcumin was prepared via inclusion complexation using a solvent evaporation technique [70]. This study demonstrated that curcumin was efficiently encapsulated in β-cyclodextrin cavities and the developed self-assemblies were confirmed by spectroscopy (FTIR, ^{1}H NMR), thermal studies (DSC and TGA), X-ray diffraction, and microscopic studies (SEM and TEM). In addition, the β-cyclodextrin-curcumin inclusion complex showed an improved uptake in DU145 cancer cells and greater potent therapeutic efficacy in prostate cancer cells compared to free curcumin.

In addition, a novel cyclodextrin complex of curcumin (CDC) was manufactured through a pH shift method using a highly alkaline solution for curcumin dissolution and contacting with hydroxypropyl-γ-cyclodextrin (HPγCD) [69]. These aqueous curcumin formulations have about 100-fold greater curcumin concentration than previously described cyclodextrin complexes of curcumin, and their stability is remarkably improved. *In vitro* tests demonstrated that CDC had more potential compared with free curcumin for cellular uptake and for antiproliferative and anti-inflammatory activities.

7. Solid Dispersion

In 1971, solid dispersion was defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting (fusion), solvent, or melting-solvent methods [73]. In recent years, increasing attention has focused on solid dispersion systems, finding that they can increase bioavailability of poorly water-soluble drugs such as curcumin [74–77].
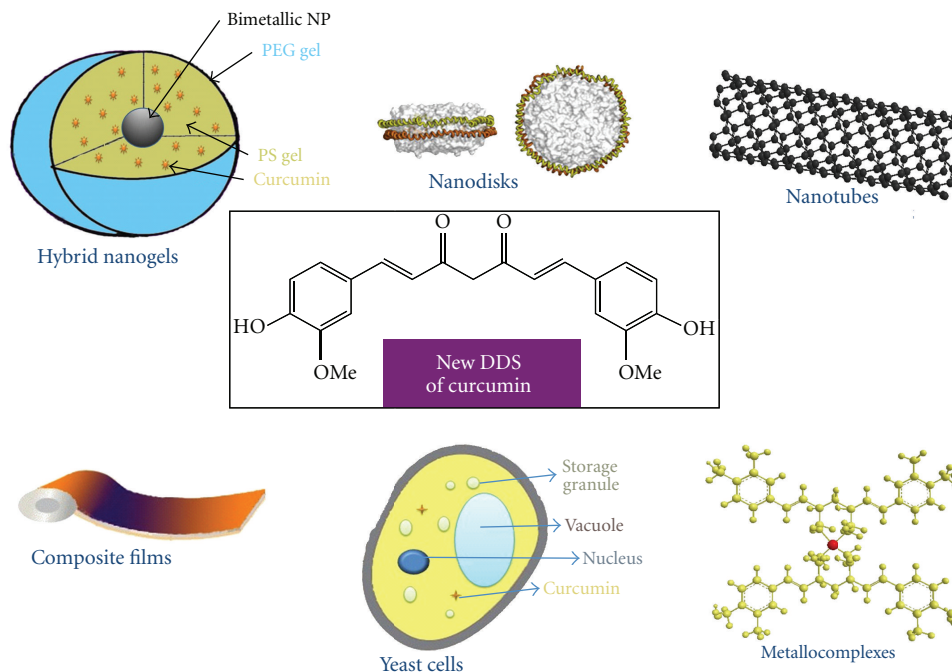
FIGURE 4: Most recent DDS of curcumin.

Crystal and amorphous solid dispersions have also been designed by wet-milling and subsequent freeze-drying with the aim of improving physicochemical and pharmacokinetic profiles of curcumin [78]. The mean particle size of curcumin was identified to be ca. 250 nm, with a small polydispersity index in crystal solid dispersion, compared to crystalline curcumin, the authors demonstrated that the rapid dissolution/dispersion behavior and oral bioavailability increased by 12- and 16-fold, respectively.

8. Miscellaneous Novel Delivery Systems

Researchers have also tried other ways to improve the biological activity of curcumin (Figure 4). The application of these techniques offered new research direction and a visual field for solving the limitations of curcumin.

A class of unique hybrid nanogels was designed to improve the therapeutic efficacy of curcumin [79]. These formulations with high drug-loading yields are claimed to be well suited for *in vivo* studies and clinical trials. Several metallocomplexes of curcumin have been synthesized, characterized, and evaluated for various biological activities. Barik et al. [63] reported that a 1 : 1 complex of copper with curcumin exhibited SOD activity and *in vitro* antioxidant activity. Nadodisks (NDs) represent a potentially novel means to deliver curcumin effectively. NDs are disk-shaped phospholipid bilayers whose edge is stabilized by apolipoproteins, they may have particular *in vivo* therapeutic applications due to their nanoscale size and ability to solubilize curcumin [80]. Paramera et al. [68] evaluated the stability of yeast cell-encapsulated curcumin in regard to environmental factors such as light, humidity, and heat. They found that yeast cells significantly protected curcumin from the detrimental effects of light, as well as from oxidative degradation at elevated relative humidity.

In addition, curcumin-loaded films were prepared using biodegradable ploymer (PLGA) and *in vitro* tests indicated that the curcumin-loaded films have better anticoagulative effects than PLGA. Recently, a combination of nanotubes and curcumin also are in application in the chemical industry [81].

9. Problems and Prospects

Since the discovery of the enhanced drug permeation and retention effect in the 1980s, the advancements in the nanotechnology are widely penetrating to the field of life sciences. We should be thankful that the nanotechnologies bring a real innovation for cracking many medical science hard nuts. An ideal nanoscale agent enables drug arrivals and acts preferentially at the selected target, hence the therapeutic effect could be markedly improved. Undoubtedly, curcumin, an excellent representative derived from traditional Chinese medicine, has been proven effective in long-term use and preclinical trials. Therefore, it is of great significance to overcome the current limitations of curcumin. In past decades, researchers have made real strides in the inhibition of nanotechnologies

on curcumin, but we should also be soberly aware that some problems still remain.

Curcumin liposome formulations are known to improve bioavailability and efficacy and reduce toxicity, but no tissue specificity is associated with the liposomes. After entering the body, liposomes are rapidly taken up by the reticuloendothelial system in the liver and spleen, leading to a short circulation time. Therefore, developing effective modifications of liposomes such as polymeric conjugation on liposome surface becomes essential to acquire better clinical outcomes. Furthermore, efficacious and simple as they are, microemulsions also contain multiple surfactants, which leads to inevitable toxicity. Thus the choice of the surfactants is critical for the formulation of microemulsions. Additionally, most of the proposed formulations were derived from synthetic polymers: long-period employments of these excipients can achieve temporary increased solubility and bioavailability, but potential harms may occur. The search for excipients has been an important part of the current pharmaceutical research and this trend seems irresistible.

Taken together, there is no doubt that development of novel delivery systems of curcumin with better curative effects will be critical for future development of curcumin as a therapeutic agent. We strongly believe that a desired preparation will not only load and keep the drug stable, but will also exactly deliver the drug to candidate cells to enhance the therapeutic effect and reduce the toxicity to normal cells. This is an arduous and complex job: only by multidisciplinary cooperation can we bring this promising natural medicine to the forefront of therapeutic agents for cancers and other diseases.

Acknowledgment

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