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The Nanoformulations of Curcumin for Cancer Therapy: New Perspectives

Aisha H. Al-Shehri[1], Ahmed M. Kabel[2,3,*], Maaly A. Abd Elmaaboud[2]

[1]King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia
[2]Pharmacology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[3]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
*Corresponding author: ahmed.kabal@med.tanta.edu.eg

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Abstract Curcumin is a natural yellow phenolic compound that is located in many types of herbs, especially Curcuma Lana (Turmeric). It is a natural anti-oxidant and has shown many pharmaceutical activities in the preclinical and clinical studies such as antioxidant, anti-microbial, anti-cancer and anti-alzheimer disease effects. In addition, curcumin was proven to be anti-diabetic, hepatoprotective, neuroprotective and anti-rheumatic and it also protects against thrombosis and myocardial infarction. The major limitation to the use of curcumin in clinical practice is its very low oral bioavailability. Therefore, many technologies have been developed and implemented to overcome this limitation. In this review, we discussed the latest perspectives regarding the design and development of nano-sized systems for the anti-diabetic agent curcumin, including liposomes, polymeric nanoparticles, micro-conjugates, micelles, peptide carriers, solid dispersions, cyclodextrins, emulsions and lipid nanopeptides and their role as a promising hope for cancer therapy.

Keywords: *curcumin, nanoformulations, cancer, perspectives*

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1. Introduction

Cancer is the most common disease and one of the most leading causes of death worldwide [1]. Traditional treatment methods such as chemotherapy, radiotherapy, adorable chemical therapy and surgical treatments are widely accepted for curing or eliminating tumor. Though chemotherapy is a very effective weapon for cancer treatment, it is often associated with large limitations and adverse effects [2].

Due to the emergence of new mechanisms by which cancer cells may resist chemotherapeutic agents, the development of new therapies is essential to cure cancer properly and to prevent distant metastasis [3]. To overcome common obstacles in cancer therapy, researchers are looking for lines of treatment other than the traditional chemotherapeutic agents including alternative medicine, complementary medicine and dietary supplements [4].

Curcumin is a natural compound that is derived from rhizomes of bringing curcuma. It was proven to have a wide variety of anti-diabetic, antimicrobial, antinflammatory, antioxidant and antiproliferative properties [5]. Recent studies suggested that curcumin may represent a promising hope for cancer therapy. This may be due to several mechanisms that affect the cell cycle, tumor startup, promotion, metastasis, apoptosis and angiogenesis [6]. Curcumin may affect thioredoxinreductase enzyme, 5-lipoxygenase, cyclooxygenase 2 (COX-2), protein kinase c, tubulin, transport factors, growth factors and the proinflammatory cytokines that play a crucial role in the pathogenesis of cancer [5]. The major limiting factor to the use of curcumin is that its oral bioavailability is very poor because it undergoes extensive metabolic changes in the small intestine and liver [7]. Pharmaceutical industries tried to prepare curcumin in formulations that improve its biotechnology and bio-relevance. However, these formulations were unable to affect the metabolic fate of the tumor. Therefore, it is highly needed to encapsulate curcumin in the form of nanoparticles that can improve its absorption, distribution and metabolic fate [8]. This review sheds light on curcumin nanoformulations that showed promising effects for cancer therapy.

2. Curcumin Nanoformulations

Recently, nanotechnology has been widely used in the field of cancer therapy. Nanoparticles can serve as ideal drug carriers due to the improved encapsulation of therapeutic drugs for targeted delivery, high surface to volume ratio which facilitates modifications to surface functional groups to obtain extensive stabilization and internalization, greater bioavailability and minimal clearance from the human body and on demand drug

release properties [9]. A large number of anticancer drug nanoformulations are available for clinical use. Albumin-bound paclitaxel (PTX) poly(lactide-co-glycolide) (PLGA) nanoformulationcan be considered as the most successful type of nanoformulations in cancer therapy [10]. The nanoformulations discussed in this review are primarily designed to obtain better solubilization of curcumin, and protect it from inactivation. These nanoformulations include polymeric nanoparticles, polymeric micelles, liposomes, cyclodextrins and conjugates [8].

2.1. Polymeric Nanoparticles

Biodegradable polymers are the most common types of polymers that have been used for preparation of curcumin-loaded nanoparticles [11]. NIPAAm, N-vinyl-2-pyrrolidone, poly (ethyleneglycol) monoacrylate and N,N0,-methylene bis acrylamide were copolymerized in water leading to formation of cross-linked nanoparticles. When nanoparticles were loaded with curcumin, they release 40% of their curcumin content in 24 hours [12]. PLGA (poly(D,L-lactic-co-glycolic) is commonly used for drug delivery due to its convenient biocompatibility and biodegradability. It was reported that curcumin loaded PLGA nanoparticles prepared by emulsion-evaporation method using PVA as surfactant showed a biphasic release pattern characterized by rapidinitial release of about 24% of the loading in 24 hours followed by sustained release of about 20% of the loading during the next 20 days [13]. A study on rats proven that the curcumin loaded PLGA nanospheres improved the oral bioavailability of curcumin to at least 9 folds when compared to curcumin administered with piperine which is acompound that inhibits curcumin metabolism by hepatic and intestinal enzymes [14]. Another study carried out by Yallapu et al. [15] encapsulated curcumin in PLGA nanoparticlesby a nanoprecipitation method using poly(vinyl)alcohol(PVA) and poly(L-lysine) as stabilizers (nano-CUR 1e6). After a small burst of around 20% of the loading, the nanoparticles showed a sustained release of 64% of the loaded curcumin for 25 days. Ghoshet al. [16] developed curcumin-loaded PLGA nanoparticles (Nano Cur) foramelioration of experimentally-induced hepatocellularcarcinoma (HCC) in rats. Nano Cur was prepared by emulsiondiffusion-evaporation method. Another study carried out by Anand et al. [17] prepared curcuminloaded PLGA nanoparticles using a nanoprecipitation method and polyethylene glycol (PEG)-5000 as stabilizer. Curcumin was almost entrapped in particles of 81 nm. The encapsulation efficiency of curcumin was more than 70% and particles with a size of 150 nmwere formed. The PLGA particles showed a continuous release of 40% of the loading in 9 days. On the other hand, the PLGA/PEG particles released 21% of curcumin in 24 h, followed by a sustained release to 57% of the loading over 9 days. The faster release of curcumin from the PLGA/PEG nanoparticles may be due to the higher water-absorbing capacity of this matrix compared to PLGA only [18].

Polymers derived from natural compounds were also used to prepare curcumin nanoparticles. Curcumin loaded chitosan/poly(ε-caprolactone) (chitosan/PCL) nanoparticles were developed by precipitation [19]. The encapsulation efficiency of curcumin was 71% and its loading was about 4%. The curcumin chitosan/PCL nanoparticles were found to release up to 68% of their content over 5 days in a sustained manner [10,20]. An in vitro release study carried out by Udompornmongkol and Chiang [21] reported that curcumin encapsulated in chitosan-gum arabic nanoparticles has superior anti-colorectal cancer activity over the free curcumin.

2.2. Polymeric Micelles

Polymeric micelles are amphiphilic block copolymers that can spontaneously form micelles in any aqueous solution above the criticalmicellar concentration (CMC) [22]. The hydrophobic core of these micelles has the ability to accommodatehydrophobic drugs. So, polymeric micelles have been widely used for solubilization and targeted delivery of drugs [23]. Curcumin was loaded into micelles ofamphiphilicmethoxy poly (ethylene glycol)-b-poly (ε-caprolactone-co-p-dioxanone) by solid dispersion. The entrapment efficiency of these micelles was more than 95% and their loading capacity was 12%. These micelles slowly release up to 80% of their content without a burst in 300 h. Also, curcumin was loaded on triblock copolymer micelles which were prepared by dialysis and have loading capacity of 4% and entrapment efficiency of 70% [10].

Ma et al. [24] loaded curcumin in micelles of different PEO-PCL block copolymers by cosolvent evaporation. They found that the PEO5000-PCL24500 showed the highest solubilization capacity whereas PEO5000-PCL13000 had the best drug retention capacity resulting in the slowest release of curcumin. Gong et al. [25] found that the encapsulation of curcumin in monomethyl poly(ethylene glycol)-poly(ε-caprolactone) (MPEGePCL) micelles by solid dispersion method resulted in formation of micelles with encapsulation capacity of 99% and drug loading capacity of 15%. These micelles were proven to release about 58% of the loaded curcumin in 14 days.

2.3. Liposomes

The term "Liposomes" refers to compounds having one or more phospholipid bilayers surrounding an aqueous core. Both lipophilic and hydrophilic compounds can be loaded on liposomes [20]. Curcumin loaded liposomes were prepared from egg yolk phosphatidyl choline (EYPC), dihexyl phosphate (DHP), and cholesterol prepared by the technique of film evaporation. In this nanoformulation, curcumin was solubilized in the lipophilic bilayer due to its high lipophilicity [26]. Curcumin loaded into the EYPC/DPH/cholesterol liposomal bilayer was proven to stabilize the system according to its content [10]. Also, curcumin loaded liposomes formed of bovine brain sphingomyelin, cholesterol, and 1,2-stearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(poly(ethylene glycol)-2000)] were developed by film evaporation technique and were functionalized with the apolipoprotein E (ApoE) peptide as targeting ligand [27]. These liposomes were proven to enhance transport of their curcumin content through thecapillary endothelial cells of the brain. This makes these nanoformulationsto be the ideal carriers for brain targeting [28]. Moreover, a cationic liposomepolyethylene glycol (PEG) polyethylenimine (PEI) complex (LPPC) was used as nanocarriers for

curcumin. Transmission electron microscopy (TEM) analysis of these liposomes had proven a spherical shape of the nanoparticles with hair like projections on the surface. The encapsulation efficiency of curcumin loaded LPPC was 45%. In vitro, these LPPC can release curcumin within 120 hours [29]. These curcumin loaded liposomes had shown high incorporation efficiency, better stability and potent anticancer effects towards pancreatic adenocarcinoma cell lines in in **v**itro studies [26].

2.4. Conjugates

It was hypothesized that conjugation of curcumin to small molecules and natural and synthetic hydrophilicpolymers may increase its oral bioavailability due to improvement in its aqueous solubility [30]. These curcumin-loaded conjugates weresynthesized in dry dioxane using N,N0-dicyclohexylcarbodiimide(DCC) as coupling agent, and (4-dimethylaminopyridine(DMAP) and triethylamine (TEA) as catalysts, and purifiedby column chromatography. These formulations may increase curcumin's aqueous solubility up to 10 folds [31]. Also, it was reported that curcumin conjugation to hyaluronic acid remained intact for 90% once incubated in aqueous solution at pH 7.4 for 8 hours while 60% of the unconjugated curcumin may undergo degradation within 25 minutes [32]. In another study, curcumin molecules were covalently linked to a block copolymer of methoxypoly(ethylene glycol) (mPEG) and PLA via a tris (hydroxyl methyl)aminomethane (Tris) spacer (mPEGePLAeTriseCur). Micelles with a size from 60 to 100 nm were prepared by dialysis There lease of curcumin from these micelles was studied using a Franz cell and PBS (pH 7.4) containing 5% sodium dodecyl sulfate as the acceptor medium [10]. It was reported that mPEGePLAeCur and mPEGePLAeTriseCur showed a rapidrelease of curcumin during the first 12 hours. Another study performed by Wichitnithad et al. [33] coupled curcumin to mPEG 2000. A log-linearrelease of curcumin in time for all conjugates tested was reported by the authors. Compared to the free curcumin, PEG bound curcumin showed a better solubility and stability and were proven to be more effective on prostate cancer cells [33,34].

2.5. Peptide/protein Carriers

Nanoparticles of cross-linked human serum albumin were suggested to have good biocompatibility and have been used for targeted drug delivery for cancer therapy [20]. Curcumin- human serum albumin nanoformulations were produced by homogenization of a mixture of human serum albumin in water and curcumin in chloroform [35]. The mean loading capacity of curcumin-loaded human serum albumin particles was 7.2%. These particles were formed by cross linking of albumin molecules via disulfide exchange due to heating associated with cavitation produced by the high-pressure homogenizer. Curcumin was solubilized in hydrophobic cavities of albumin. This formulation was proven to result in a 300 fold increase in solubility of the loaded curcumin [10]. Beta casein which is an amphiphilic polypeptide with molecular mass of 24,650 Da, was found to spontaneously forms micelles. It was proven that when curcumin was loaded in the hydrophobic core of these casein micelles, its solubility increased 2500 fold [36]. Curcumin-casein nanoformulations was reported to ameliorate the growth and metastasis of breast cancer, possibly due to affection of various breast cancer signaling pathways [37].

2.6. Cyclodextrins

Cyclodextrins representa large group of oligosaccharides that have a hydrophilicouter surface and a lipophilic core that can solubilize hydrophobic compounds such as curcumin [38]. For example, a b-cyclodextrin (b-CD)-curcumin inclusion complex was developed by a solvent evaporation technique. First, b-Cyclodextrin (CD) was dissolved in deionized water. Then, different amounts of curcumin in acetone were added while stirring overnight to evaporate acetone. After that, b-cyclodextrin (b-CD)-curcumin inclusion complexes were recovered by freeze drying. Poly(b-CD)/curcumin self-assembled formulations were synthesized by drop-wise precipitation method. Analysis of these formulations showed that a curcumin/poly(b-CD) inclusion complex was self-assembled into nanoparticles with a size of 250 nm [10]. An in vitro study showed that more than 70% of the loaded curcumin were retained in the nanoparticles during 72 hours of incubation at pH 7.4 proving a good compatibility between this carrier and curcumin [39]. Also, 2-hydroxypropyl-g-cyclodextrin (HPgCD) was used to form a complex with curcumin by a pH shift method. Briefly, curcumin was dissolved initially in an alkaline solution and then the pH was adjusted to 6.0. This shift in pH renders curcumin to be more hydrophobic and consequently embedded in the hydrophobic core of the CD [10,40]. Curcumin-cyclodextrin complexes were found to potentiate the effects of gemcitabine on experimentally-induced model of lung cancer [41].

2.7. Solid Dispersions

Solid dispersions can be considered as dispersions of a certain drug or a compound inan inert matrix. To enhance the solubility and dissolution rate of poorly water-soluble drugs, these dispersions can be prepared by melting or solvent evaporation technique [42]. Lyophilized 2-hydroxypropyl-b-cyclodextrin (HP-b-CD)-curcuminco-precipitates are examples of solid dispersions used to carry curcumin to improve its pharmacokinetic properties.To load curcumin on these dispersions, HP-b-CD and curcumin should bedissolved in methanol and converted into an amorphous coprecipitate which subsequently will be lyophilized. This lyophilisationis reported to enhance dissolution andhydration of curcumin [43]. Moreover, it was reported that curcumin-polyethylene glycol-15-hydroxystearate solid dispersions prepared by a solvent evaporation technique showed increased solubility of curcumin up to 560 mg/ml. Upon incubation in buffer, 90% the loaded curcumin in this nanoformulation was released within 1 hour [10]. In in vitro studies, microparticles containing curcumin solid dispersion were proven to have potent anti-inflammatory, antiapoptotic and antitumor effects [44].

2.8. Miscellaneous Nanoformulations

Curcumin loaded nanoparticles formed of glycerol monooleate and Pluronic F127 were prepared and showed entrapment efficiency of about 90% and long term stability. When dispersed in buffer, these nanoparticles of curcumin protect curcumin from hydrolysis and thus, enhancing its stability [45]. Anuchapreeda et al. [46] prepared a curcumin nanoemulsion based on soybean oil with a concentration of curcumin of 0.9 mg/ml. This formulation was stable for 60 days and 25% of the loaded curcumin was released from these nanoemulsionsin 72 h when dispersed in PBS, pH 7.4, containing 25% humanserum. Moreover, a study that loaded curcumin on lipid-core poly(εcaprolactone)nanocapsules coated with polysorbate 80 (C-LNCs)was carried out by interfacial deposition of preformed polymer. This nanoformulation showed 100% encapsulation efficiency and released up to 35% of the loaded curcumin within 2 hours of administration [47].

3. Clinical Trials on Curcumin Nanoformulations

Curcumin both in its free form and as nanoformulations has shown clinical benefits for patients with pancreatic cancer, colorectal cancer, multiple myeloma and breast cancer. Because of the low bioavailability of curcumin, curcumin nanoformulations were investigated in a number of clinical trials [48]. In one study, a single oral dose of 650 mg curcumin of lipid nanoparticles was administered to healthy volunteers. This formulation was able to achieve a mean Cmax of 22 ng/ml. On the other hand, no curcumin concentrations were detected in the plasma after administration of the same dose of the unformulated curcumin. Also, higher doses of this solid lipid nanoparticle formulation were administered to patients with osteosarcoma and unfortunately, the higher doses did not lead to significant increase in the plasma concentrations of curcumin compared to the original dose. The researchers of this study attributed the non-proportional increase in plasma concentrations of curcumin to complex absorption kinetics and the inter-individual variability in healthy individuals and osteosarcoma patients [49].

A Cmax value of 29 ng/ml was reached in another study on healthy volunteers after oraladministration of curcumin nano-colloidal dispersion formulation prepared by a high pressure homogenizer ata single oral dose of 30 mg, whereas oral administration of the same dose of curcumin resulted in very low plasma concentration (1.8-2.0 ng/ml) [50]. Moreover, the authors of this study had proven that curcumin nano-colloidal dispersion formulation enhances gastrointestinal absorption and bioavailability of curcuminin a dose-dependent manner [10,50]. The increase in curcumin dose in this nanoformulation was not associated with any observed toxic effects. Sasaki et al. [51] investigated the effect of curcumin nano-colloidal dispersion formulation (Theracurmin) on healthy human volunteers after drinking alcohol. An oral dose of 30 mg Theracurmin was given to these individuals after drinking 0.5 mg/kg ethanol and the ethanol and acetaldehyde levels in blood were assessed at different time intervals. Theracurmin was proven to significantly reduce the acetaldehyde plasma levels after alcohol intake. This may ameliorate the effects of alcohol and its metabolites on carcinogenesis [52]. A total of 16 patients (14 patients with pancreatic cancer and 2 patients with biliary tract cancer) who failed standard chemotherapy were enrolled in a study carried out by Kanai [53] to investigate the effect of theracurmin on these tumors. Interestingly, fatigue- and functioning-associated quality of life scores were significantly improved following administration of theracurmin. Also, an in vitro study carried out by Kang et al. [54] had proven that theracurmin efficiently inhibits the growth of human prostate and bladder cancer cells via induction of apoptotic cell death and cell cycle arrest.

In another study, curcumin conjugated plant exosomes which were formed by the inside budding of large multivesicular bodies in cytosol were investigated depending on the hypothesis that these exosomes strongly absorb curcumin by hydrophobic interactions [55]. Also, these curcumin conjugated exosomes were taken up by the intestinal cells as well as the immune cells present in the wall of the intestine and therefore may be considered as ideal nanoformulations to treat intestinal diseases [56]. Tablets containing plant curcumin-loaded exosomes as well as tablets containing 3.6 g of free curcumin were given daily for 7 days to healthy volunteers and to patients suffering from colorectal carcinoma. Comparison between these two forms of curcumin was carried out regarding tosafety, immune response, histochemical staining, effect and the concentration of curcuminin normal and cancerous tissues. The results of this comparison revealed promising effects of curcumin conjugated exosomes on colorectal carcinoma compared to the free curcumin [10,57].

4. Challenges to Curcumin Nanoformulations

Due to the promising results of the clinical trials that use curcumin nanoformulations in treatment of a wide range of human diseases including cancer, curcumin formulations may benefit from obtaining early approval from the FDA provided that the studies carried out on these formulations followed evident scientific techniques, characterization tools, purity and stability and precisely recorded toxicity and safety profiles [58]. However, curcumin formulations are considered to be as Abbreviated New Drug Applications (ANDAs) or New Drug Applications (NDAs). FDA is responsible for inspection and examination of records to nanotechnology, monitoring the post-marketing safety and identifying adverse events [59]. Based on such criteria FDA can pose ban if it is necessary.Evidence of promising anticancer properties of curcumin nanoformulations exist for all the strategies and types but further manufacturing of these curcumin nanoformulations should strictly follow the commonly applied laboratory and manufacturing practices using FDA approved compounds [60]. Then, thesuitable curcumin nanoformulations can be selected based on the appropriate priorities that are well established for the development of nanotechnology and its therapeutic applications on human diseases [20].

5. Conclusion

In spite of the vast number of studies that suggest that curcumin haspromising anticancer properties, its poor solubility, higher metabolic activity and poor pharmacokinetics represent serious obstacles to its emergence as anticancer agent. Also, some regulatory and intellectual property right issues in regard to using curcumin as a drug exist because curcumin is a natural compound. Curcumin nanoformulations are one of the promising areas in medicine that may improve human health care and ameliorate many human diseases including cancer. These nanoformulations have many advantages including improved efficacy, tumor targeting, reduced adverse effects, convenience and better compliance of the patients. A simple and standardized approach that complies with the FDA guidelines is necessary to develop curcumin nanoformulations. In this aspect, curcumin nanoformulations based on cyclodextrin assembly, PLGA and magnetic nanoparticle formulations are strongly appropriate. Oral and intraperitoneal administration of these nanoformulations are more preferred as they reduce the patient visits and the cost. Future studies are needed to gain more information about curcumin nanoformulations and their applications in cancer therapy.

Conflict of Interest

The authors had no conflict of interest to declare.

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