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Mini Review

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Nanotechnological Approaches for Enhancing the Oral Bioavailability of Curcumin

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ABSTRACT

Turmeric is a member of the ginger family (*Zingiberaceae*). It contains i) curcumin, ii) demethoxycurcumin, and iii) bisdemethoxycurcumin. Curcumin is the active component in the turmeric and has promising pharmacological properties. Despite promising clinical potentials, it has limited clinical use due to poor bioavailability. Thus, improving the water-solubility and bioavailability of curcumin are very interested. One of the approaches to overcome low bioavailability of curcumin is the formulation of curcumin into nanoscale drug delivery systems working as nanocarriers. They are emerging strategies for therapeutic agents that cannot be used effectively as conventional drug formulations. In addition, they have many advantages such as improving the stability, ease of preparation, reducing the dose, reduction of side effects, and solubility enhancement. For this purposes, the aspects and role of nanoscale drug delivery systems in the solubility enhancement of curcumin was presented and discussed in this review.

Key words: (1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione, Drug delivery, Bioavailability, Nanomedicine.

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1. INTRODUCTION

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-hepta- dien-3,5-dione], is a poly phenolic compound in the rhizome of turmeric (1). Chemical structure of curcumin is shown in Figure 1 (2). It has a molecular weight of 368.38 Da and the melting point of it is about 183 °C (3). It is used as a coloring agent in many foods (4). Due to hydrophobic nature, it is practically insoluble in water, but is soluble in ethanol, methanol, and acetone (5).

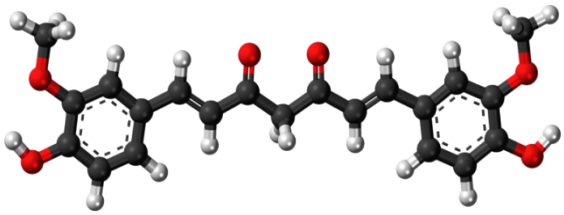

Figure 1. Chemical structure of curcumin (2)

Curcumin has a wide clinical applications and is used in traditional medicine for treatment of urinary tract infections, arthritis and rheumatism (6). Beneficial pharmacological effects of curcumin are including anti-depressant, anti-bacterial, anti-cancer, anti-inflammatory, anti-epileptic, anti-oxidant, anti-viral, anti-atherosclerotic and anti-proliferative (7-15). Despite its pharmacological effects, its usage has been limited; the low solubility of curcumin in aqueous solutions is a major barrier as its low bioavailability and low clinical efficacy (16). To date, the

oral route is the preferred mode of drug administration, especially for chronic therapies due to its comfort (17). About 40% of new drugs, display poor aqueous solubility, which lead to restrict for clinical using of it (18). Major barrier contributing to the low bioavailability of oral drug appear to be due to their low water solubility, instability in gastrointestinal tract and rapid metabolized in the intestine (19, 20). In this regard, curcumin is almost insoluble in water and unstable at both acidic and basic pH values (21, 22). Studies have shown that it can be administered safely at oral doses 12 g/day and has not appeared to be toxic to human (23, 24). But even at high does, serum concentration of curcumin is very low (only 1% in rat) (25). This limitation should find a solution through using novel drug delivery systems. Recent developments in nanotechnology have provided excellent opportunities for design of novel drug delivery systems (26). Nanotechnology is the engineering and manufacturing of materials at the length scale of approximately 1-100 nanometer in at least one dimension (27). Such systems are characterized by unique features including a large surface area to mass ratio and high surface reactivity, and with altered physicochemical properties such as changed solubility, and flexible surface chemistry (28). Up to now, various nanoparticles-based drug delivery systems have been reported for increment in the efficacy of curcumin such as chitosan (29, 30), PVP capped gold nanoparticles (29, 30), cyclodextrin (31), lipid (32), liposome (33), structural analogues of curcumin (34) and phospholipid complexes (35). These approaches showed a significantly improvement of the therapeutic efficacy of curcumin by increasing its bioavailability. On the other hand, nanoparticles-based drug delivery systems have many advantages such as protection of curcumin from enzymatic degradation, improving biodistribution, prolonged blood circulation, and changing its pharmacokinetics (36, 37).

2. CURCUMIN NANOFORMULATIONS

Poly-(lactic-co-glycolic acid) (PLGA) is generally used for drug delivery purposes since it is a biocompatible and biodegradable material. Tsai et al. reported that curcumin-loaded PLGA nanoparticles were prepared by the high-pressure emulsification-solvent evaporation method. The entrapment efficiency was 46.9%. Indeed, formulation significantly raised the serum concentration of curcumin and prolonged retention time of curcumin in the cerebral cortex and hippocampus (38). In addition, in another research curcumin in PLGA nanoparticles in the presence of poly-vinyl alcohol and poly-L-lysine stabilizers was prepared using a nano-precipitation technique. Results of this study suggested that therapeutic efficacy of curcumin was enhanced by such PLGA nanoparticles. This last nano-curcumin formulation is presented Schematically in Figure 2 (39).

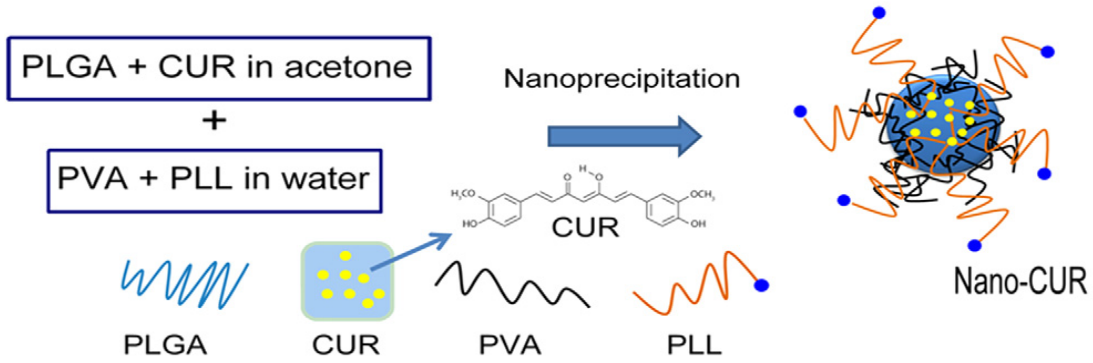

Figure 2. Schematic representation of nano-curcumin formulation using PLGA nanoparticles (39)

In another study, hydroxypropyl-β-cyclodextrin (HP-β-CD) was selected to prepare inclusion complexes with curcumin. The inclusion complexes were prepared using three different methods. Formation of inclusion complexes was confirmed by differential scanning calorimetry (DSC) and fourier transform infrared (FTIR). Among the three preparation methods, solvent evaporation was the most suitable method for preparation of curcumin-HP-β-CD inclusion complex, although all the three methods significantly increased the curcumin solubility (40). Maiti et al. was developed a novel formulation of curcumin in combination with the phospholipids to overcome its absorption limitation. The results proved that curcumin-phospholipid complex has better hepatoprotective activity due to its superior antioxidant property, Maximum concentration (C_{max}) increased from 0.50 to 1.2 µg mL^{-1}, and serum concentration was higher than pure curcumin (35). In recent years, emulsion systems have been considered as ideal approaches for enhancement in the oral bioavailability of poorly water-soluble drugs. There are different self-emulsifying systems comprising fine oil droplets dispersed in water formed by high-energy emulsification methods and low-energy emulsification methods. Self-emulsifying drug delivery system (SEDDS) are isotropic mixtures of oil, surfactants, and cosurfactants. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. Yan et al. developed a SEDDS containing curcumin with at least 3 months stability. After oral administration to rats, this formulation resulted in significant improvement in absorption. C_{max} was reached to 155.56±18.34 ng ml^{-1}, and area under the curve of

curcumin concentration versus time (AUC) increased by 7.6-fold (32). Setthacheewakul et al. loaded curcumin into self-microemulsifying drug delivery systems (SMEDDS). Curcumin-SMEDDS had a small size range of 25.8-28.8 nm with a narrow size distribution. Releasing of curcumin from SMEDDS was about 16-fold higher, and plasma concentration-time profile obtained from *in vivo* studies showed 14-fold increment in the absorption of curcumin, compared to the aqueous suspension of curcumin. Also, formulation was found to be stable up to 6 months under intermediate and accelerated conditions (41). In another investigation, encapsulation of curcumin into self-nanoemulsifying drug delivery system (SNEDDS) was performed. Transmission electron microscopy (TEM) analysis revealed a spherical shape for the droplets with a narrow size distribution, which are in accordance with particle size analysis. The curcumin content in the curcumin-loaded SNEDDS was obtained as 23±5%, and then orally evaluated in rat. The results showed a significant increment of 3.95 times in C_{max}, and 194.2% in bioavailability, compared to the curcumin suspension. The development of the SNEDDS formulation had a great potential as a possible alternative for curcumin administration (42). Novel organogel-based nanoemulsions have been developed for oral delivery and improvement of bioavailability of curcumin. Researches demonstrated the application of organogel-based nanoemulsions in the oral delivery of lipophilic compounds, and were provided a promising formulation platform for the delivery of poorly soluble drugs. *In vivo* pharmacokinetics analysis on mice confirmed that 9-fold was increment in the oral bioavailability of curcumin (43).

3. CURCUMIN AS LIPOSOMES

Liposomes composed of natural phospholipids that are biologically inert and weakly immunogenic. They possess low intrinsic toxicity. In addition, they are soluble in water from one end, while, another end is water insoluble. Hydrophilic drug added to the water are trapped inside the aggregations of the hydrophobic ends, and lipophilic drugs were incorporated into the phospholipid layer (44). Takahashi et al. prepared liposome-encapsulated curcumin from commercially available lecithins. The resulting encapsulated liposome was then evaluated for curcumin bioavailability and showed a faster rate and better absorption. The encapsulated liposome gave higher C_{max} and shorter T_{max} values, as well as a higher value for the area under the blood concentration-time curve (33). In another study, encapsulated curcumin in a liposomal delivery system was evaluated in *in vitro* and *in vivo* environments. Encapsulated curcumin suppressed pancreatic carcinoma growth in murine xenograft models and inhibited tumor angiogenesis (45). Esmaili et al. made an amphiphilic self-assembling protein (camel B-CN) that can be used as a carrier system for hydrophobic therapeutic agents such as curcumin. The solubility study was assessed according to the solvent-evaporation technique. Presence of camel B-CN increased the solubility of curcumin at least 2500-fold. Additionally, the cytotoxicity of curcumin to human leukemia cell line was enhanced in the presence of B-CN micelles giving inhibitory concentration values of 26.5 and 17.7 mmol L^{-1} for free and encapsulated curcumin, respectively. Antioxidant activity of curcumin encapsulated in B-CN was also higher than of both free B-CN and curcumin (46). Gao et al. employed biodegradable monomethoxy poly (ethylene glycol)-poly (lactide) copolymer (MPEG-PLA) micelles to deliver curcumin. The curcumin loaded polymeric micelles with a 8% drug loading was monodisperse particles of ~30 nm in diameter, and could release curcumin in an extended period. Their results clearly showed that the area under curve and C_{max} were about 300 mg L^{-1} h^{-1} and 166 mg L^{-1}, respectively (47).

4. CONCLUSION

Curcumin has a numerous biological and pharmaceutical properties. However, the major limitation of its usage is low solubility. Nanomaterials have been successfully manipulated to create a new drug delivery system, and these materials, due to their unique features, can increase the curcumin bioavailability and solubility. Thus, it will be useful to provide methods for enhancing the oral bioavailability of curcumin. Indeed, nanomaterials are promising delivery systems for enhancing the bioavailability of lipophilic drug such as curcumin.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

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