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Review on Nanoformulations of Curcumin (*Curcuma longa* Linn.): Special Emphasis on Nanocurcumin®

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Abstract

The three major diphenolic, hydrobhobic orange coloured compounds derived from the rhizome of *Curcuma longa* Linn. (turmeric) of Zingiberaceae family, namely diferuloylmethane, demethoxycurcumin and bisdemethoxycurcumin has been exhibited several pharmacological efficacies both in preclinical and clinical studies through its anti-inflammatory, anti-microbial, anticancer and anti-Alzheimer properties. Furthermore, these curcuminoids were also showed hepatoprotective, nephroprotective, neuroprotective, cardioprotective, hypoglycaemic activities. Researchers were also observed the antioxidant properties of these novel compounds in a significant level. Therefore, all the curcuminoids were considered as an important bioactive molecule in the natural product market and herbal industry. Despite being a robust pharmacologically active agent, all the three curcuminoids were exhibited very poor solubility in water and therefore the systemic bioavailability were also very low, which attributed very poor absorption, faster metabolism and systemic elimination after oral administration. Consequently, its therapeutic actions were also diminished in a significant percentage. In this scenario researchers have been designed and developed several nanotechnological delivery system for curcuminoids to overcome this limitation. Here, in this article, we have summarized the various methods of nanocurcumin including polymeric nanoparticles and micelles, liposomes, cyclodextrins, solid dispersions, peptide carriers, lipid nanoparticles and emulsions.

Key words: Nanocurcumin, nanotechnology, nanoparticle, solubility, bioavailability, pharmacological activity, Nanocurcumin®

1. Introduction

Researchers (Vogel and Pelletier, 1815) were first attempted to purify curciminoids. Thereafter the diferuloylmethane structure was established (Milobedzka, et al., 1910). The chemical structure was confirmed in Roughley and Whiting (1937). Workers (Payton et al., 2007) further confirmed the solution structure. Curcumin is a mixture of three compounds, namely diferuloylmethane (77%), demethoxycurcumin (18%) and bisdemethoxycurcumin (5%) (Basnet et al., 2010) (Fig. 1 and 2). Curcuminoids are readily soluble in organic solvents (dimethylsulfoxide, ethanol, acetone etc.), but practically insoluble in water.

In physiological conditions curcuminoids could occur in enol and di-keto form and coexist in equilibrium manner (Fig. 3). The keto form prevails in solid, neutral and acidic conditions and donates H-atoms; on the other side the enolic form predominates in alkaline conditions (≥pH 8) and the phenolic part of the molecule performs as an important fragment for donating the electron (Jovanovic et al., 1999).

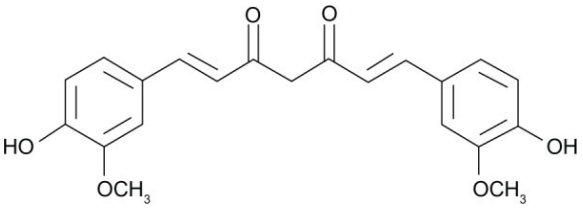

Figure 1. Chemical structure of curcumin.

Curcumin is a member of linear diarylheptanoid class whose chemical structure is elucidated as 1, 6-heptadiene-3, 5-dione-1, 7-bis-(4-hydroxy-3-methoxyphenyl)-(1E, 6E). The structure is overall symmetrical having alternatively arranged single (-C-C-) and double bonds (-C=C-). It is comprised of two phenolic rings (carrying two methoxy and two hydroxyl groups) that are linked via two α, β-unsaturated carbonyl groups.

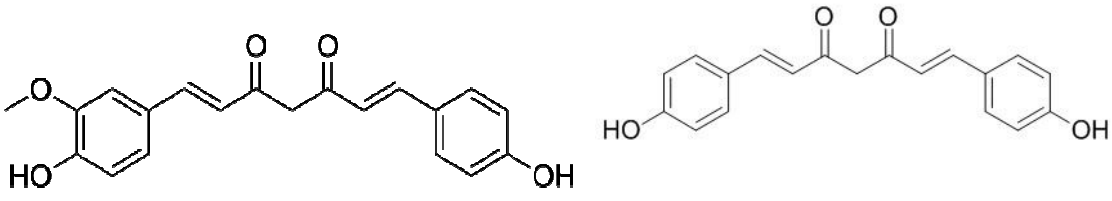

Figure 2. Structure of demethoxycurcumin and bisdemethoxycurcumin.

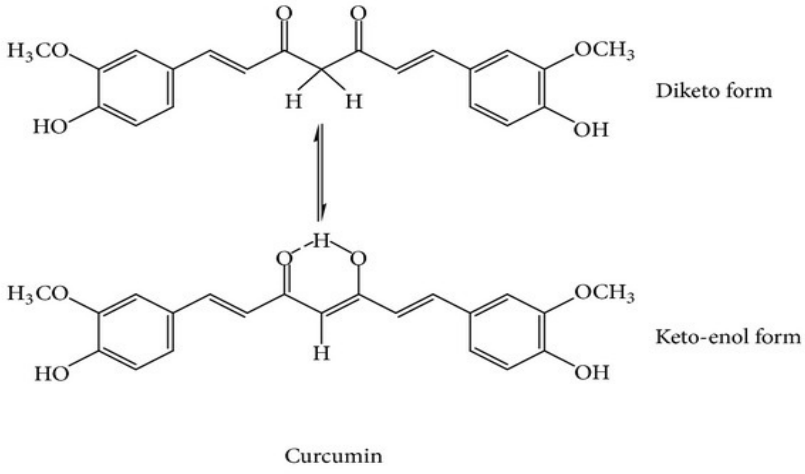

Figure 3. Tautomerism of curcumin under physiological conditions. Under acidic and neutral conditions, the bis-keto form (top) predominates, whereas the enolate form is found above pH 8.

Curcuminoids (Fig. 4) are naturally occurring low molecular weight bioactive agent that has a long history of using as a nutritional spice, colouring agent, and food preservative specially in Southeast Asian countries. It has wide range of pharmacological activities that includes anticancer, antiviral, antifungal, antioxidant, antiangiogenic, and anti-inflammatory properties (Chattopadhyay et al., 2004; Maheshwari et al., 2006; Aggarwal and Harikumar, 2009).

Figure 4. *Curcuma longa* (Turmeric) fresh rhizome and Curcumin powder.

Despite being a robust pharmacologically active agent, all the three curcuminoids were exhibited very poor solubility in water and therefore the systemic bioavailability were also very low, which attributed very poor absorption, faster metabolism and systemic elimination after oral administration. Consequently, its therapeutic actions were also diminished in a significant percentage. Therefore, researchers have been designed and developed several nanotechnological delivery system for curcuminoids to overcome this limitation.

Through the constant advancement of nanotechnology, the nano-molecules have its own importance in novel drug delivery system. This nanoparticle formulation has great impact on drug discovery process. The advantages of using nanoparticles are large surface area, controlled particle size, site-specific targeting, bioavailability, stability, biodegradable and controlled release of drug. Metallic nanoparticles like silver, gold, platinum, copper, etc., have been synthesised and used for clinical applications (Rupareli et al., 2008; Wang et al., 2012).

Therefore, introduction of nanotechnology in curcumin provides a solution towards increased bioavailability and therapeutic efficacy.

2. Clinical Importance of Curcumin Nanoparticles

2.1. Anticancer activity

Across the world Cancer is the most dreadful disease. Cancer patients usually undergoes chemotherapy, radiation therapy and surgery which cause harmful side effects. Therefore, this is very important to develop harmless and safest substitute to treat the patients. At present it is observed that the plant based natural compounds mainly phenolic compounds are attributing to treat various type of cancer like breast, prostate, skin, pancreatic, oral, ovary etc. Currently, the formulation of nano curcumin enhanced the water solubility, bioavailability, systemic elimination, hence improved the specific tumour cell targeting to trigger the cancer tissues.

On the basis of the role of methoxy group of phenyl ring the tumor necrosis factor (TNF)-induced nuclear factor-kappaB (NF-kB) activation potency of curcuminoids are falling on the following decreasing order (Sandur et al., 2007) curcumin > desmethoxycurcumin > bisdesmethoxycurcumin. The cardioprotective, neuroprotective and antidiabetic activities are significantly high in Curcumin in comparison to other two curcuminoids. Remarkably the synergistic effect is observed against nematodes in the mixture of curcuminoids as compared to individual compounds.

2.2. Breast cancer

Breast cancer is a predominant ailment mostly impairing woman. Against the triple negative breast cancer xenografts, the curcumin in polymeric micelle form showed increased bioavailability, cytotoxicity and longer half-life, observed in *in vitro* studies (Cridge et al., 2013). Such type of malignancy is highly aggressive and resistant to chemotherapy (Carey et al., 2010). The anticancer activity of curcumin impregnated nanoparticles showed significant result against triple negative breast cancer (MDA-MB-231 cell line) (Yallapu at al., 2012). The encapsulated nanocurcumin made up of

electroporation technique showed efficient anticancer activity against MCF-7 breast cancer cells (Lin et., 2014).

2.3. Ovarian cancer

Ovarian malignant cells are usually resistant to chemoradiation therapy (Yallapu et al., 2012). Formulated monoclonal antibody which conjugates with curcumin nanoparticles for enhancing the site specificity and sensitivity of the chemoradiotherapy resistance of ovarian cancer cells. Ganta and Amiji (2009) showed the anticancer activity of paclitaxel and curcumin-encapsulated nanoemulsion against drug resistant SKOV3 and SKOV3 (taxol-resistant) human ovarian adenocarcinoma cells. The curcumin nanoemulsion down-regulated P-glycoprotein (Pgp) expression and inhibited the activity of nuclear factor kappa B (NFκB). The nano particle conjugates of curcumin lowered the cell proliferation of cisplatin-resistant A2780CP ovarian cancer cells.

2.4. Pancreatic cancer

Bisht et al. (2010), used co-polymers N-isopropylacrylamide, N-vinyl-2-pyrrolidone and poly (ethylene glycol) monoacrylate which was prepared with curcumin-loaded polymeric nanoparticles. It acts as a potential agent to inhibit the tumour growth in xenograft models of human pancreatic cancer. The tumour growth was also arrested when the treatment was done combinedly with nanocurcumin and drug gemcitabine; further decline in stimulation of NFκB and countenance of matrix metalloproteinase MMP-9 and cyclin D1 also were observed. The beneficial action of nanocurcumin was established by cell viability. The magnetic nanoparticles of curcumin significantly inhibited the growth of HPAF-II and Panc-1, the human pancreatic cancer cells in animal model. This formulation of curcumin with magnetic nanoparticle exhibited more stability with enhanced bioavailability and distribution in comparison to native curcumin (Yallapu et al., 2013).

2.5. Prostate cancer

Prostate gland of human reproductive system is very much prone to prostate cancer. After manifestation of malignant cells, they may proliferate to bones and lymph nodes (Ruddon., 2007). Curcumin-filled poly (lactic-co-glycolic acid) (PLGA) nanoparticles (Bisht et al., 2010) showed the anticancer property against prostate cancer cells. After the incorporation of Curcumin-PLGA nanoparticles into the cancer cells, curcumin released in the cytoplasom then it started to inhibit the expression of nuclear β-catenin and androgen receptors, STAT3 and AKT phosphorylation and supressed the principle anti-apoptotic protein molecules leading to apoptosis (Yallapu et al., 2014).

2.6. Antimicrobial activity

Numerous antimicrobial studies have been performed about the effectiveness of nanocurcumin against several microbial strains. Researchers (Gopal et al., 2016) compared the antibacterial activity of macro, micro and nanocurcumin against *E. Coli*, *Salmonella enteritidis* 12021, *Streptococcus mutans* 11823 and *Staphylococcus aureus* observed that the augmented bactericidal property of nanocurcumin in comparison to macro and micro curcumin. The wet milling technique was adopted to prepare this nanocurcumin. Bhawana et al. (2011), were also found the antimicrobial activity of nanocurcumin prepared by wet-milling technique. The nanocurcumin prepared by fabrication (Vimala, 2011) of Curcumin encapsulated chitosan-PVA silver nanocomposite films by in situ fabrication chitosan-PVA-silver nanocomposite films which was confirmed the effectiveness against *Staphylococcus, Micrococcus, E. Coli, Pseudomonas, Candida albicans*.

2.7. Anti-HIV activity

Gandapu et al. (2011), found that curcumin-loaded apotransferrin nanoparticles prepared by sol-oil technique was very effective to thwart HIV-1 replication by transferrin-mediated endocytosis. Normally, transferrin receptors expressed by HIV-infected cells. The nanoparticles loaded by curcumin and apotransferrin combined specifically to the receptor and transport the drug inside the infected cell. After releasing, active ingredients inside the cell the viral cDNA synthesis is blocked and finally terminating the replication of HIV-1.

2.8. Antimalarial activity

Curcumin-loaded chitosan nanoparticles helped to cure the infected animal with *Plasmodium yoelii* by blocking the synthesis of hemozoin (Akhtar et al., 2012).

2.9. Anti-inflammatory activity

In traditional system of medicine turmeric has been using for relief of swelling, pain, inflammation and healing of wound. The effectiveness of curcumin against inflammation related ailments has been significantly comparable with some modern drug like phenylbutazones observed both in vivo and invitro studies (Luthra et al., 2001; Duvoix et al., 2005).

Workers (Sing and Vinayak, 2015) were found that curcumin reduces inflammation by modulating of antioxidant enzymes and supressed the secretion lavel of lL1β, IL-6 and TNF-α.

Researchers (Rocha et al., 2014) has been compared the anti-inflammatory activity of native curcumin versus nanocurcumin in animal model. The nanocurcumin showed its activity at the dose level of 50mg/kg body weight whereas native curcumin dose was 400mg/kg body weight to express similar

activity. Therefore, the dose of nanocurcumin was 8 time less than to native curcumin to show the anti-inflammatory property. The encapsulated exosome of curcumin was showed the effectiveness against lipopolysaccharide induced septic shock mouse model. Curcumin-encapsulated exosomes were studied for their potency in lipopolysaccharide-induced septic shock mouse model (Sun et al., 2010).

2.10. Alzheimer's disease

Amyloid beta *(Aβ)* has been usually treated as one of the hallmarks of Alzheimer's disease (AD) pathogenesis. Alzheimer's disease patients generally possess senile plaques, neurofibrillary tangles and extensive neuronal loss in brain.

AD is a progressive neurodegenerative disorder associated with memory loss and gradually decreasing the number of brain cells. Again researchers (Cheng et al., 2013), showed in their study, that nanocurcumin was orally administered for three months to mice and the memory of animal was estimated.

The Nanocurcumin-treated group of animals showed improved memory in respect to contextual fear conditioning test and more working memory in the radial arm maze test (Cheng et al., 2013). The conjugated PLGA-coated curcumin with Tet-1 peptide possess anti-amyloid activity and which is very much potent to treat AD (Methew et al., 2012).

3. Conclusion

Improvement of bioavailability, curtailing the deterioration of curcumin during the time of metabolism, enhancement of delivery capacity into the tumor cells and increasing the systemic elimination time are the important purposes to formulation of nanoparticles of curcumin. The nanoparticles could easily deliver the formulated curcumin into the target site. The nanocurcumin dissolved in water, showed more stability, bioavailability against curative and therapeutic action thereof.

4. Nanocurcumin®

Nanocurcumin® is registered product of Biotex Life Solution Pvt Ltd, Hyderabad, India. This is formulated with curcumin and a drug delivery system by a proprietary process. Nanocucumin® is fully water-soluble preparation (Fig. 5). It is found that the intensity of Size Distribution of Nanocurcumin® is 10nm (particle diameter) (Fig. 6 and 7).

Recently, it is observed that the Particle size plays most important role in drug delivery system, mainly in the mode of action of drug including the interaction of particles with a biological system, its distribution in tissue, accumulation, attachment etc are all depending upon the size of particle.

The diameter of Nanocurcumin® is 10nm, therefore the rate of absorption and permeation is higher, and which finally led to enhancement of bio-distribution and higher circulation, furthermore the bioavailability also increases in manifold.

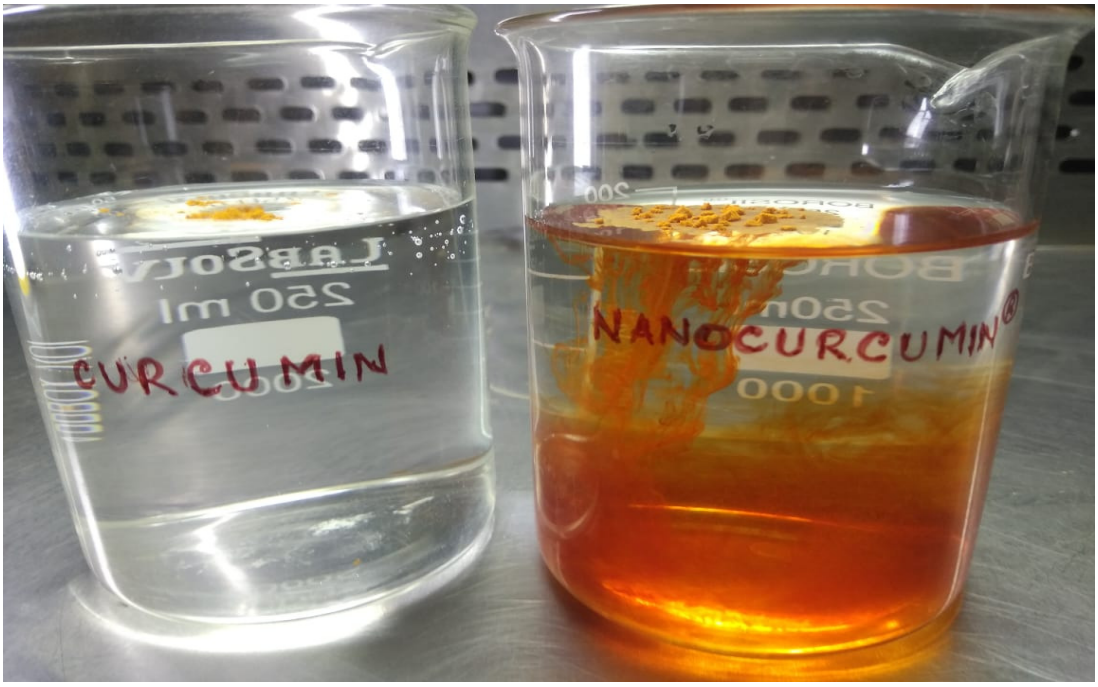

Figure 5. Solubility in water: left side- Only Curcumin, where the sample was not at all dissolving in water, it was floating on water surface; whereas in right side- Nanocurcumin is automatically dissolving in water.

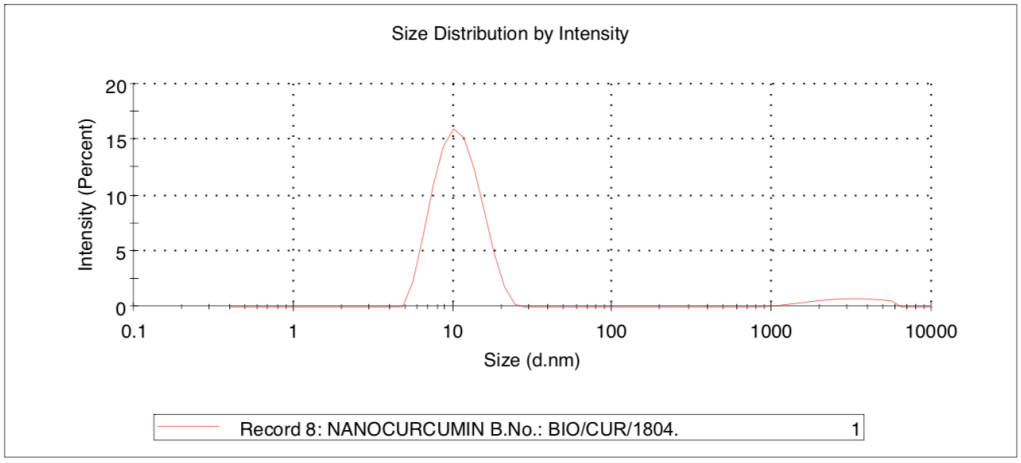

Figure 6. Size Distribution of Nanocucumin®.

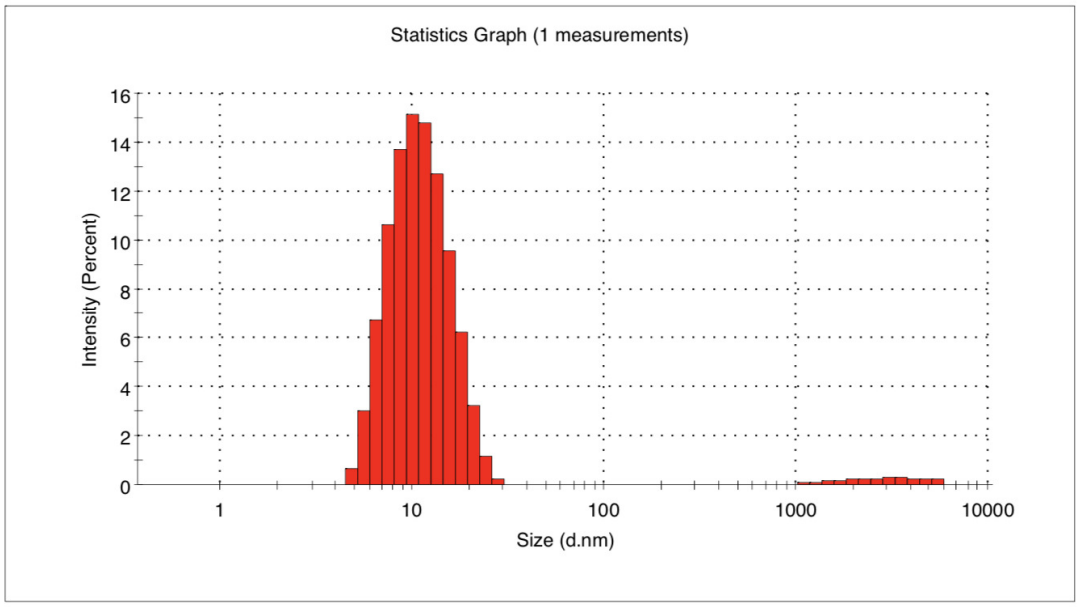

Figure 7. Size Distribution of Nanocucumin®.

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