Curcumin nanoparticles: The journey so far

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Abstract: Extensive scientific research on Curcumin demonstrates a wide spectrum of therapeutic effects such as anti-inflammatory, antibacterial, antiviral, antifungal, antitumor, antispasmodic and hepatoprotective. The clinical effects of curcumin have been known for centuries but are reduced due to its poor bioavailability and aqueous solubility. The studies have indicated that curcumin taken orally has poor absorption and poor bioavailability which severely limits its clinical utility. The various nanoformulations prepared have contributed to improve its bioavailability and aqueous solubility, thereby resulting in opening doors for the clinical applications in the field of treatment of various diseases, especially cancer.

The herb turmeric (Curcuma longa) belongs to the ginger family (Zingiberaceae). It is widely grown and used in south and Southeast Asia as a flavoring agent, colouring agent, for home remedies etc. The ancient text of ayurveda describes as 'haridra', which literally means that which improves the complexion of skin. It is an integral part of the Indian cuisine and is also used in Hindu religious functions, weddings and festivals since centuries. Curcumin is the principal curcuminoid of turmeric, the other two being desmethoxycurcumin and bis-desmethoxycurcumin. The ayurveda describes the therapeutic properties of turmeric as anti-inflammatory and antioxidant (1). The ancient text of Chinese traditional medicine describes the uses of turmeric for the treatment of diseases that are associated with abdominal pain (2). Extensive scientific research on Curcumin demonstrates a wide spectrum of therapeutic effects such as anti-inflammatory (3), antibacterial (4), antiviral (5), antifungal (6), antitumor (7), antispasmodic (8) and hepatoprotective (9). Recently, its potential utility in autoimmune deficiency syndrome (AIDS) has been demonstrated (10, 11, 12). But even after the therapeutic effects known for Curcumin for about 6000 years, it did not get its due in the medical field. The clinical applications have been limited due to its poor aqueous solubility and poor bioavailability. Sharma et.al (13) carried out the dose-escalation pilot study of oral Curcumin in the form of standardized Curcuma extract (440-2200mg/day equivalent to 36 to 180mg of curcumin) in the patients with advanced colorectal cancer refractory to standard chemotherapy. The aim of this study was: i) to evaluate the safety of Curcumin administered p.o. as Curcuma extract, ii) to investigate the suitability of two potential biomarkers of pharmacological efficacy of Curcumin in patients blood leukemia and iii) to test the hypothesis that Curcumin or products of its metabolism can be detected in blood or excreta of humans. Blood, urine and feces were collected on day 1, 2, 8 and 29 and analyzed. During the trial it was observed that the oral curcumin extract was well tolerated and dose-limiting toxicity was not observed. Neither Curcumin nor its

metabolites were detected in blood or urine and are recovered in feces. Leukolytic M1G levels were constant in each patient and unaffected by the treatment. The study concluded that although Curcuma extract can be orally administered upto 2.2gm(about 180mg of Curcumin), it has a very low bioavailability as the major portion of the curcumin was found in feces on analysis with HPLC.

Further Sharma et.al (14) carried out the phase I clinical trials of oral curcumin. They studied the three biomarkers of the potential activity of curcumin in the blood leukocytes: glutathione S-transferace activity, levels of M1G and PGE2 production included ex vivo. They observed that the curcumin and its glucuronide and sulfate metabolites were detected in plasma in 10nmol/L range with a daily dose of 3.6gm per day, although abundant amount was recovered in feces. These findings were further confirmed by Garcea G. et al (15) who performed the studies in the same concentration range in hepatic tissues and portal blood of patients following oral administration. Cheng AL et al (16) carried out the Phase I trial with dose escalation upto 12,000mg/day and found that above 8000mg/day, the bulky volume of the drug was unacceptable to the patients. The serum concentration was also very low even after 1hr of the administration which reconfirmed low bioavailability. These studies indicate that although it is well established that curcumin has a great potential in the medical field, but due to its lower bioavailability, the desired clinical effects could not be obtained.

In order to overcome this problem, scientists tried to explore the possibility of complex formation of curcumin with phospholipids. Lan Li et.al.(28) prepared liposome-encapsulated curcumin and studied in-vivo and in-vitro effects on the prolification, apoptosis, signaling and angiogenesis using human pancreatic carcinoma cells as in-vitro model and female athymic nu/nu mice for in-vivo studies. The following procedure for liposomal curcumin preparation was adopted: First, the curcumin was dissolved in 50mg/ml of DMSO. The lipid was dissolved in 20mg/ml tert-butanol. The 2 solutions were mixed, filtered and lyophilized. On treating the cells lines with liposomal curcumin, it was observed that antoprolification effect of loposomal curcumin was equivalent or better than those of free curcumin at similar concentrations and are at least partially irreversible. The effect of liposomal curcumin was also reported to be quite apparent with liposomal curcumin inhibiting the growth of NF-κB. The treatment when administered n-vivo at the concentration of 40mg/kg of body weight resulted in reduced tumor size and blanching of tumors. Kuntal Maiti et. al. (17) prepared a complex of Curcumin with hydrogenated soy phosphatidyl choline (HSPC) and demonstrated the protective effect of curcumin-phospholipids complex (equivalent of curcumin 100 and 200 mg/kg body weight) and free curcumin (equivalent of curcumin 100 and 200 mg/kg body weight) by measuring various enzymes in oxidative stress condition. It was observed that the curcumin-phospholipids complex significantly protected the liver by restoring the enzyme levels of liver glutathione system and that of superoxide dismutase, catalase and thiobarbituric acid reactive substances with respect to CCl_4 treated group. During the in-vivo studies it was observed that it provided better protection to rat liver than at the same doses. Serum concentration was also observed to be higher (C_{max} 1.2µg/ml) than free curcumin (C_{max} 0.5µg/ml) and also sustained for longer duration in rat serum. Still, the concentration of curcumin in serum was not encouraging enough for significant clinical impact.

This encouraged the scientists to design a formulation that can help in better solubility of curcumin in water which can further help to increase its oral bioavailability. Savita Bisht et. al. (26) for the first time utilized nanotechnology-based drug delivery approach as a solution to this problem. They prepared a copolymer of NIPAAM (N-isopropylacrylamide), VP (vinylpyrrolidone) and AA (acrylic acid) and dissolved them in water in 90:5:5 molar ratios and were polymerized, dialyzed, lyophilized to obtain a dry powder. The curcumin was loaded and the curcumin-loaded nanoparticles were then lyophilized to dry powder for subsequent use. The TEM and SEM analysis determined the particle size of Curcumin nanoparticles to be about 50nm. They carried out the in-vitro (on human pancreatic cell-lines) and found that nanocurcumin was effective in its ability to block clonogenicity. They demonstrated that nanocurcumin robustly inhibits NFκB function in cell lines. The study opened a new field of cancer therapy for poorely-soluble drugs.

Sriniwas Ganta et al.(18) for the first time prepared a nanoformulation of Curcumin with another anticancer drug Paclitaxel to overcome multidrug resistance (MDR) in cancer cells. The flaxseed oil-containing nanoemulsions were prepared by coarse homogenization followed by high energy ultrasonication. The size of the nanoformulation thus obtained is about 133nm. Further on analysis of paclitaxel and curcumin combined therapy, it was observed to have significantly suppressed the growth of cancer cells even at lower doses, thus confirming the effect of nanoformulation in significant enhancement in cytotoxicity, especially in drug-resistant ovarian adenocarcinoma cells.

Another approach adopted by scientists is to use mesoporous-type spherical hollow silica nanoparticles and selectively immobilizing curcumin onto its internal surface(19). Dalsaem et.al. presented a novel method of preparing mesoporous-type spherical hollow silica nanoparticles using a self-assembled alanine-based amphiphile as a template and then functionalizing them with curcumin molecule attached to the internal surface of the nanostructure by covalent bonding. The particle size analysis of curcumin-immobilized mesoporous hollow silica nanoparticles(C-MHSP) by TEM and SEM revealed that the spherical structures has 100-150nm outer diameter with 90-140nm hollow cavities with a worm-like structure. Approximately 35% of the curcumin was selectively immobilized onto the internal surfaces of mesoporous hollow silica nanoparticles by covalent bonds. The study also included the release pattern of curcumin at pH 10 in aqueous phase. It showed that curcumin was released into the aqueous phase over 120min at pH 10 which indicated that the curcumin attached to the inside of the silica particle was effectively hydrolyzed by strong base.

Zhiguo Zheng et.al(20) presented a novel sonication-assisted synthesis procedure of polyelectrolyte-coated curcumin nanoparticles. In this procedure, they dissolved curcumin in water: ethanol (40:60 v/v) at a concentration of 2mg/ml. The drug nucleation was initiated by gradual worsening of the solution by the addition of an aqueous polyelectrolyte assisted by ultrasonication for 45 min. The very impressive particles size of 60-100nm were obtained depending upon component concentrations, sonication power, and initial solvent from the initial size of 20µm.

Recently another sonication-based wet-milling procedure for the preparation of curcumin was proposed by Bhawna et.al (21). Here the curcumin stock solution of 2mg/ml was prepared in dicloromethane and was sprayed on the boiling water while sonication. After

concentration and freeze drying, the curcumin nanoparticles in the form of an orange-coloured powder were obtained. By using TLC, UV spectroscopy and NMR, it was confirmed to be curcumin. The TEM and SEM analysis of the powder obtained confirmed the particle size of the nanoparticles to be 2-40nm. The dry lyophilized nanocurcumin powder was found to have a good physical and chemical stability and was readily dispersible in water. I was found to be stable for upto 6 months at room temperature without any decomposition or aggregation.

A new type of nanoformulation derived from silk fibroin was recently reported by Vishal Gupta et.al (22). They blended silk fibroin and chitosan in various proportions or pure to prepare the nanoformulations of curcumin using capillary-microdot technique. The curcumin-polymer conjugates were frozen, lyophilized, suspended in phosphate-buffered saline for characterization and tested for efficacy against breast cancer cells. A very impressive particle size of >100nm for all formulations, except one (0.1% w/v 50:50 silk fibroin: chitosan) was obtained. The formulation assumes a greater advantage as the silk-fibroin is biodegradable and hence eco-friendly. The study concluded that formulation shows a great potential to treat in vivo breast tumor cells by local, sustained and long-term therapeutic delivery as a biodegradable system.

Curcumin-loaded PLGA (poly (lactide-co-glycolide)) was proposed by Preetha Anand et. al (23). They applied a polymer-based nanoparticle approach in order to improve the bioavailability and were able to encapsulate curcumin with upto 97.5% efficiency in the formulation. They used the technique of nanoprecipitation to prepare the curcumin encapsulated nanoparticles. The PLGA-PEG and curcumin were mixed in acetonitrile, added dropwise to the aqueous solution containing surfactant. The resulting nanoparticles were vacuum evaporated, centrifuged, washed with water and freeze-dried. The in-vivo study on rats further confirmed the better bioavailability of curcumin nanoparticles in mice with enhanced cellular uptake. Another part of study conducted on human chronic myeloid leukemia cell lines confirmed that curcumin nanoparticles induces apoptosis of tumor cells, inhibits proliferation of tumor cells, Supresses NF-κB activation, inhibits the expression of NF-κB-regulated gene products. The hypothesis was further confirmed by Kan Jing Lim et. al (24) in their study in which they investigated the effect of curcumin nanoparticles (Nanocurc^{TM}) on both medulloblastoma and glioblastoma. In their study they concluded that curcumin nanoparticles inhibit the growth of brain tumor cell lines via programmed cell death and G_2/M cell cycle arrest. A 3 day treatment of 10μM curcumin resulted in 35% growth reduction in DAOY medulloblastoma cells. The curcumin nanoparticles were also found to be able to inhibit clonogenicity and deplete stem-like cells from malignant brain tumor cultures. Compared to vehicle-treated cells, 5 and 10μM curcumin significantly reduced the normalized clonogenicity of DAOY cells from 100 to 10% and 1-8% respectively. The similar observation was reported in glioblastoma cells also when treated with 10μM nanocurcumin. In order to prepare nanocurcumin, they predistilled the monomers of NIPAAM (N-isopropylacrylamide), VP (vinylpyrrolidone) and AA (acrylic acid) and mixed them together in a ratio of 60: 20: 20 respectively. They performed polymerization, dialysis and the solution was finally lyophilized for the post loading of curcumin. The resulting solution was snap frozen on a dry-ice/ acetone bath and lyophilized and stored at 4°C.

Anitha et.al, (2011) successfully prepared a nanocurcumin formulation using dextran sulfate and chitosan and achieved a particle-size of 200-220nm and drug-entrapment

efficiency of about 74%. They carried out in-vitro study done by direct-dispersion method which showed a controlled and pH dependent curcumin release over a period of one week. The procedure used for the preparation was as follows: 0.1% dextran sulfate was added to 0.1% chitosan (in 1% acetic acid) under vigorous stirring in the ratio of 3:2 and curcumin was loaded into nanoparticles in 5% wt of polymer.
A very recent development has been curcumin nanodisks reported by Ghosh et. al.(27). In this formulation, the curcumin is sandwiched between a lipid bilayer. The particle-size of the nanodisks has been reported to be 48±9nm with thickness of 5.3±0.8nm when examined with atomic-force microscopy. They formulated curcumin-loaded nanodisks at a 6:1 phospholipid-to-curcumin molar ratio. The results indicate that incorporation of curcumin into nanodisks enhances its ability to inhibit hepatoma cell growth and induces apoptosis in Jeko cells due to its enhanced bioavailability.

Conclusion

Although the clinical effects of curcumin have been known for centuries, still the scientists had a challenge of poor bioavailability. The studies have indicated that curcumin taken orally has poor absorption and poor bioavailability which severely limits its clinical utility. The various nanoformulations prepared have contributed to improve its bioavailability and aqueous solubility, thereby resulting in opening doors for the clinical applications in the field of treatment of various diseases, especially cancer. Also, its enhanced bioavailability has been achieved without compromising its potential biological activity. Its effects have been marked in the treatment of variety of cancers as it hampers the cancer pathway in more ways than one. The numerous in-vitro studies on a variety of cell lines suggest that the curcumin in the form of nanoformulation retains its biological activity, although its hydrophilic characteristics are altered leading to better bioavailability due to better aqueous solubility.
This has been ably supported by numerous in-vivo studies on various animal models. The effect has been of greater significance in case of carcinomas that are resistant to chemotherapy. Curcumin nanoparticles have given a ray of hope to the patients with MDR (multi drug resistance).
The proposed work plans to improve the bioavailability and aqueous solubility of Curcumin without compromising on its biological activity by preparing the silica nanoparticles doped with curcumin.

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