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Review Article

Curcumin and Food Nanotechnology

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Abstract

In this mini-review the developments in curcumin nanoformulations as part of food nanotechnology in general are discussed with a special emphasis on the application of curcumin nanoformulations in oncology. Although these nanoformulations overcome poor curcumin bioavailability, there is no evidence for a significant role of curcumin in oncology until now, despite thousands of studies. Long-term toxicity of nanoformulations in food technology and biopharma is not known at all. Therefore, an international framework is required to guarantee the safety of consumers and patients.

Introduction

Curcumin, a natural diphenolic compound derived from tumeric Curcuma longa, has proven to be a modulator of intracellular signalling pathways that control cancer cell growth, inflammation, invasion and apoptosis. Curcumin's use for various disease indications cover a wide range of diseases varying from cancer, Alzheimer's disease and other neurodegenerative disorders, rheumatoid arthritis, infectious diseases, diabetes and cardiovascular diseases [1-3].

Curcumin is by far, the most prominent polyphenol widely used as a food colouring agent since ancient times, and consumed on a daily basis along with food in India, Eastern Asia and some African countries. However, like many other lipophilic small drug molecules, curcumin has also limitations for its efficient use in clinical medicine. These include low hydrophilicity and intrinsic dissolution rates, low physicochemical stability, rapid metabolization, low bioactive absorption, poor pharmacokinetics and bioavailability and low penetration and targeting efficacy [4-6].

All these factors significantly hampers the efficient use of curcumin as a therapeutic molecule. However, it also encouraged nanotechnologists to design or formulate useful nanocurcumin formulations for improved solubility, stability, cellular uptake/internalization efficacy, specificity, tolerability and therapeutic index [7-12]. In this mini-review the developments in curcumin nanoformulations as part of food nanotechnology in general are discussed with a special emphasis on the application of curcumin nanoformulations in oncology. Other potential applications are beyond the scope of this mini-review.

Food Nanotechnology

Advances in nanoscience and nanotechnology intend new and innovative applications. Nanotechnology is an efficient method in many fields, particularly the food industry. Food nanotechnology comprises a wide spectrum of applications in this industry, involving the whole food chain.

Nanoemulsions display numerous advantages over conventional emulsions due to the small droplet size they contain, high optical clarity, excellent physical constancy against gravitational partition and droplet accumulation, and improved bioavailability of encapsulated materials, which make them suitable for food applications [13].

This new rapidly developing technology impacts every aspect of the food system from production to processing, packaging, transportation, shelf life and bioavailability. Commercial applications of nanomaterials in the food industry will grow because of their unique and novel properties. Therefore, also human exposure will continue to increase and the health impact of nanomaterials in food is of prime public concern. The ability to quantify the nanomaterial throughout the food life cycle is critical for manufacturing consistency, safety and potential benefit of the consumer product. Public acceptance of food and food-related products containing nanomaterials will depend on their safety. A uniform international regulatory framework for nanotechnology is a must, according to Hayes and Sahu [14]. The same techniques used in the food nanotechnology are also applied in biopharma, as the development of curcumin nanoformulations shows.

Curcumin Nanoformulations

During the last decade numerous nanoformulation-based approaches have been undertaken to enhance curcumin use *in vitro, in vivo* and in pre-clinical settings that involve the use of adjuvants, stabilizers, conjugates/polymer conjugates, lipid/liposomes, hydro/micro/nanogels and nanoparticles [7,11,12]. Many of these efforts initially dealt with improved bioavailability, but newer formulations pay attention to efficient targeting of curcumin at the diseased area with the aid of antibody, aptamer and peptide medication [10].

Nanoparticles have been the most widely used in curcumin nanoformulations. In particular, biodegradable nanoparticles have been used for encapsulation of curcumin due to its biocompatibility and biodegradability and some systems have reached clinical practice.

Liposomes are generated from phospholipid bilayers and are the second most widely used vehicle to solubilize/encapsulate curcumin. Various types of liposomes have been tested for delivery of a number of clinically used drugs [15].

Cyclodextrins are cyclic oligosaccharides that can solubilize curcumin in a lipophilic cavity, and the hydrophilic outer surface helps in greater dispersion of the formulation.

Polymers have been used to improve solubility and bioavailability of curcumin. Polymeric carriers have been widely studied for efficient delivery of curcumin.

Conjugates are made by conjugation of curcumin to small molecules and hydrophilic polymers to increase aqueous solubility.

Micelles or polymeric micelles are composed of amphiphilic block polymers that spontaneously form 20-100nm (nanometre) micelles in aqueous solution at the above critical micellar concentration,The hydrophobic core of micelles can effectively house curcumin for solubilization and targeted delivery.

Dendrimers are composed of highly branched and star-shaped networks of macromolecules. Typically, dendrimers are formed symmetrically around the core at nanometre-scale dimensions and are three-dimensional spherical in morphology. These carriers are highly suitable for conjugation and loading of curcumin.

Lipid nanoparticles are typically spherical in shape with a lipid core matrix that can solubilize curcumin. The lipid core is stabilized by surfactant molecules.

Nanogels are hydrogel nanoparticles of swollen physical/chemical cross-linked networks composed of hydrophilic or amphiphilic polymer chains. These carriers can be designed to transport various drug molecules including curcumin. These carriers mimic human tissue due to its swollen nature.

Gold nanoparticles are emerging as a novel platform of photo thermal agents, contrast agents and radio sensitizers. In addition, their use is supported in the delivery of curcumin.

Magnetic nanoparticles are a class of nanoparticles that can be used for multifunctional purposes including delivery of drugs (curcumin),magnetic resonance imaging, and hyperthermia.

Solid dispersions are dispersions of curcumin in a suitable inert matrix.

Therapeutic Applications

It is evident that poor solubility, bioavailability, and poor pharmacokinetics are major barriers to the clinical translational use of curcumin. Recent clinical studies demonstrate that curcumin nanoformulations exhibit improved bioavailability and provide a strong rationale once additional mechanical properties are understood. Until now there is no report out there demonstrating clinical benefit of curcumin nanoformulations, but since curcumin nanoformulations showed superior outcomes over free curcumin in both *in vitro* and *in vivo* studies [7,10] further research is warranted.

Anti-Cancer Activity

Curcumin has attracted great attention in the therapeutic activity due to chemo-preventive, antitumor, radiosensibilizing, and chemosensibilizing activities against various types of cancer cells. These malignancies include breast, ovarian, prostate, leukemia's, lymphomas, multiple myeloma, brain cancer, melanoma and skin and lung cancers. Curcumin mediates its ant proliferative, anti-invasive and apoptotic effects on cancer cells through multiple molecular mechanisms.

The oncogenic pathways inhibited by curcumin encompass the members of epidermal growth factor receptors (EGFR),sonic hedgehog (SHH)GLIs and Wnt/beta-calenin and downstream signalling elements such as Akt, nuclear factor-kappa-B (NF-kB) and signal transducers and activators of transcription (STATS).

The selective delivery of synthetic analogs or nanotechnology-based formulations of curcumin to tumors, alone or in combination with other anti-cancer drugs, may improve their chemo-preventive efficacies against cancer progression. Novel curcumin formulations may also be used to inhibit the drug resistance, eradicate the total cancer mass and improve the ant carcinogenic efficacy in patients.

Studies have indicated that curcumin is a safe and potent drug with no major toxicity. Curcumin protects normal cells and organs at least in part by up-regulating the nuclear factor erythroid-derived-2-related factor 2 (Nrf2) induced antioxidant gene products. In the study of Zaman *et al.* prepared poly (tactic-co-glycolic-acid) predicated curcumin nanoformulation demonstrates that the polymeric nanoparticle efficaciously inhibits the cell growth, induces apoptosis and cell cycle arrest in cervical cancer cell lines as compared to the native curcumin [16].

Mukerjee *et al* prepared nanospheres of curcumin with encapsulation of PLGA and studied their activity against prostate cancer cell lines,LNCaP,PC3 and DU 145. IC 50 value of cells treated with polymer encapsulated nanocurcumin was less than for the native or free curcumin treated cells [17].

Various polymeric nanoformulations of curcumin were synthesized by cross-linking of N-isopropyl acrylamide, N-vinyl-2-pyrrolidone and polyethylene glycol monoacrylate. Their ant proliferative activity has been studied against pancreatic cancer cells and amended results were obtained in the case of polymer loaded nanoparticles as compared to native curcumin [18].

Hoshikawa *et al* prepared alpha, beta and gamma-cyclodextrin/polyethylene glycol conjugated gold multifunctional nanoparticles and studied their *in vitro* cytotoxic effect on A549 cells of a lung cancer cell line. All cur-CD-GNPs exhibited cytotoxic effects comparable to curcumin solution and CD-GNPs without curcumin were not cytotoxic [19].

Anti-cancer activity was also studied against breast cancer cell lines by induction of apoptosis using transferrin-mediated solid lipid nanoparticles (SLNs) of curcumin. Flow-cytometry results concluded that the transferrin mediated SLNs nanocurcumin has anticancer activity compared to the native curcumin [20].

It is obvious from these studies that the ideal curcumin nanoformulation in oncology has not been found yet, because various factors as particle size, surface properties, shape, aggregation, encapsulation efficacy and drug content and release profile all play a crucial role.

Particle Size

Particle size plays a major role in the mode of action, tissue distribution and rolling, firm adhesion of nanoparticles, phagocytosis and accumulation. The rate of excretion is greater for large particles (>1um) that aggregate under physiological conditions and don't pass capillaries. Sethacheewakul *et al.* revealed the self-emulsifying liquid nanoformulations with a particle size of 30-50nm increased the absorption rate of curcumin 10-14 folds compared to the same oral native curcumin in rats [21].

Surface Properties

The most important characteristics of surface properties of nanoparticles are its surface area, electrical charge and hydrophylicity. The nanoformulaton of any particle ranges from 1um to 1000m. Reduction in size increases surface area to volume ratio. This may result in enhanced reactivity which dictates the bio-distribution among the tissues, body organs and rate of excretion from the body. The surface charge of the nanoparticle is an important determinant of the accumulation rate at the site of interest. Negatively charged particles have reduced adsorption rate of serum proteins, resulting in longer circulation half-lives. The positively charged particles have a high non-specific role of cellular uptake in the majority of cells [22].

Shape

Particle shape is another essential property of nanoparticles that plays a pivotal role in its therapeutic activity. The shape of the nanoparticle affects its blood circulation, ability to transport, binding affinity, targeting and internalization in the affected cells and tissues, and circulation time. For a nanoparticle it is necessary to evade uptake by macrophages, particularly in the reticulo-endothelial system (RES) to increase their circulation time and retention power in the cell. Bio distribution studies have shown that spherical particles have an advantage over the uptake of particles with high aspect ratios. Tailoring of shape and dimension improved the effect of tumour therapy. For example, trastazumab coated nanorods exhibited a 5 fold greater cell inhibition of BT-474 breast cancer cells compared to equivalent nanospheres at the same nanoparticle dose. This leads to a 66% increase in binding ability and uptake by the cells of the nanorods compared to the nanospheres [23-26].

Particle Aggregation and Agglomeration

Aggregation and agglomeration affects cellular uptake and interactions. The formation of large NP (nanoparticle) complexes in suspension is due to the effect of van der Waals attraction forces when these are greater than the electrostatic repulsive forces produced by the nanostructure surface. Particle agglomeration is influenced by a number of factors, including primary particle characteristics as well as the properties of the suspension medium. The aggregation states of nanoparticles also influence their toxicities. They depend on size, surface charge and composition. Carbon nanotubes are mainly accumulated in liver, spleen and lungs without manifesting any acute toxicity, but they induce cytotoxic effects mostly because of accumulation of aggregates for longer periods. Agglomerated carbon nanotubes can cause pulmonary interstitial fibrosis [27-31].

Particle Encapsulation Efficiency

Encapsulation efficiency or surface coating influences its solubility and interaction with other biological entities. It also affects their chemical reactivity and pharmacokinetic properties of nanoparticles. Many researchers used polymeric materials like Poly(lactic-co-glycolic) acid (PLGA, polyethylene glycol (PEG), and surfactant polymers for maintaining higher stability of the nanoparticle system. Curcumin loaded PLGA nanoparticles showed a neuroprotective effect in Alzheimer's [32-38].

Drug Content and Release Profile

The content of drug loaded and its release profile at the site of interest of any nanoparticle system is highly dependent on the type of nanoparticle used and its method of preparation in the case of curcumin nanoparticles. In most of the curcumin nanoformulations the *in vitro* release follows a biphasic pattern. The sustained release profile of curcumin nanoparticles may vary on nanoformulation, composition, location of entrapment and amount. Tailoring of nanoparticle design is aimed at an intrinsical capacity of high drug entrapment efficiency and loading capacity.

Clinical Trials

Clinical trials using curcumin alone or in combination with chemotherapetics are still in their infancy. A wide range of clinical trials have been undertaken. Some have been withdrawn, but results are rather poor, often failing to meet primary outcomes. A recent review found that there have been more than 120 clinical trials of curcumin against several diseases, mostly cancer, but no trial of curcumin has been successful [39,40]. The authors conclude that low systemic exposure levels reported in clinical trials, even when using nanoformulations, do not support its further investigation as a therapeutic. They added that they believe that much of the research into curcumin is "much ado about nothing" [40].

Finally, supplementation with turmeric and curcumin may not be without harm. Laboratory findings show that dietary curcumin may actually inhibit the anti-tumour activity of chemotherapeutic agents such as cyclophosphamide and doxorubicin [41]. At this time there isn't enough evidence to recommend curcumin for preventing or treating cancer [42].

Conclusion

Curcumin has been strongly advocated as a natural anti-oxidant benefiting a lot of diseases by the complementary alternative medicine (CAM) community. Most research has been performed regarding the anti-cancer activity of curcumin. A host of studies (thousands), *in vitro, in vivo* and clinical are not able to provide evidence for a significant role of curcumin in the prevention or treatment of cancer until now [42]. Even when modern curcumin nanoformulations were used to overcome poor curcumin bioavailability problems, this holds true.

In the meantime long -term toxicity of curcumin nanoformulations and nano-emulsions in food technology is not known at all. Because 'nano' does not mean "too small to see" an international framework for food-and biopharma nanotechnology is required to guarantee the safety of consumers and patients [14]. Much work has to be done in food-and biopharma technology, therefore.

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