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Review Article

Role and development of nanoparticle in enhancing the therapeutic potency of curcumin: A review

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ABSTRACT

Turmeric, a traditional perennial herb widely used as a spice in most of the Asian countries [China, India, Iran]. Curcumin, a yellow hydrophobic polyphenol derived from the rhizome of Curcuma longa L., has been widely used in medicine for centuries. Curcumin has wide spectrum of biological and pharmacological activities such as anti-diabetic, anti-inflammatory, anti-carcinogenic, anti-bacterial, anti-HIV, anti-ageing, hepatoprotective activity, cardiovascular benefits, neurodegenerative and psychological disorders. All the above positive features were over shadowed by its poor bioavailability, which appears primarily due to poor absorption, rapid metabolism and rapid systemic elimination. This led to the formulation of solid liquid nanoparticles encapsulating curcumin. This imparted curcumin improved resistance to hydrolysis due to gastric juices or small intestinal enzymes. Thus, the available information suggests that Nano-formulation of curcumin maybe used as a novel drug delivery nutrient system.

Key Words: Curcumin, Nanoparticle, PLGA, Edudragit-hyaluranon liposomes, Eudragit nutrisomes, LBL Technology

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INTRODUCTION

Curcumin, a yellow coloured substance obtained as a b0y-product of turmeric has been long used traditionally as a base for food, medicine and cosmetics. In most South Asian countries like India, curcumin finds its use in Ayurveda system [1]. In Ayurveda medicine it is used to treat inflammatory diseases including asthma, allergies, rheumatism, sinusitis, cough, diabetes. In Chinese traditional medicine it was used to treat abdominal pain, to treat sprain and muscle pain and also to treat intestinal bowel syndrome (IBS)[2], psoriasis and Alzheimer's. As a traditional medicine it has been used to strengthen the overall energy of body, relieving gas, dispelling worms, improving digestion, regulating menstruation, dissolving gall stones. In dermatology it has been used as an antiseptic for cut, burns, bruises, as antibacterial, anti-inflammatory, anti-fungal agent. It is also used to cleanse skin and wound for the recovery and regeneration of new cells for glowing of the skin. Because of its wider use in Indian Ayurveda system it is often referred as Indian solid gold [3]. Unani practitioner used it to expel phlegm or "kapha", as well as to open blood vessels to improve blood circulation and also it is used as cholagogue stimulating bile production in liver and helping in excretion of bile via gall bladder in order to improve the digestion ability of fats.

History and discovery of curcumin: About two centuries ago, Vogel and Pelletier discovered curcumin by isolating a "yellow coloured compound" from the rhizome of Curcuma longa, turmeric which was then named curcumin[4]. This substance was then found to be a mixture of resin and turmeric oil, which is composed of sesquiterpene ketones and alcohols; α-turmerone, β-turmerone, curl on, zingiberene, returner, turmerol A, turmerol B. A pure preparation of curcumin was obtained by Vogel Jr. in 1842[5]. A number of possible structures of curcumin were reported by several chemists in decades that followed[6-8]. But it was not until 1910 that Milobedzka and Lamp identified curcumin chemically as diferuloylmethane, or 1,6 heptadiene 3,5 Dione 1,7 bis (4 hydroxy 3 methoxy phenyl) - (1E,6E)[9] (fig1). It also exhibits keto-enol tautomerism having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium(fig2). Besides these major constituents, three minor constituents can be isolated which are presumed to be the geometrical isomers of Curcumin. One of these is assumed to be the cis-trans geometrical isomer of compound curcumin(fig3) (which has the trans-trans configuration) based on its UV spectrum, lower melting point and lower stability in solutions and in the presence of light when compared to compound above. Following this, 1949 marked the identification of Anti-bacterial effect of curcumin by Schraufstatte[10]. Eventually Srinivasanet al. adopted various chromatographic techniques to separate and quantify various components of curcumin[11]. Cholesterol lowering[12], anti-diabetic[13], anti-inflammatory[14] and anti-oxidant[15]effects were a few of the many diverse characteristics of curcumin that were discovered by three independent groups and scientific investigations in 1970's. Invitro and Invivo studies were performed by Kuttan and colleagues to demonstrate anti – cancer activity of curcumin in 1980's[16].In 1995 Subash C. Gupta et al. were the first to demonstrate that curcumin exhibits pro inflammatory transcription factor nuclear factor (NF), and delineated the molecular mechanism of the inhibition[17]. In order to overcome the poor absorption, rapid metabolism and rapid systemic elimination, curcumin nanoparticles were subsequently formulated[18,19].

DEVELOPMENT OF CURCUMIN NANO PARTICLES

The major objective of this study is to systematically delineate the advancements in the development of Curcumin nanoparticles over the years. It also explains the limitations associated with the following studies discussed.

2009

In 2009, Vishal Gupta et al, fabricated biologically derived nanoparticles (<100nm). They encapsulated curcumin in various proportion of Silk fibroin (SF) and Chitosan (CS) polymers(75:25, 50:50, 25:75 SF: CCF) to formulate silk fibroin derived curcumin nanoparticles, which imparted them with properties like local and sustained therapeutic delivery of curcumin to cancer cells. The polymer conjugates thus formulated were subjected to various processes like freezing, crystallisation, suspension in phosphate buffer saline for characterisation and finally tested for efficacy against breast cancer cells. Observations over eight days showed that SF derived nanoparticles as compared to all SFCS blends showed the highest entrapment and release of curcumin. It was concluded that SF derived curcumin nanoparticles showed highest efficacy against breast cancer cells and have the potential to treat in vivo breast tumours by local, sustained and long-term therapeutic delivery as a biodegradable system[20].

2010

Cystic fibrosis is a life-threatening hereditary disease. Lungs, pancreas, sweat glands and male fertility are the principle functions of the body it affects. Its primary effect is on the body's ability to move salt and water in and out of the cells as a

result of which the lungs and pancreas secrete abnormally thick mucous that blocks the passage way and hinders proper function. Curcumin is a natural constituent of curcuma longa (turmeric spice). This hydrophobic, lower molecular weight dietary poly phenolic compound is a non-toxic, low affinity SERCA(Sarco(endo) plasmic reticulum Ca ATPase) pump inhibitor. It is assumed to permit the δF508 CFTR escape from endoplasmic reticulum. The major pathophysiology of cystic fibrosis lies in the inability of the delta F508 CFTR, although functioning as a CAMP-gated chloride channel, in reaching the epical plasma membrane of airway, pancreas, intestinal epithelial cells. Consequently, sweat and water secretions by epithelium are compromised[21,22]. This work majorly focused on synthesising PLGAC (Poly lactic. Co glycolic acid) Nano particles encapsulating curcumin to partially correct the phenotype defects of cystic fibrosis. Various mechanisms of action had been proposed for this property of curcumin[23]. Several cell lines and mice were taken as experimental objects in which curcumin showed its effect of partially correcting the defective phenotypes[24].The poor bioavailability of curcumin which is a major challenge was improved by formulating it as PLGA encapsulated Nano particles. The results indicated that the oral administration of PLGA Nano particles encapsulated curcumin had enhanced effect on micein comparison to the delivery of non-encapsulated curcumin.

New dosage forms of purely soluble drugs are formulated using LBL technology (layer by layer) with polymer coatings for the preparation of novel drug delivery system. This novel method in the nanoparticle formulation was demonstrated on curcumin. Ultra-sonification was adopted for deagglomeration and dispersion of Nano particles, which can remain in suspension for a number of months[25,26,27]. For various anti-cancer drugs (paclitaxel, tamoxifen, etc) previously, micelles were the only Nano scale delivery system. The major limitation of this method is that the micelles contained very small percentage of the desired drug [28,29,30]. Another approach for the drug Nano formulation includes ultrasonicated decomposition of drug powder into polymeric coacervates[31,32,33]. The major disadvantage of this study is that for such formulations the usual size of such carriers is small enough and hence inefficient for most of the medicated applications[34]. This study showcases a new approach for the preparation of drug Nano colloids (diameters less than 100nm). Ultra-sonification assessed nucleation of drug particles from their solutions in organic solvents (that are miscible with water/ethanol). Drug nucleation was initiated by gradual worsening of the polyelectrolytes using layer by layer shell assembly. Formulation of shells with two bilayers of biocompatible polyelectrolytes allowed slow drug release.

2011

Human cerebral malaria is a serious complication with high mortality. The major factors contributing to high mortality in human cerebral malaria are break down of blood brain barrier, action of inflammatory cytokines on brain mRNA, and sequestration of parasitized RBC and CD_{8+}T -Cells in brain. This paved the way for the invention of an urgent therapy despite having the existing standard therapy using Artemisinin and its derivatives.

The most effective mechanisms of action of curcumin are preventing the breakdown of blood brain barrier, inhibiting the action of inflammatory cytokinins, chemokinetic receptor $CXCR_3$and its ligand $CXC\alpha_{10}$ on brain mRNA and an increased action of anti-inflammatory cytokine $I\alpha_{10}$.This was demonstrated in the serum cytokine and chemokine levels[35].The results showed that PLGA curcumin has potential as an adjuvant drug to treat malaria in reference to native curcumin because an oral administration of 5mg PLGA curcumin encapsulating 350mg of curcumin showed a prolonged presence of curcumin in brain and three to four times higher concentrations than that was obtained with 5mg of native curcumin demonstrating bioavailability of PLGA curcumin. Nano form of curcumin was shown to significantly increase retention time in cerebral cortex and hippocampus.

Acute lung injury is also commonly referred to as acute respiratory distress syndrome. Patients with this condition may experience shortness of breath, fast breathing, blue skin from poor circulation, coughing, increased carbon dioxide level in blood muscle weakness, capillary leakage, reduced lung compliance and hypoxia. Pulmonary illnesses such as lung injury remain a clinically challenging problem for a number of reasons including for a poorly understood complex physiology and patient heterogeneity. The absence of biomarkers that predict disease onset, progression and severity have led a negative impact on our ability to develop effective pharmacotherapy aimed at improving mortality and morbidity in patients with critical illnesses[36].A novel formulation of curcumin was developed by chelation of the compound with hydroxy propyl gamma cyclo dextrin(CD)[37,38,39]. This resulted in greatly enhanced solubility, attenuated multiple markers of inflammation and injury including pulmonary oedema and neutrophils in Broncho alveolar lavage fluid and lung tissue. It was also known to reduce oxidative stress in lungs and inactivation of the proinflammatory transcriptional factor.

2013

Diabetes is a metabolic disease that impairs the body's ability to process blood glucose, otherwise known as blood sugar. Uncontrolled or poorly controlled diabetes can lead to micro (blindness, neuropathy, nephropathy) and macro vascular complications[40].Curcumin when taken through diet, as turmeric, delays diabetes induced cataract in rats but due to its low preoral bioavailability its clinical utilisation is limited. When streptozotocin induced diabetic cataract in rat is taken as object and injected with curcumin encapsulated Nano particle there was noteworthy increase in effectiveness of curcumin in delaying diabetic cataracts in rats when administered orally at a dose of 2mg per day than non-capsulated curcumin [41]. The ability of curcumin to get interceded in the biochemical pathways of disease progression such as 1) Polyol pathway 2) Protein in solubilisation 3) Protein glycation 4) Crystalline distribution 5) Oxidative stress attributed to its remarkable delay in advancement of diabetic induced cataract by Nano curcumin.

The fundamental abnormality in Alzheimer's disease is the self-accumulation of two proteins (Aβ and tau) in specific brain regionsin the form of oligomers and amyloid fibrils, likely asa result of excessive production and defective removal. Plaques are deposits of aggregated Aβ peptide in the neutrophil while tangles are aggregates of the microtubule binding protein tau, which develop intracellularly and then persist extracellularly after neural death. Neurotoxicity exhibited by oligomers and plaque formation by fibrils along with chaperon proteins damage neurons and attract reactive astrocytes and microglia causing increased damage to brain[42,43,44] Curcumin is effective in treating Alzheimer's disease as it binds to Aβ and prevents aggregation[45] even at low concentration because of its ability to cross blood brain barrier. It can prevent Aβ fibril formation, plaque burden and reducing brain amyloid level. Curcumin had a very low plasma concentration of 1.77μM[46]. When administered at a dose of 8g/day is, the bioavailability of curcumin can be improved through Nano technology techniques which effect the final stability and particle size. Plasma concentration of curcumin was high when administered in the form of Nano curcumin.

2014

Bacterial infections complicate traumatic injuries (burn wounds) which can lead to morbidity and mortality because avascular wound beds are rich sources of nutrition facilitating bacterial growth. These pathogens (Methicillin resistant Staphylococcus aureus MRSA and pseudomonas aeruginosa) penetrate into the tissues and spread in blood stream as haematogenous dissemation[47]. Toxicity, incomplete anti-microbial coverage, inadequate wound bed penetration and growing bacterial resistance are the leading drawbacks of existing conventional anti-microbials. Curcumin, known for its anti-microbial, anti-inflammatory, wound healing activities is short listed for clinical trials but its poor bioavailability, solubility, rapid degradation are major restrictions for potent use. Hence encapsulated curcumin is most acceptable and advisable to enable Curcumin's pharmacokinetic properties. Neovascularisation is enhanced but keratinocytes migration was not influenced by Curcumin[48]. Aimme E and co. workers through sol-gel processing which is a wet chemical technique including hydrolysis and polycondensation of sol to form gel like systems and drying process removed the solvent phase. Through this process Aimme E concluded that Curcumin shows its inhibitory effect on cellular proteins Ftsz and sortase A which are helpful in interrupting the cytokinases and cellular adhesion[49].

2015

Regenerative medicine is defined as the process of replenishing or restoring lost or damaged organs through the transplantation of ex-vivo fabricated body parts. It also includes restoration of the levels of function of the damaged tissue or organs [50]

Newer alternatives for post-transplant cell tracking in cell-based therapies are still under infant stages. Hence, Bassam, Felipe and Mogharbel used stem cell labelling as an efficient technique Their study included the usage of bio-polymers like curcumin in their Nano forms. Anti-oxidant and anti-cancer properties of curcumin ensures the survival of adipose-derived mesenchymal stem cell (ADMSC) after transplantations, by expressing heme-oxygenase-1 which prevents cell death caused by oxidative stress and also improves the myocardial recovery by increasing vascular endothelial growth factor production, enhanced anti-apoptotic ability, improved neo vascularisation in infracted areas. Stem cell labelling has become a crucial strategy for monitoring and maximizing benefits of cell-based therapies like post-transplant cell tracking [51] because of their (MSCs) presence in adult solid organs and in mesoderm of embryonic tissue. Curcumin loaded nanoparticles (NPC) provides the best way to assess tissue regeneration, histological examination, real time imaging, transplantation using Vero cells(in-vitro) and NPC labelled adipose derived mesenchymal stem cells (NPC-ADMSCs) (in-vivo). Curcumin which is a prototype polyphenolic ingredient of turmeric has many drawbacks like low aqueous solubility and bioavailability which preclude it's use as an effective functional food ingredient for nutraceutical [52] applications. For the effective

functioning of curcumin, it was mono encapsulated in self-assembled Nano carrier made of biodegradable lipid and polymer. The supramolecular Nano assemblies formed by electrostatic interactions of two oppositely charged lipid and polymer have been prepared and thus used as Nano carrier for curcumin to improve its bioavailability and solubility. These curcumin Nano carrier systems were characterised with respect to their size (dynamic light scattering), morphology, zeta potential (laser Doppler velocimetry) and encapsulation efficiency (CE). Stability of these Nano carriers was assessed at different storage times as a function of varying pH and temperature. The physiochemical characterization of Nano assemblies was demonstrated using Fourier transform infra-red spectroscopy (FT-IR) and differential scanning calorimetry (DSC). The invitro anti-oxidant lipid peroxidation (TBARS), radical scavenging (DPPH, NO, H2O2), reducing power and activity of powdered curcumin and Nano encapsulated curcumin were demonstrated. The resulted curcumin Nano carrier systems were roughly spherical in shape with high positive zeta potential, and pH range of 2to 6 and good stability which enhanced antioxidant potency. Thus, Nano encapsulation of nutraceutical ingredients opens a new gateway to technology domain of food and nutraceutical industry to address various issues related to food ingredient stability, bioavailability and solubility[53].

2016

Curcumin has been detected with wide range of biological activities including anticancer property but the major problem is its poor bioavailability which can be improved by addition of carrier such as diamond nanoparticles. They are carbon allotropes which imparts them with biocompatibility resulting in their easy imbibition by the cell DN particles. They are also predicted to be nontoxic particles having antiangiogenic properties with potential application in cancer therapy[54]. Their large surface area is responsible for the development of a promising compound in drug delivery system for bio active agents such as DN. They are used to create bio complexes in a fast and simple process. Investigations revealed the cytotoxicity of such bio complexes against liver cancer cells and normal fibroblasts showing that the conjugation of curcumin with DN significantly improves its activity by increasing the bioavailability in a hydrophilic environment.

2017

Ischemic reperfusion is a temporary impairment of blood flow to particular organ, associated with neutrophils and inflammatory cytokines[55]. Ischemic reperfusion injury also called "reoxygenation injury" is the damage caused to tissue during restoration of blood flow to the Ischemic tissue. It results in inflammation and oxidative damage which disturb the normal functioning of the organ. Oxidative stress and lipid peroxidation promote the process of inflammation during Ischemic reperfusion. Clinical conditions such as haemorrhagic shock [56], renal transplantation[57], and acute renal failure[58] appear in company with renal ischemic reperfusion injury. Anti-oxidant property of curcumin improved tubular necrosis by reducing formation of noxious oxidants to a greater extent [59]. Due to its poor solubility and its ease to metabolise there is restricted use of curcumin. To enhance the use of curcumin it is modified into new dosage form which had better pharmacological effects. If curcumin is administered using Nano particles system it had various advantages such as target deliver, slowed release, high stability, relatively low toxicity[60,61]. Nano particles dispensed from distearoyl phosphatidyl ethanolamine-polyethylene glycol (DSPE-PEG) were soluble both in water and fat. This bidirectional solubility increased encapsulation efficacy and water solubility of fat-soluble drugs. PEG exhibited good water solubility and was excreted through urine in an unchanged form from kidney [62]. PEG had low immunogenicity. DSPE exhibited good drug encapsulation efficiency, therefore was used as core [63]

2018

According to the Farlex Partner Medical Dictionary 2012, Plasmodium berghei is defined as a species of protozoan that is the etiologic agent of rodent malaria from Central Africa, an important source of experimental nonprunate mammal malaria. It occurs naturally in the rats, transmissible experimentally to other rodents. Pharmacotherapy of malaria includes treatment with various oral agents like chloroquine, atovaquone-proguanil (malarone), artemether-lumefantrine, mefloquine(larien), quinine. Curcumin is an inexpensive, less toxic antimalarial compound that is efficacious across a diverse population. Oral administration of curcumin to mice infected with the murine malaria parasite: Plasmodium berghei reduced blood parasitaemia by 80-90% and enhanced the survival of mice. It's anti-plasmodial effect was shown to delay the death of mice by about 10 days and prevent the cerebral malaria, which is the most severe and rapidly fatal neurological complication of the disease. All the above promising results of this interesting polyphenol have been hindered by it's extremely reduced solubility, low serum and tissue levels regardless of the route of administration owing to its extensive intestinal and hepatic metabolism along with rapid elimination. This study reviewed

the oral administration of the curcumin encapsulated liposomes formulated using anion copolymer eudragit ® s100 containing either hyaluronan. (Edudragit-hyaluranon liposomes) or the water-solubledextrin nutriose ® FM06. (Eudragitnutrisomes). These Nano formulations were orally administered after rehydration and freeze drying at a dose of 25/27 mg curcumin kg-1 day-1. CUR Nano formulations have shown its Anti-plasmodial action in a dose dependent manner. The survival of the Plasmodium yoebii infected mice was improved from 6-7 days to 11 days upon the oral administration of Eudragit-nutrisomes, showing its antimalarial action. Eudragit-hyaluron liposomes Indica lower solubility by not improving the survival of the mice. Thus, polymer nanovesicles hold a promising, feasible and novel advancement in the management and treatment of malaria[64].

CONCLUSION

Since the ancient times Curcumin has proven to offer enormous therapeutic applications in the field of science and medicine. But its utility was greatly hindered due to some of its major associated challenges like poor absorption, low bioavailability, rapid systemic elimination and high metabolism inhibiting its therapeutic action. To overcome these drawbacks and to increase its therapeutic efficacy Curcumin was encapsulated with the nanoparticles using various technologies over the years. Remarkable advancement was noticed in development of Curcumin nanoparticles of various sizes, shapes, colour and its increasing potential in treating numerous diseases. Research is still ongoing and eventually the Curcumin nanoparticles may become an ideal medicine.

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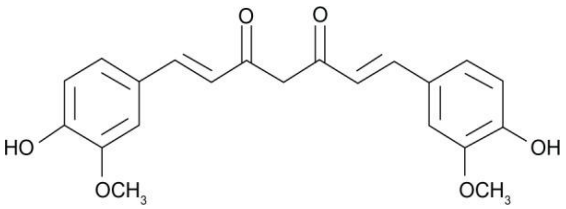

Figure 1: Strcture of Curcumin

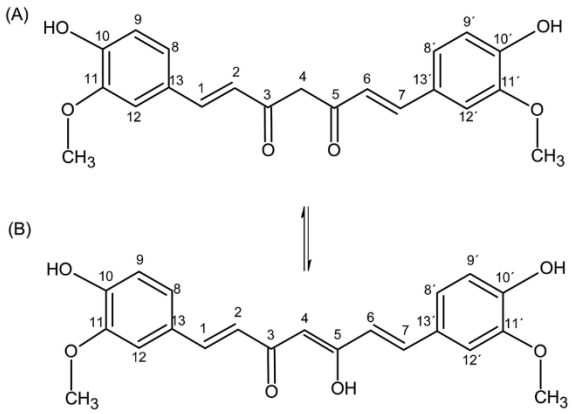

Figure 2: Alpha beta tautomerism: bis- alpha, beta – unsaturated beta-diketone

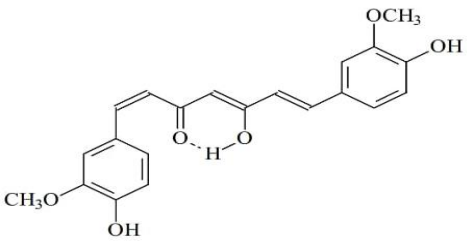

Figure 3: Cis- trans geometrical isomer of curcumin

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