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Recent advances in curcumin nanoformulations

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ABSTRACT

Curcumin, a yellow polyphenolic compound present in the rhizome of turmeric possess a wide range of therapeutic and pharmacological properties. However, its biomedical potential is limited due to poor aqueous solubility, absorption, systemic bioavailability and rapid metabolism in the human body. Lot of emphasis has therefore been given to improve the biodistribution of native curcumin. Adjuvants, bioconjugates and structurally modified derivatives/analogues were used in order to overcome various issues associated with curcumin. Although, they improved the bioavailability but the targeted delivery of curcumin to the diseased cells/tissues was still a major concern. The development of nanorange formulations of curcumin such as liposomes, polymeric nanoparticles, micelles, nanogels, dendrimers, and solid lipids nanoparticles paved way for making curcumin a better therapeutic agent. For example, liposomal curcumin formulation has greater growth inhibitory and apoptotic effects on cancer cells and also shows better antioxidant effect. Nanocrystals on the other hand provide higher stability to curcumin even at high pH. These curcumin nanoformulations are thus able to perform a wide spectrum of actions due to better multitargeting behaviour. These nanoformulations exhibits sustained and efficient curcumin delivery. Nanocurcumin thus is a promising therapeutic agent that will help in management of many life threatening diseases in humans.

KEYWORDS

Curcumin;
Biomedical potential;
Curcumin nanoformulations;
Bioavailability;
Drug delivery.

INTRODUCTION

Plants divert a significant proportion of assimilated carbon and energy for the synthesis of secondary metabolites. In contrast to primary metabolites which are directly involved in the growth and development of a plant, secondary metabolites are not essential to the functioning of the plant. These compounds however, play a significant role in the life of plants. They act, for example, as free radical scavengers or as defence against infectious microorganisms, with the aim of increasing a plant's chance for reproduction and hence survival. These metabolites help the plant in maintaining the intricate balance with the environment, often adapting to match the environmental needs. They are also of great use to mankind due to their antimicrobial and antioxidant potential. Secondary metabolites are classified into three main groups: terpenes (plant volatiles, cardiac glycosides, carotenoids and sterols), phenolics (phenolic acids, coumarins, lignans, stilbenes, flavonoids, tannins

and lignin) and nitrogen containing compounds (alkaloids and lucosinolates). Phenols, one of the secondary metabolites are the subject of increasing scientific interest because of their possible beneficial effects on human health. Several studies strongly suggest that plant polyphenols offer protection against development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases[1].

Turmeric has been used extensively in Ayurveda, Unani and Siddha medicine as home remedy for various diseases. Even today, unlike many other natural products within the ethno-medicinal tradition, turmeric still evokes great interest as a food additive, dietary supplement and prospective medicine. The plant is also considered as a medicinal herb in the West, as evidenced by WHO and Commission E monographs[2,3]. The biological properties of turmeric are due to curcuminoids, a group of the phenolic compounds present in the rhizome of turmeric plant. Of these, curcumin is the most active phenolic compound exhibiting a vast range of unique properties such as antitumor, antioxidant, anti-inflammatory, etc. The biological potential of curcumin is hindered due to its hydrophobicity, degradation at alkaline pH, photodegaradability and rapid metabolism. Nanotechnology is an emerging field that has found unprecedented growth in the field of research and applications. Nanomaterials have unique physicochemical properties such as ultra small size (< 100 nm), large surface area to mass ratio and high reactivity. The use of materials in nanoscale provides unparallel freedom to modify fundamental properties such as solubility, diffusivity, blood circulation half-life, drug release characteristics and immunogenicity. There is increasing optimism that nanotechnology, as applied to medicine, will bring significant advances in the management of life threatening human diseases[4,5]. Nanoformulations enhance the bioavailability and the solubility of lipophilic compounds in the drug delivery systems. Considering all above benefits, various methods such as adjuvants and nanoscale drug delivery system (nanoparticles, liposomes, micelles, phospholipid complex, dendrimers, phytosomes, etc.) are developed to overcome the limitations exhibited by natural curcumin. These curcumin nanoformulations improve the therapeutic effects of curcumin by protecting it from enzymatic degradation, providing controlled release and prolonged blood circulation, thus changing its pharmacokinetics. Curcumin nanoformulations are emerging as potential alternatives to enhance the therapeutic properties of curcumin. These nanoformulations overcome the limitations of curcumin such as low solubility, instability, poor bioavailability, rapid metabolism and its targeting capacity to diseased tissues. An attempt has been made in the present review to compile the information available in literature on curcumin nanoformulations focussing on its multiple pharmacological roles in the interest of scientific community.

CURCUMIN

Turmeric derived from the dried rhizome of *Curcuma longa* Linn, a major component in the spice curry and frequently used as a natural colorant (E 100) by the food industry. It is used as food additive, preservative and colouring agent in Asian countries including China and South East Asia and also considered as auspicious. Indian turmeric is considered the best in the world due to presence of high curcumin content[6,7]. The most important chemical components of turmeric are a group of compounds called curcuminoids- the yellow natural phenols with antioxidant, anti-inflammatory and chemotherapeutic activities. They include curcumin I (diferuloylmethane) (80%), curcumin II (demethoxycurcumin) (5%) and curcumin III (bisdemethoxycurcumin) (15%), instead these it also contain protein, fat, minerals, carbohydrates and moisture[8,9,10]. Of all these polyphenols, curcumin I is the best studied compound and constitutes 3.14% (on average) of powdered turmeric. Curcumin was first isolated in 1815 and its chemical structure was determined by Roughley and Whiting (1973)[11]. It is a bis-α, β-unsaturated β-diketone with two ferulic acid moieties joined by a methylene bridge. It is low molecular weight polyphenol has various functional groups which occurs in keto and enol form.

Curcumin is known for its pharmacological properties such as antioxidant[12,13], antimicrobial[14,15], antiseptic, wound-healing, antiamoebic[16] and anticarcinogenic activities[17]. In fact, it is a pleiotropic molecule also exhibiting anti-inflammatory properties possibly by interacting with molecular targets involved in inflammation[18]. *In vitro* studies have shown that it

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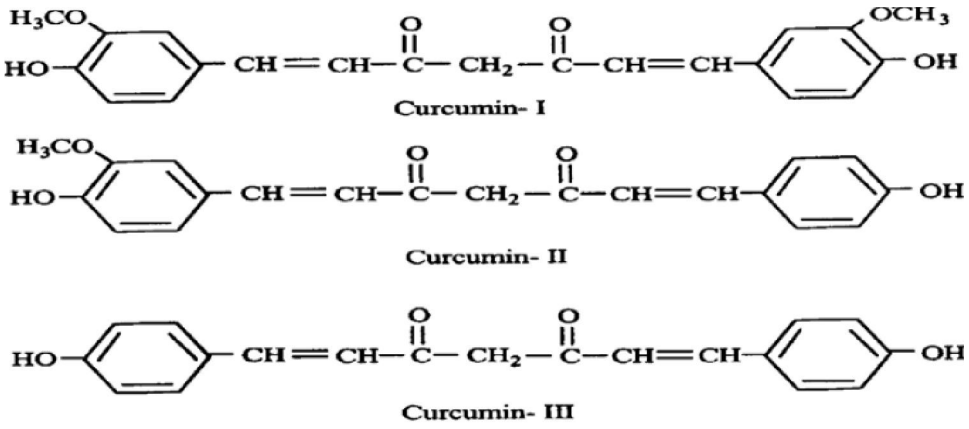

Figure 1 : Structure of natural curcuminoids. (Current science, vol. 87, no. 1, 10 July 2004)

modulates the inflammatory response by down-regulating the activity of enzymes like cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase besides inhibiting several other enzymes involved in inflammation mechanisms[19,20,21]. Additionally, it also shows hepato- and nephro-protective, thrombosis suppressing, myocardial infarction protective, hypoglycaemic, and anti-rheumatic effects. It may be effective in treating malaria, psoriasis, Alzheimer's disease, ischemia, diabetes, obesity, depression, fatigue, and AIDS[22].

Inspite of it possessing rich biological activities, the optimum potential of curcumin is limited due to its low bioavailability. This is mainly due to low intrinsic activity, poor gastric or intestinal absorption rate, high rate of metabolism, inactivity of metabolic products, rapid elimination and high degradation rate. Due to the limitations, curcumin is rated as second class drug in the Biopharmaceutics Classification System[23]. The bioavailability of curcumin is limited by its intestinal and hepatic glucuronidation. As a result of the above reasons, approximately 60–70% of an oral dose of curcumin gets eliminated in the feces[24]. For better therapeutic effects on the human body, curcumin is required to be consumed in large doses (about 12-20g/day) which mean 24 to 40 curcumin capsules of 500mg to be swallowed daily. But these doses are considered to be too high, and are not feasible in normal life and not even for clinical trials due to side effects like unbearable after-taste to mouth, nauseatic feeling and toxicity[25].

Several studies have been carried out to explore the uptake, distribution and excretion of curcumin administered either orally or intraperitoneal (i.p.) in mice/rats. Wahlstrom and Blennow (1978) reported negligible amount of curcumin in blood plasma of rat after oral administration of 1 g/kg of curcumin showing poor absorption of curcumin. When a dose of 40 mg of curcumin/kg was given to rats intravenously, it was found that there was complete plasma clearance after one hour[26]. A high oral dose of 500 mg/kg given to rats resulted in a peak plasma concentration of only 1.8 ng/mL, the major metabolites identified being curcumin sulfate and curcumin glucuronide[27]. When tritium-labelled curcumin was administered orally in dose of 10-400 mg per animal, only a trace amount of curcumin could be detected in the serum due to its poor biodistribution[28]. When curcumin was given in dose of 2 g/kg to rats orally, a maximum serum concentration (0.23μg/mL at 0.83 h) was observed in rats but when the same dose of curcumin was administered in humans, curcumin showed undetectable serum levels (0.005 μg/mL at 1 h)[29]. However, when curcumin oral dose was increased to 4–8 g in humans, it showed plasma levels peak at 0.41–1.75 μM after 1 h[30]. Similarly, in a human clinical trial, 3.6 g of curcumin via oral route was found to produce a plasma curcumin level of 11.1 nmol/L after an hour of dosing[31]. Yang et al. (2007) showed that 10 mg/kg of curcumin given i.v. in rats gave a maximum serum curcumin level of 0.36 (0.05 μg/mL), whereas a 50-fold higher curcumin dose administered orally gave only 0.06 (0.01 μg/mL) maximum serum level[32]. Pan et.al.,(2007) explored the pharmacokinetic properties of curcumin administered either orally or intraperitoneal (i.p.) in mice and showed a maximum plasma level (0.22 μg/mL) in 1 hour[33]. These studies

clearly suggest that the role of route of administration of curcumin is important for its uptake, biodistribution and biological activity, yet only a limited number of studies have been done in this aspect[34].

DELIVERY SYSTEMS TO ENHANCE BIOAVAILABILITY OF CURCUMIN

Various delivery systems have been proposed in recent years as means of improving the bio- availability of curcumin. The advantages attributed to the various delivery systems are that they provide longer circulation, increase the cellular permeability and slow down metabolic transformation processes. Two main delivery systems explored by the scientists to enhance the therapeutic potential of curcumin are adjuvants and curcumin nanoformulations. These are discussed below:

Adjuvants

Adjuvants are inorganic or organic chemicals, macromolecules with pharmacological or immunological effects that modify the effect of other agents. Adjuvants block metabolic pathways of curcumin which is one of the important mean to improve its bioavailability. Curcumin conjugated with ligand like folic acid that can recognize specific surface of target cell which helps in targeted delivery. This conjugate enables the curcumin to enter into cells via Catherin independent endocytosis that specifically over express folic acid receptors[35]. The roles of adjuvants which can block the metabolism of curcumin are of great interest. It has been demonstrated that piperine, an inhibitor of glucuronidation, could be administered concomitantly with curcumin to increase its bioavailability. Curcumin-piperine complex was administered in rats and healthy human volunteers and maximum serum concentration of curcumin observed was 154% and 2000%, respectively. This was due to decreased elimination rate of curcumin as glucuronidation inhibiting effect of piperine made curcumin glucuroinides less active thus increasing its bioavailability[29]. This clearly shows the effect of piperine on bioavailability of curcumin to be greater in human than in rats. Radio-labelled fluoropropyl-substituted curcumin with piperine showed better uptake of curcumin in brain tissue of mice[36]. Beside these, adjuvants like quercetin, eugenol, epigallocatechin- 3-gallate etc. also showed synergistic effect when used with curcumin. When quercetin was used in combination with curcumin, it also showed a synergistic effect that improved bioavailability of curcumin and increased its theraputic value[37]. Curcumin and genistein complex also showed synergistic inhibitory effect on the cellular proliferation in diseased tissue and the effect observed was superior to the individual effects of curcumin and genistein[38]. showed that the inhibitory effect of curcumin and genistein given concomitantly is less as compared to curcumin-genistein complex against breast carcinoma cell lines (MCF-7). Curcumin with and without eugenol or terpeneol pretreatment showed that eugenol and terpeneol enhance curcumin absorption through skin[39]. Epigallocatechin-3-gallate has also been shown to enhance the pharmokinetics of curcumin[40]. All the above studies clearly showed that the biological activity and solubility of curcumin can be enhanced using curcumin with different ligands.

CURCUMIN NANOFORMULATIONS

Nanotechnology can be a potential tool in enhancing the pharmacokinetic properties and therapeutic value of curcumin by providing longer circulation, better permeability and resistance to metabolism and degradation, thus making it a potent therapeutic agent. Some of the curcumin nanoformulations designed to improve solubility, distribution, bioavailability and pharmacokinetic properties of curcumin are discussed below:

Nanocrystals

Nanocrystals are nanoscopic crystals of the substances having a greater dissolution rate due to larger surface area. Nanocrystal synthesis is achieved by using any of the bottom-up approaches but basically a nanosizing method is used to increase the bioavailability of hydrophobic drugs like curcumin[41]. The chemical reactions and physical assembly depends upon the stabilization process for example curcumin nanocrystals synthesis takes around 90 min. in a solution of alcohol and water[42]. Curcumin nanocrystals synthesized exhibited improved dissolution rate, better solubility and bioavailability of poorly soluble curcumin in the body[43]. Curcumin-nanocrystal solid dispersion (CSD-cur) pre-

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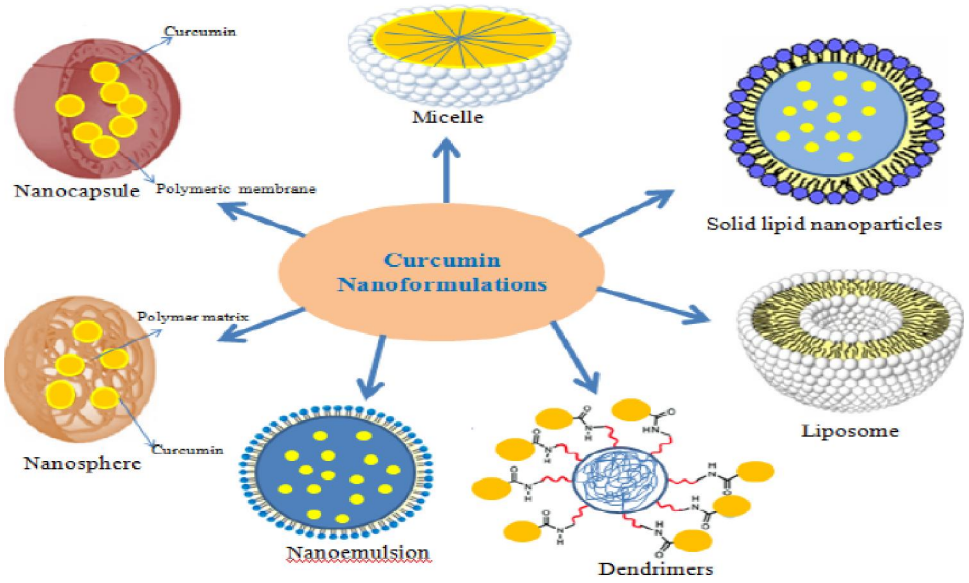

Figure 2 : Various types of curcumin nanoformulations which improves solubility of curcumin

pared through wet milling method with stabilizers of 250nm size showed 16 fold increases in its oral bioavailability and high photochemical stability. Curcumin nanocrystals prepared by high pressure homogenizer technique using stabilizers and found no change in the crystalinity of curcumin[44]. The surfactant molecules like sodium dodecyl sulphate, cetyltrimethylammonium bromide, pluronic polymers Tween 80 and Triton X-100 etc. stabilizes curcumin nanocrystals and makes them more potent in biomedical applications. Plasma proteins also stabilize curcumin so it is used as carrier molecule[45]. In addition to these, PVA, PVP and TPGS also make the curcumin nanocrystals physically stable and increase their distribution in the gastrointestinal tract. Curcumin nanocrystal is an important approach to improve oral bioavailability of curcumin and help in increasing the therapeutic value of this natural product.

Microemulsions

Microemulsions are also a suitable drug delivery system for lipophilic drugs like curcumin. They are about 50-100nm in size and are droplet in shape[46]. They are most widely used due to high drug entrapment efficiency with long term stability. Microemulsions are prepared by mixing of lipophilic and hydrophilic molecules in the presence of suitable surfactants. They improve drug solubility, thermodynamic stability and diffusion rate and provide high potential for delivery of lipophilic compounds. The size and incorporation efficiency of curcuminoid loaded emulsions were found to depend upon the concentration of the lipids, emulsifiers and other additives[47,48]. Tiyaboonchai et.al. (2007) prepared curcuminoids loaded SLNs by a micro-emulsion technique at a temperature range of 70–75°C[49]. Microemulsions formulation with hydrogel patches of chitosan not only prevented degradation of drug at high pH in the presence of light and oxygen mediated reactions but also exhibit increased stability and controlled release at a particular site[50]. Microcapsules of curcumin prepared with gelatin using ethanol/acetone as coacervating agents improved aqueous solubility of curcumin, increased drug loading and entrapment efficiency. Curcumin-based microemulsions also improved curcumin delivery via local and transdermal routes for scleroderma, psoriasis and skin cancer[51]. According to Liu et.al, (2011) eucalyptol- based curcumin microemulsions increased curcumin solubility and penetration capacity through skin as compared to oleic acid and oil-based microemulsions[52]. Microemulsions of limonene, polysorbate 80, ethanol and water also improve curcumin adsorption into the skin. The coacervating technique is used to prepare myristic, palmitic, and stearic acids based solid lipid NPs in the presence of polymeric non-ionic surfactants. This encapsulates 50 mg/ml of curcumin and releases it completely in 10 minutes to the targeted area. Curcumin–gelatine microemulsions are suitable for delivery of curcumin to the lungs targeting for immediate therapeutic effects[53].

Curcumin and paclitaxel nanoemulsions formulations also improve bioavailability of curcumin thus enhancing its therapeutic value[54].

Nanoparticles

Nanoparticles (NPs) are potential drug delivery system which increase the bioavailability of hydrophobic drugs and minimize their side effects. Nanoparticle based drug delivery system was found suitable for drugs like curcumin which are poorly water soluble. Nanoparticles of curcumin (100 nm in size) have been reported to exhibit better biomedical application than free curcumin[55]. Some of the nanoparticulate drug delivery systems explored for curcumin are PLGA (poly lactide-co-glycolides) and PEG (polyethylene glycol) NPs[56]. NIPAAM (Nisopropylacrylamide) NPs containing PEG-monoacrylate, PLGA NPs coated with thiolated chitosan, Butylcyanoacrylate NPs coated with poloxamer, NIPAAM NPs multi layered with PLGA, surface modified DMPC SLNs (dimyristoyl phosphatidylcholine solid lipid nanoparticles) for parenteral administration of curcumin. The encapsulation of curcumin into core of amphiphilic polymers or phospholipids also increases its bioavailability along with its stability[57]. The polymeric nanoparticles are used in various biomedical applications as they display superior properties like biocompatibility, biodegradability and solubility[58]. Wang et.al (2012) synthesized biodegradable poly (□-Caprolactone)-poly (ethylene glycol)-poly (□-caprolactone) (PCL-PEG-PCL) copolymer and used them to deliver curcumin for cancer treatment[59]. Bisht et.al. (2009) synthesized polymeric curcumin nanoparticles using different functional groups like thiol, which altered surface properties and increased circulation time of curcumin[60]. PLGA NPs prepared with thiol group on their surface increased retention time and facilitated controlled release[61]. Letchford et.al, (2008) reported that curcumin attached with MePEG-b-PCL, has greater aqueous solubility[62]. Curcumin after conjugating with PEG and cyclodextrin showed increased solubility and reduced degradation rate[35]. Studies carried out on curcumin loaded PLGA nanoparticles showed enhanced inhibitory effect of curcumin on cancer cells[63]. Dextran sulfate-chitosan nanoparticles with curcumin showed preferential killing of cancer cells as compared to normal cells[64]. Curcumin formulated with phosphatidylcholine and PEG derivatives have been shown to be more efficient in systemic delivery of curcumin than free curcumin[65]. Yallapu et.al, (2010) reported that theraputic effects of curcumin increases after encapsulation with PLGA nanoparticles which entrapped more than 90% of curcumin. Nisopropylacrylamide (NIPAAM) with N-vinyl-2-pyrrolidone (VP and polyethyleneglycol) monoacrylate (PEG-A) polymeric nanoparticle encapsulating curcumin were synthesized and they showed better properties as compared to native curcumin[66,67,68]. Apolipoprotein-E 3 mediated curcumin loaded poly (butyl) cyanoacrylate nanoparticles showed photostability, better entrapment capacity and improved in vitro release study. Natural polymers have also been found to be good carriers for curcumin encapsulation and delivery[69]. Various curcumin nanoparticle formulations were prepared using three biocompatible polymers like alginate (ALG), Chitosan (CS) and pluronic and they exhibited beneficial properties like slow release and better delivery in cancer model cell line. Nanoparticle-based system for curcumin delivery is still in its infancy and more investigations are carried out in this area because of potential increase of the in vivo efficacy of nanocurcumin.

Liposomes, micelles, and phospholipid complexes

Structurally, liposomes are small vesicle composed of a single hydrophobic core in which hydrophobic drug can be loaded with a hydrophilic cover. Liposomes are excellent drug delivery systems as they carry both hydrophilic and hydrophobic molecules. Moreover, small size, biodegradability, hydrophobic and hydrophilic character also enhances its potential for drug delivery. Depending upon the driving force for drug release, liposomes can be classified as conventional liposomes, pH sensitive liposomes, cationic liposomes, immunoliposomes and long circulating liposomes. They can also be classified on the basis of their size and structure as multilamellar, large unilamellar or small unilamellar[70]. These lipid based formulation enhances the solubility of poorly water soluble drugs and provide an optimum environment for drug entrapment[72]. The delivery of lipophilic drugs like curcumin, resveratrol, and N-acetyl cysteine is enhanced significantly through liposomes[73]. Prostate membrane antigen (PSA) antibodies based

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specific liposomal system of curcumin has been constructed to study its partitioning potential[73]. DMPC based liposomes (100–150 nm) exhibit greater encapsulation efficiency as compared to liposomes prepared with Dipalmitoyl phosphatidylcholine (DPPC) and egg phosphatidylcholine (PC). Furthermore, DMPC liposomes inhibitied (70–80%) cellular proliferation of the human prostate LNCaP and C4-2B cancer cells as compared to free curcumin. Both in vitro and in vivo studies have shown that liposomal curcumin is much more effective than free curcumin at same concentrations emphasizing that the liposomal delivery of curcumin enhanced the uptake and hence better bioavailability or activity into the cells[49,74,75,76,77,78]. A curcumin loaded liposomal formulated with dimyristoyl-sn-glycero-3-phosphocholine was tested against proliferation, apoptosis and angiogenesis of human pancreatic carcinoma cells and it was found to suppress the growth of BXPC3 and MiaPaCa2 tumors in a xenograft murine model[79]. Anand et.al, (2007) reported curcumin loaded liposome to possess *in vitro* and *in vivo* antitumor activity against human pancreatic carcinoma cells and antiangiogenic effects. These curcumin loaded liposomes were also effective in suppressing the pancreatic carcinoma growth in mice as compared to untreated mice[36]. Liposomal formulations can also be delivered transcutaneously through hair follicles providing a reservoir for locally applied drug. The penetration depth of liposomal formulations at slightly acidic pH was measured to find out the efficiency of delivery of curcumin via trans-follicular. It was found that liposomes can penetrate ~35 to 69% of the follicle length based on the charge of the liposomes which explained its ability for both therapeutic as well as chemopreventive purposes[80]. A tetrahydrocurcumin (THC) cream formulation developed using phospholipid-derived THC liposomes found that these are not only safe but also devoid of irritation potential as compared to the reference material. It was also reported that neutral liposomal curcuminoid's have antitumor and antioxidant activities in mice[81,82,9].

Drugs entrapped in liposomes can distribute either in the phospholipid bilayer, in the interior aqueous phase, or at the bilayer water interface due to their lipophilic character. Curcumin-loaded liposomal formulation are a better delivery vehicle due to significant absorption and fluorescence levels in lymphoma cells compared with normal cells[79]. Curcumin lecithin complex after administration of oral dose of 100 mg curcumin/kg body weight showed two fold increases in the concentration of curcumin in rat plasma as compared to free curcumin[83]. Curcumin and resveratrol in liposome showed combined effects on cell growth, apoptosis and the cell cycle[84]. Curcumin- loaded poly (d, l-lactide-co-glycolide)-β-poly (ethylene glycol)-β-poly (dl-lactide-co-glycolide; PLGA-PEGPLGA) micelles also showed improved uptake[85,86].

Curcumin–phospholipid complex significantly protect the liver from carbon tetrachloride-induced acute liver damage in rats by maintaining levels of SOD, catalase and thiobarbituric acid[87]. Phospholipid complexes improve the gastrointestinal absorption of natural drugs, thus showing improved bioavailability due to enhanced plasma levels and lower kinetic elimination[36]. When curcumin and curcumin–phospholipid complex was administered in same amount orally to rats curcumin–phospholipid complex produced a maximum plasma curcumin level. Curcumin–phospholipid complex significantly increased circulating period of active curcumin in rats due to increased half-life of complex to about 1.5 fold[88]. Curcumin–phospholipid complex also increased three-fold greater aqueous solubility, increased the oral bioavailability and exhibited better hepatoprotective effect as compared to free curcumin[87].

Structurally, micelles are composed of a single hydrophobic core covered in hydrophilic groups. Due to this property, micelles are also a potential delivery vehicle for curcumin delivery and stability. The intestinal absorption of curcumin and micellar curcumin formulation with phospholipid and bile salt was found to be higher when administrated into everted rat. The biological transformation of curcumin in micellar formulation also increased its intestinal absorption from 47% to 56%[89]. Liu et al., (2006) reported that curcumin loaded micelle increased about a 1.5-fold half-life, bioavailability, and circulation time of curcumin over native curcumin[88]. Ma et al.(2007) through a pharmacokinetic study demonstrated that a polymeric curcumin micelle increases biological half-life of curcumin in rats as compared to free curcumin to about 60-fold[85]. Wang et. al, (2012) prepared curcumin formulation with stearic acid-g- chitosan oligosaccharide (CSO-SA)

polymeric micelle with a size 114.7 nm which showed more encapsulation efficiency and exhibited increased accumulation of curcumin into tumor cells[90]. Marczylo et al., (2007) explored curcumin formulation with phosphatidylcholine and observed 5-fold higher plasma level as compared to native curcumin. Liver also shows higher curcumin level when formulated curcumin administration with than unformulated curcumin[91]. Esmaili et. al, (2011) reported that curcumin micellar formulation not only to exhibits better theraputic values of curcumin but also increases its potential as functional healthy food[92]. Letchford et al, (2008) showed a 13×10^5 fold increased in curcumin solubility in a polymeric micellar formulation containing methoxy poly (ethylene glycol)-block-polycaprolactone diblock copolymers (MePEG-b-PCL) and this increased the solubility of curcumin making it a promising formulation in the treatment of various disorders[62]. Maiti et.al, (2007) reported a 3-fold increase in aqueous solubility and a better hepatoprotective effect of curcumin phospholipid complex than free curcumin[92].

Solid lipid nanoparticles

Solid Lipid Nanoparticles (SLNs) is another excellent drug delivery system range between 100-1000nm[93]. These are prepared by replacing the liquid lipid by a solid lipid, to overcome the disadvantages associated with the liquid state of the oil droplets. Initially, SLNs were prepared using hot homogenization and warm microemulsion techniques but recently newly emerged techniques like high pressure homogenization, solvent emulsification evaporation or diffusion, high speed stirring, double emulsion method and ultrasonication are used in their preparation. These nanoformulations improve the oral bioavailability of poorly water soluble drugs like curcumin and also protect its degradation.

The unique properties of SLNs like small size, large surface area, high drug loading capacity and the interaction of phases at the interface are attractive and help to improve performance of the hydrophobic drugs. SLNs therefore act as important alternative system for controlled drug delivery as compared to emulsions, liposomes and polymeric nanoparticles. SLNs protect the labile and hydrophobic drugs from light, pH and heat mediated degradation, facilitates controlled release, provide biocompatibility and uniform dispersion in aqueous environment. Various investigations have shown SLNs to possess significant potential for the delivery of lipophilic compounds like curcumin[94]. Curcumin SLNs were prepared using dimyristoyl phosphatidylcholine (DMPC) and the surface was modified using L-glutamic acid, N-(3-carboxy-1-oxopropyl)-1, 5-dihexadecyl ester and PEG (polyethylene glycol) and their delivery to different tissues was determined[95,96]. These SLNs were detected in macrophage rich sites such as bone marrow, spleen and liver even after 6 hrs of injection. Curcuminoids loaded SLNs showed nearly 70% incorporation efficiency and were rapidly taken up by cancer cells due to their spherical shape and large surface area[49]. Bawarski et.al, (2008) also reported SLNs to be suitable drug delivery carriers for curcumin and other chemopreventives like resveratrol and β-carotene[70]. Curcumin-loaded solid lipid nanoparticles (C-SLNs), with an average particle size of 134.6 nm have been reported to exhibit improved bioavailability as compared to free solubilized curcumin[97]. Mulik and co-workers modified the surface of the SLNs with transferrin to enhance the anticancer activity and photostability of curcumin[98]. Teichmann et.al, (2007) synthesized the curcuminoids loaded SLNs (with a mean particle size of less than 450 nm) with 70% encapsulation efficiency to deliver curcumin easily through the stratum corneum[99]. Due to their lipophilic nature, these SLNs can cross the blood brain barrier (BBB) which makes it a prominent system for the delivery of hydrophobic drugs that unable to cross the BBB[100].

Dendrimers

Dendrimers are the nanoformulations introduced in the mid-1980s. They are a group of highly branched globular polymers, with a core, branched interiors, and numerous surface functional groups and cavities. Due to their polymeric structure, large amount of drug can be added to this spherical molecule in a highly controlled manner. They are synthesized by divergent synthesis and convergent synthesis by the repetitive addition of branching units to an amine core (ethylene diamine or ammonia) of 10 nm -100 nm sizes[101]. They can be synthesized in different sizes, molecular weights and chemical compositions by controlling the degree of polymerization[102]. This nanospace provides an isolated

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environment which increases the drug loading capacity and decreases toxicity at the same time. The well-defined organization, dense spherical form, size, monodispersity, and surface functionalities of dendrimers make them brilliant applicants for drug delivery[103]. Dendrimers are therefore of great significance in theranostic as they can hold both therapeutic and diagnostic agents and also release drug to the targeted site[104]. The dendrimer curcumin conjugates have been proved to be an effective cytotoxic agent against breast cancer cell lines[105]. Yallapu et al, (2011) studied the interaction of curcumin dendrimers with cancer cells, serum proteins and human red blood cells to evaluate the acute toxicity and hemocompatibility. Curcumin-dendrimer incubated with human red blood cells showed a high binding capacity of the dendrimer curcumin nanoformulation to plasma protein with no significant change in the zeta potential. However, this formulation destabilized the cell membrane and induced cell lysis. This limitation was overcome by polyethylene glycol conjugation of dendrimer formulations[106, 107,108]. Cao et al, 2013 investigated the interactions between polyamidoamine-C (a dendrimers) and curcumin by using fluorescence spectroscopy and molecular modelling methods with larger values of binding constants; indicating that polyamidoamine-C12 25% holds the curcumin strongly[109]. Dendrosomal nanoparticle-curcumin also significantly suppressed proliferation of human and mouse carcinoma cells. In vitro studies showed an increased uptake of curcumin but inhibited the growth of cancer cells as compared to normal ones. Investigation carried out under in-vivo conditions showed significant decrease in tumor incidence, weight and size after treating with dendrosomal nanoparticle-curcumin-treated group. In another study, antiproliferative and anticarcinogenic effects of dendrosomal nanoparticle-curcumin was evaluated in rat colon cancer and potential anticancer effect of dendrosomal nanoparticle-curcumin was observed[110,111]. Due to dendrimers properties, curcumin-dendrimers complexes are more attractive agents for biomedical applications as compared to other nanovectors such as micelles, liposomes or emulsion droplets. Debnath et.al, in 2013 reported that Dendrimer-curcumin conjugate exhibited both water solubility and cytotoxicity against SKBr3 and BT549 breast cancer cells. This complex are more effective in inducing cytotoxicity, as measured by the MTT assay and effectively induced cellular apoptosis measured by caspase-3 activation when compared with curcumin dissolved in DMSO and dendrimer-curcumin conjugate dissolved in water was significantly more. So dendrimer-curcumin conjugate is water soluble and capable of inducing potent cytotoxic effects on breast cancer cell lines and it may prove to be an effective anti-cancer therapy for human beings[105].

Self-assemblies and nanogel

Self-microemulsifying drug delivery system is one of the most promising techniques to improve the pharmacokinetic properties of poorly water-soluble drugs.[112]. Setthacheewakul et al. (2010) successfully developed self-microemulsifying drug delivery systems to improve the solubility and oral absorption of curcumin[113]. Tonnesen et.al, (2002) reported that these formulations provide low degradation, high bioavailability and stability to curcumin. Cyclodextrin–curcumin complexes show improved curcumin water solubility and stability and are effective in medical and pharmaceutical applications[114,115]. Curcumin–rubusoside (CUR–RUB) complexes showed increased curcumin solubility, stability, anticancer applications under physiological conditions. Bcasein (B-CN) also increases the solubility of curcumin in aqueous solution[92]. An ideal nanogel drug delivery carrier possess properties like small size, high biocompatibility, long blood circulation time, higher amount of drug loading capacity and protection to degradation from enzymes in the body. The free network structures in hydrogel NPs provide large space to load lipophilic drug molecules[55]. The cross linked co-polymer nanogels of N-isopropylacrylamide, Nvinyl-2-pyrrolidone were synthesized in the presence of PEG monoacrylate using redox-free radical polymerization process. Curcumin-loaded hydrogel system was found to facilitate the slow release of curcumin and increase its solubility in aqueous condition. When hydrogel nanocurcumin formulation was tested on pancreatic cancer cell lines, it was observed that they the possess the potential to overcome cancer due to improved systemic bioavailability and hence increase in therapeutic efficacy of curcumin[116]. Varaprasad et al. (2011) fabricated curcumin- encap-

TABLE 1 : Curcumin nanoformulations: Their size, form and influential effects

Types of nanoformulations	Size	Form	influential effects
Adjuvants	Micron and submicron	Not specific shape	(a) More uptake by brain tissue (b) More inhibited cellular proliferation (c) Enhanced absorption rate through skin (d) Enhanced pharmacokinetics
Nanoparticles	1-2500nm	Rods, fibers, spheres etc.	(a) Increase Solubility and stability (b) Provide photostability (c) Increase circulation time and better controlled release (d) Better anti-tumour effect
Nanocrystals	50-1000nm	Spherical	(a) Increased circulation of blood (b) Improved brain delivery (c) Increase solubility
Microemulsions	5-50nm	droplet	(a) Improved aqueous solubility and thermodynamic stability (b) Increased drug loading and entrapment efficiency
Liposomes	20-205nm	Globular	(a) Enhance solubility, stability and tissue distribution (b) Provide optimum environment for hydrophobhic drugs and enhance uptake (c) Enhance anti-tumour and antiangiogenesis effect (d) Increase antioxidant activity
Micelles	10-100nm	Spherical	(a) Increase intestinal absorption (b) Enhance stability and theraputic value (c) Enhance bioavailability
Phospholipid complexes	10-200nm	Spherical	(a) Better hepatoprotective effects (b) Improve bioavailability and gastrointestinal absorption
Solid-Lipid Nanoparticles	10-1000nm	Spherical	(a) Enhance anticancer activity and photostability (b) Better brain delivery (c) Improved oral bioavailability
Self-assemblies and nanogel	10-100nm	Cross-linked polymer network	(a) increase stability, solubility (b) Better Anticancer effect (c) Provide high biocompatibility and long blood circulation time (d) Provide more surface area for drug loading
Dendrimers	15-150(nm)	Globular polymer	(a) Improve stability (b) Therapeutic and diagnostic agents (c) Increase solubility and antitumor
Phytosomes	50nm-100μm	Globular	(a) Increase bioavailability and protect from degradation (b) Improves solubility and Pharmacological applications (c) Improved retention time in blood

sulated chitosan–PVA silver nanocomposite, poly (acrylamide) – poly (vinyl sulfonic acid) silver nanocomposite, and poly (acrylamide)–carboxymethyl cellulose magnetic nanocomposites to improve the therapeutic effects of curcumin as these complexes increase the bioavailability of curcumin[117].

Derivatives and analogues

The chemical structure of curcumin plays a prominent role in its biological activities. Hence, the biological activity of curcumin can be enhanced by modifying its structure[118]. Mosley et al., (2007) reported that EF-24 a curcumin analogue exhibits increased antitumor

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action in comparison to free curcumin[119]. Another strategy that can be adopted to improve the biological activity of curcumin is to chelate it with metals. The presence of phenolic and methelene group in curcumin molecule makes it an excellent ligand for the chelation. Several metal chelates of curcumin are reported which possess more activity as compared to free curcumin. Copper complexes of curcumin and its derivatives showed improved anticancerous effect[120]. Vanadyl curcumin complex showed 2-fold increase in antirheumatic and 4-fold increase in antitumor activity[121]. Sui et al. (1993) synthesized curcumin-boron complexes with 10-fold more inhibitory activity for HIV-1and HIV-2 proteases[122]. Indium and gallium complexes with curcumin also produce structural modification in curcumin structure and shows improved biological activity[36].

Phytosomes

These are novel formulation to overcome the problems related to poorly soluble drugs. Polyphenols have strong bonding affinity with phospholipids and this property has been explored to increase the bioavailability of various phenolic compounds as they can cross the lipid rich membrane and remain protected from degradation. The phytosome unit is a molecular association of two or more molecules like two molecules phosphatidylcholine (PC) and one polyphenol. The size of phytosomes varies from 50nm to a few 100 μm[123]. The phytosome technology creates intermolecular bonding between individual polyphenolic molecules and one or more molecules like phospholipid and PC. It improves the solubility of poorly soluble drugs and pharmacological applications of polyphenols to make them a prominent delivery vehicle. Phytosome administered orally, enhanced the polyphenol levels in the blood by increasing its bioavailability at least 2-6 times[124]. This technology plays prominent role in medical applications of polyphenols like curcumin because it improves its solubility and bioavailability. The conversion of the curcumin into phytosome overcomes various issues associated with free curcumin as the encapsulation of curcumin molecule in PC molecule increased its stability and also improves retention time in blood sample of rat. The absorption and bioavailability of curcumin in phytosome form has been shown to be significantly more than curcumin in non-phytosome formulation[125,126].

CONCLUSION AND FUTURE PROSPECTUS

Curcumin derived from the popular Indian spice turmeric has been used for centuries as a remedy for many health ailments. Curcumin also has the ability to modulate multiple cellular targets and possesses preventive and therapeutic value against various diseases including cancer. It has a large range of molecular targets like transcription factors, growth factors and their receptors, cytokines, enzymes and genes regulating cell proliferation and apoptosis. In spite of many advantages, rapid rate of metabolism, poor aqueous solubility and limited bioavailability of curcumin are the limitations which reduces its therapeutic value. Curcumin nanoformulations are one of the main strategies to improve the bioavailability and therapeutic value of curcumin. Some of the curcumin nanoformulations investigated are nanoparticles, curcumin self assemblies, curcumin crystals, liposomes, phospholipids complexes and phytosomes. These nanoformulations offer advantages like targeted drug delivery and enhanced solubility, stability and bioavailability; thus enhancing the medicinal value of curcumin.

Nanoformulations studies have definitely paved way for solving many issues and provide a proper basis for unraveling the wide variety of biological actions of curcumin but some problems still remain unsolved. Although, curcumin loaded liposomes increase bioavailability, efficacy and reduce toxicity but it has its limitation with regard to tissue specific delivery. Therefore, effective modifications of liposomes are required for example through conjugation with antibodies, chemotherapeutic and contrast agents which help in cell targeted delivery. Microemulsions though effective but have limitation of being attached to many surfactants which may cause toxicity. The novel delivery systems of curcumin have more drug loading capacities and effective drug stability but issues like targeted drug delivery and toxicity to the healthy tissue is also of great concern. Concerted efforts are required to gain more information on curcumin nanoformulations to make it a potent drug either alone or in combination with other therapeutic modalities. With the help of nanotechnology, curcumin can be a promising natural nanomedicine for treatment of various life threatening diseases in the near future.

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