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Review article

Curcumin-hybrid Nanoparticles in Drug Delivery System

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ABSTRACT: Extensive studies on curcumin have improved that it has certain therapeutic impact for different kinds of diseases such as cancer. Regardless of its positive features, its application is hampered by its low water solubility, bioavailability, and low cellular uptake. During recent years, several ways have been developed to protect curcumin from degradation and increase the capacity of targeting unhealthy cells. The progress in nanotechnology encouraged nanotechnologists to formulate nanoparticles encapsulating curcumin, such as polymer nanoparticles, solid nanoparticles, liposome/lipid nanoparticles, micelles, dendrimers, polymer conjugates, etc. to enhance sustained release of curcumin at target cells and to improve curcumin bioavailability. Nowadays, newer formulations of nanoparticles as called Hybrid nanoparticles are designed in order to achieve efficient and specific curcumin targeted compound that result in the improved therapeutic efficacy of curcumin with high biocompatibility associated with aptamers, folic acid, chitosan coated halloysite loaded with curcumin-Au hybrid nanoparticle etc. This review describes a number of formulated hybrid nanoparticles and their efficacy in specific targeting to cancerous cells.

KEYWORDS: Curcumin, Nanoparticles, Hybrid nanomaterials, Drug Delivery, Smart nanostructures.

1. Introduction

Nanotechnology is a new field of science that takes advantage of the peculiar properties of matter at the nanoscale. The extremely high ratio of surface area to mass that is typical of nanoparticles, allows them to interact efficiently with their environment, but yet they can act as contained carriers for their constituent molecules as opposed to the same molecules in solution. Nanoparticles are therefore promising carriers for targeted delivery of therapeutic agents. The particle size (ranging from a few nanometers to the micron range) can directly influence cell

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uptake. Different nanocarriers such as liposomes, micelles, polymeric nanomaterials, mesoporous silica, gold and magnetic nanoparticles have improved biomedical applications including drug and gene delivery. On the other hand, suitable functionalization of the nanoparticle surface, not only can increase specific targeting by ligand-recognition, but can also enable the monitoring drug delivery by attached imaging reporters. Moreover, nanoparticle drug delivery vehicles significantly decrease the side-effects of drugs, (particularly anticancer chemotherapy) by increasing their water solubility and therefore decreasing the required overall dose[1-3].

Curcumin is a polyphenolic hydrophobic substance derived within the rhizome of Curcuma longa. It has been proved that usually curcumin provides anticancer impact against different types of malignancies, anti-inflammatory, anti-oxidant, anti-microbial, anti-diabetic and anti-rheumatic actions[4, 5]. Curcumin can target different molecules in the cells including proteins such as thioredoxin reductase, cyclooxygenase 2(COX-2), protein kinase C(PKC), 5-lipoxygenase(5-LO), tubulin; transcription factors, growth factors, enzymes, cytokines[6-8]. Various formulations of curcumin products such as tablets, capsules, creams, extracts, gels, nasal sprays, etc. have been designed by pharmaceutical companies[9, 10]. Curcumin has such negative properties particularly poor water solubility, instability, low bioavailability, low penetration and targeting efficacy effectively reduce its usage as therapeutic molecule. Therefore different approaches have been developed to improve curcumin bioavailability and delivery to target cells[11, 10]. It seems that Nano formulation-based approaches such as using adjuvants, stabilizers, conjugates/ polymer conjugates, lipid/liposomes, hydro/micro/nanogels and nanoparticles can encapsulate and protect curcumin from

degradation and effectively deliver to target cells (Figure 1)[12, 9]. Curcumin loadeds nanoparticles will help to enhance the solubility and circulation time of curcumin in the body rather than free curcumin. Moreover, the progression in the nanotechnology arena has caused enhancing the bioavailability of lipophilic drugs[13, 14]. Recently, new generation of nanovehicles is developed which have been known as hybrid nanoparticles. These hybrid nanoparticles represent more cytotoxicity effects even at pH 5.5 and do not have side effects for healthy tissues[15]. Here in this review article, we will discuss a number of hybrid nanoparticles that have been applied for delivery of curcumin to cancerous cells[16-18].

Curcumin or diferuloylmethane ($C_{21}H_{20}O_6$) is a yellow crystalline powder extracted from the rhizome of the *Curcuma longa* and it has been used for a long time as an anti-inflammatory substance in medicine. Curcumin I (Diferuloylmethane) has the highest percentage (~77%) of commercial curcumin; other components are curcumin II (~17%) (Demethoxycurcumin), and curcumin III (~3%) (Bis-demethoxycucumin)[19, 20]. There is keto-enol tautomerism in the curcumin structure; keto form in neutral and acidic media, and enol structure in high pH solutions is predominant[20]. According to the Food and Drug Administration (FDA) report, curcumin is Generally Recognized as Safe (GRAS)[20, 21]. Extensive research has demonstrated that curcumin has widespread pharmacological properties such as antibacterial, antioxidant, anti-inflammatory and has hepato-protective, nephron-protective and anti-rheumatic activities[22-24, 10]. On the other hand, therapeutic effects of curcumin for several diseases like cancer, metabolic syndrome, Alzheimer's and brain diseases, hypertriglyceridemia, osteoarthritis, non-alcoholic fatty liver disease is defined[19, 23,

25, 10]. It should be noted that curcumin can operate as anticancer treatment drug against many cancers such as melanoma, lung, prostate, breast, pancreatic, skin and ovarian cancer[26, 20, 23]. Curcumin has low water solubility (0.0004mg/ml at pH 7.3), low physicochemical instability, and low bioavailability in biological systems and quick metabolization significantly limit its therapeutic application as a therapeutic molecule[26, 23, 10]. Preclinical studies for oral administration of 10 or 12 g/ml of curcumin in patients lead to around 50 ng/ml concentration of curcumin in plasma, because of its low water solubility and rapid metabolism by the liver[9].

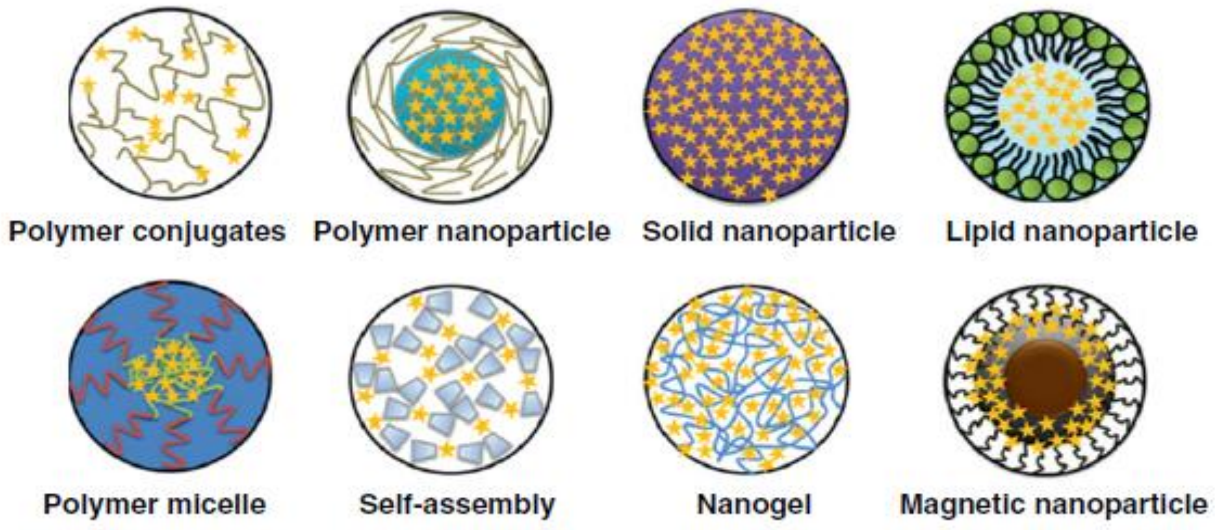

Fig. 1. Different types of the Curcumin-based Nanoformulations[9]

2. Applicable Strategies of Curcumin in Drug Delivery Systems

Primary attempts to increase bioavailability of curcumin by using piperine promoted over 100% and 2000% curcumin bioavailability in rats and humans respectively, but they could not be delivered curcumin to specific target tissue[27, 20]. Hence, various approaches have been applied to increase curcumin delivery,

bioavailability and its therapeutic effect in specific target cells, being protected from degradation and metabolism[9] including different kinds nanoparticles (NP) as drug carriers such as microemulsion, nanogels, liposomes, micelles, polymeric NPs, and more recently, curcumin-hybrid nanoparticles, curcumin conjugated hybrid molecules like antibody or other natural compounds[20, 23, 28, 9]. Some of the increasing curcumin bioavailability approaches describe in following.

Nanomedicine is a new field of science combined of chemistry, physics, biology, pharmaceutics engineering and medicine to improve drug efficiency and bioavailability. Most recently nanotechnology could increase the medicinal effects of hydrophilic drugs through their protection against degradation by enzymes, controlling drug releasing during time, changing drug pharmacokinetics and even for the time dependents process[13, 29, 30]. Different kind of therapeutic nanoparticles designed to improve curcumin bioavailability toward target specific cells, such as liposome, micelles, NPs, nanoemulsion (NE), nanosuspension, solid lipid NPs (SLNPs), etc.[13, 31].

2.1. Liposomes

Liposomes are spherical vesicles containing phospholipid bilayer surrounding an aqueous core. Liposomes have not any side effects and can carry and distribute different hydrophobic and hydrophilic drugs[13]. Due to the hydrophobic characteristics of curcumin it will be encapsulated within the liposome bilayer[32]. Many CUR-loaded liposomes have been investigated and their potency to deliver CUR as a drug was evaluated[33, 34]. For example CUR partitioned into liposome composed of dimyristoyl phosphatidyl choline (DMPC) and cholesterol resulted in 70-80% suppression of cellular propagation with any influencing viability of human prostate cancer

cell lines (LNCaP and C4B2)[35, 36]. Oral administrations of liposome-encapsulated curcumin (LEC) in rat represent high bioavailability, faster and better absorption of curcumin as compared to curcumin[37]. Covering liposomes by synthesized cationic-hydrophobic chitosan make them go through cell membrane simply and release curcumin in a controlled manner[38, 39]. Although liposomes have great biocompatibility, they suffer from some disadvantages such as curcumin leakage and instability while storage, that causes limitation to use them for drug delivery purposes[40, 41].

2.2. Solid lipid nanoparticles

Solid lipid NPs (SLNs) are nontoxic drug nanocarriers (NCs) derived from natural or synthetic lipids. These particles can deliver lipophilic drugs like curcumin. Several studies demonstrated that hydrophobic and lipophilic drug encapsulation in SLNs increases their bioavailability[13, 1]. Using SLNs as NCs for CURs delivery enhance photostability of them, protect them from pH-mediated degradation and increase their capability for targeting the interest tissue or cell[13, 42]. Vandita et al. showed 32-155 times bioavailability increase for CUR merged into the solid lipid nanoparticles and 54-85% decrease in IC_{50} values by CUR-SLNs, through inducing cellular apoptosis because of caspases activation, inhibition of NF-κβ activation and upregulation of TNF-R for CUR-SLNs, as compared with free CUR in human cancer cell lines (HL-60, A549, and PC3)[43].

2.3. Polymeric nanoparticles

Polymeric NPs (PNPs) are biodegradable nanoparticles (NPs) have been developed as drug delivery vehicles possess some advantages including improved encapsulation or solubilization of drugs to protect and deliver them, capability to deliver different kinds of therapeutic drugs, biocompatibility, high pharmacokinetics and slight clearance from

body, high endocytosis efficiency[44, 1, 20]. Numerous natural or synthetic biodegradable polymers have been identified for example Poly (lactic-co-glycolic acid) (PLGA), polyvinylalcohol (PVA), N-vinyl-2-pyrrolidone, polyethylene glycol monoacrylate (NIPAAM [VP/PEG A]), N-isopropylacrylamide (NIPAAM), silk fibroin and chitosan. Various NPs composed of NIPAAM, vinylpyrolidone(VP), and acrylic acid (AA) and curcumin have prevention effect against hydrogen peroxide- mediated cell damage[45].

Poly (lactic-co-glycolic acid) (PLGA) is a non-toxic and biodegradable copolymer comprise glycolic acid and lactic acid and permitted by Food and Drug Administration (FDA) as drug delivery particle[46].*In vitro* PLGA-curcumin uptake by HT-29 cells represented superior uptake of curcumin versus free curcumin solution[44]. *In vitro* and *in vivo* analysis reveals that PLGA-CUR NPs can be internalized to prostate cancer cells effectively and have high aggregation and retaining towards each period stage versus unmodified curcumin. Also PLGA-CUR NPs inhibit growth of prostate cancer cell through apoptosis, lysosomal activity and prevention of AR and nuclear β-catenin activity[47]. The biological system can recognize hydrophobic particles and remove them as foreign objects by reticulo-endothelial system (RES) from circulation system to liver or spleen. In addition, some modification in NPs could solve this problem. One of the main methods is changing their outward by addition of polymers like polyethylene glycol (PEGlation) to the NPs that increase the circulation time of the particles through inhibition of elimination by reticuloendothelial system and enhance the accumulation of NPs in sites[48]. PLGA-polyethylene glycol (PEG) NPs was designed as a new formulation and show increased curcumin average half-life[48].

2.4. Cyclodextrins

Cyclodextrins (CD) are cyclic oligosaccharide containing glucose monomers range from six to eight units creating typical CDs, α-CD, β-CD and γ-CD respectively. Different types of cyclodextrins (β-CD, γ-CD, 2- hydroxypropyl-γ-CD, 2-hydroxypropyl-β-CD, and poly β-CD triazine) are the most common compounds in the curcumin formulation. They have interior hydrophobic and outer hydrophilic surface that make a cavity to embed hydrophobic drugs such as curcumin delivering[13, 32].

2.5. Chitosan

Chitosan (CS) is a natural and linear polysaccharide has amino groups, therefore, it has positive charge and could be able to dissociate in acidic solutions. CS is a biocompatible and biodegradable polymer with low toxicity and immunogenicity so the researchers were interested to using them as NPs[49, 50]. Chitosans based nanoparticles (CSNPs) have been extensively studied in drug delivery system[51].

2.6. Polymeric micelles

Polymeric micelles are composed of amphiphilic copolymers in aqueous solution which have a hydrophilic layer such as PEG and poly (vinyl alcohol) and a hydrophobic internal part like L-lysine, propylene oxide, aspartic acid and D, L-lactic acid. Polymeric micelles are stable and are able to encapsulate hydrophobic compounds such as curcumin to protect them from degradation, improve its stability, and enhance its circulating time and targeting to desired cells [13, 52]. Curcumin delivery to the cancerous cells employing micelle delivery system appears to have been stated in numerous reports. Another precious research would be a curcumin-loaded TPGS/F127/P123 mixed polymeric micelle for cervical cancer treatment. It was shown that this system presents enhanced stability and

sustained release after 6 days, selective target to NIH3T3 cancerous cells and higher cytotoxicity rather than free curcumin[53]. Another study using curcumin embedded into MPEG2K-P(CL-co-LLA) micelle represent high aqueous solubility and stability at pH 7.4 and they show increased cell apoptosis induction in comparison to free curcumin[54]. Martin et al. synthesized a new nanoparticle that can loaded gold nanorods (GNRs) and curcumin into polymeric PLGA-b-PEG nanomicelle simultaneously and evaluated its efficiency to *in vivo* photothermal therapy of Barrett Esophagus (BE). *In vitro* exposure of BE cell lines to GNR-1/Cur@PMs affected cancerous cells lead to death. *In vivo* preclinical trials represented specific targeting of the nanomicelle with no effect on surrounding normal cells[55].

3. Novel Approach: Hybrid-based

3.1. Hybrid nanoparticles

During last two decades, various drug delivery systems have been formulated in order to improvement of controlling the rate of drug delivery. Hybrid nanovehicles have attracted many researchers to improve the efficacy of drug delivery. There are some criteria that if we have, we could be able to develop a suitable drug delivery system that are: 1) the potential of formulated nanoparticles to encapsulate enough drugs. 2) Any drug leakage or destruction during transporting to target cells. 3) Control drug delivery[56]. Hybrid nanoparticles are nanoparticles combined of two or more different nanoparticles assembled to form a new and more functional nanoscale structure[57].

Several structures of hybrid nanovehicles designed and a number of them have been used to create curcumin hybrid nanoparticles.

3.2. Gold- curcumin hybrid nanoparticles

Gold nanoparticles (AuNPs) are used extensively in various biomedical fields, for example as biosensors, immunoassays, photothermolysis of cancer cells, drug delivery, etc.[58, 59]. Gold NPs have low toxicity and high surface area, ease of synthesis, high *in vivo* stability and high biocompatibility[60, 61] so they can be used as suitable drug-delivery particles. Gold NPs are form in different shapes and sizes that are suitable for different application[62, 58]. In recent years different kinds of drugs encapsulated as Au-NPs have been used to treat various cancers such as pancreatic cancer and lungs cancer and decreased adverse and nonspecific effects on noncancerous tissues of anticancer drugs that are used in chemotherapy[63, 58, 64]. Chemotherapy is a routine method to suppress the tumor cells. However, even conventional chemotherapy has some disadvantages, such as harmfulness effect on normal cells and tissues and multidrug resistance. Nanoparticles based drug delivery will help to resolve these problems by specific distribution, enhance the solubility of drugs[65-67]. In one study Manju et al. evaluated physicochemical properties, biocompatibility and their ability to target cancer cells using water solubilized CUR conjugated to AuNPs and then functionalized through folic acid conjugated polyethylene glycol (PEG-FA), for instance, PEG-FA conjugated HA–Cur@AuNPs which has been shown in Figure 2. It is shown that water-soluble hyaluronic acid (HA) has increased cytotoxicity and therapeutic efficacy in target cells[68]. On the other hand, HA receptors (CD44 and RHAMM) may over express in tumor cells. So CUR conjugated HA is able to attach and uptake in to cancerous cells. In the following water soluble HA-CUR conjugated to gold nanoparticle and then further modification was functionalized by using folic acid conjugated PEG. As many studies

showed, PEG efficiently increases the cellular uptake and prolongs the blood circulation period. Folic acid receptors may overexpress in various types of tumors and they can act as marker to differentiate between normal and cancerous cells. Results represent mean hydrodynamic diameter of PF-HA-CUR@Au nanoparticles and HA-CUR@Au nanoparticles is 63.4 ± 0.2 nm and 120.6 ± 2.2 nm, respectively. Zeta potential of PF-HA-CUR@Au nanoparticles was more than of HA-CUR@Au nanoparticles but it creates sufficient repellent force to avoid aggregation during storage for a long time. Cell viability of three cell lines (Hela cells, glyoma cells and coco-2 cells) incubated with conjugated curcumin show more dose dependents toxicity than free curcumin and it can be due to increased cellular uptake and increased aqueous solubility of PF-HA-CUR@Au nanoparticles. Cellular uptake studies demonstrate the 56% uptake for HA-CUR@Au nanoparticles and 95% for PF-HA-CUR@Au nanoparticles that represent the importance of folic acid role in internalization of nanoparticle via endocytosis due to folate receptors on the cell membrane in addition to presence of hyaluronic acid receptor. The Results of the studies on the accumulation and activation of platelet and platelet alpha granule secretion (PF4) trial to assess hemocompatibility of PF-HA-CUR@Au nanoparticles show any accumulation of platelets following incubating accompanied by PF-HA-CUR@Au nanoparticles, so they can be suitable for *in vivo* applications[65]. Recently Rao et al. developed a new method to make CUR-Au hybrid nanoparticles attached to halloysite nanotubes (HNTs) coated with chitosan (Figure 3). Halloysite nanotubes (HNTs) are alumino silicates having hollow tubular shape. HNTs are cheap, high quantity and highly biocompatible[69]. Because of their tubular microstructure, they can be loaded by

chemical and biological substances like herbicides, gene and protein delivery, and drugs. HNTs advantage is their higher drug loading; slow drug release and this feature is intensified by coating the HNTs with polymer. Hydroxyl groups on the surface of HNTs are low so they are hydrophobic characteristics[51, 70]. There are several studies about CUR loaded HNTs and evaluation of their efficacy for drug delivery. In one study, CUR attached to HNT through GSH- and pH-responsive bonds. The HTN-Cur nanoparticle was stabled under physiological condition (pH 7.4), but presence of glutathione or decrease in pH of cellular microenvironment of hepatic cancer cells causes the release of curcumin because of reduction of disulphide bond between Cur and HNT by presence of GSH and the pH-sensitivity of imine bond conjugating curcumin to halloysite[71]. Charge differences between positive inner and negative outer layer of HNT interact with Au ions and hydroxyl surface groups of HNT interact with curcumin through hydrogen bonding. Finally, HNT@CUR-Au nanoparticles coated with chitosan (CS) via electrostatic interaction-to surface cage structure of HNTs. CS as cationic polymer contain -NH_2 functional groups that make it sensitive to pH of environment. It increases nanoparticle stability and increases pH control of CUR discharge in the tumor site because of protonation of amino groups under acidic condition. FTIR results show the presence of hydrogen binding interaction amongst CUR and CS, which can increase loading capacity of hybrid NPs up to 12% that was higher than 3.4% CUR loading by chitosan grafted HNTs[72]; and any CUR missing from HNT@CUR-Au /CS. CUR release profile in two pH conditions (7.4 and 5.5) show more than 95% CUR release from hybrid nanoparticle in low pH condition but it was 10% at pH7.4 after 48 h while *in vitro*

CUR release pattern from HNTs-*g*-CS/Cur at pH 7.4 and cell lysate was only 5.79% and 84.21% respectively after 48 h [73, 72, 74, 71, 61]. Cytotoxicity evaluations represent enhanced anticancer activity of HNT@CUR-Au/CS hybrid nanoparticle for MCF-7 in intracellular condition at pH 5.5 rather than extracellular environment at pH 7.4[61].

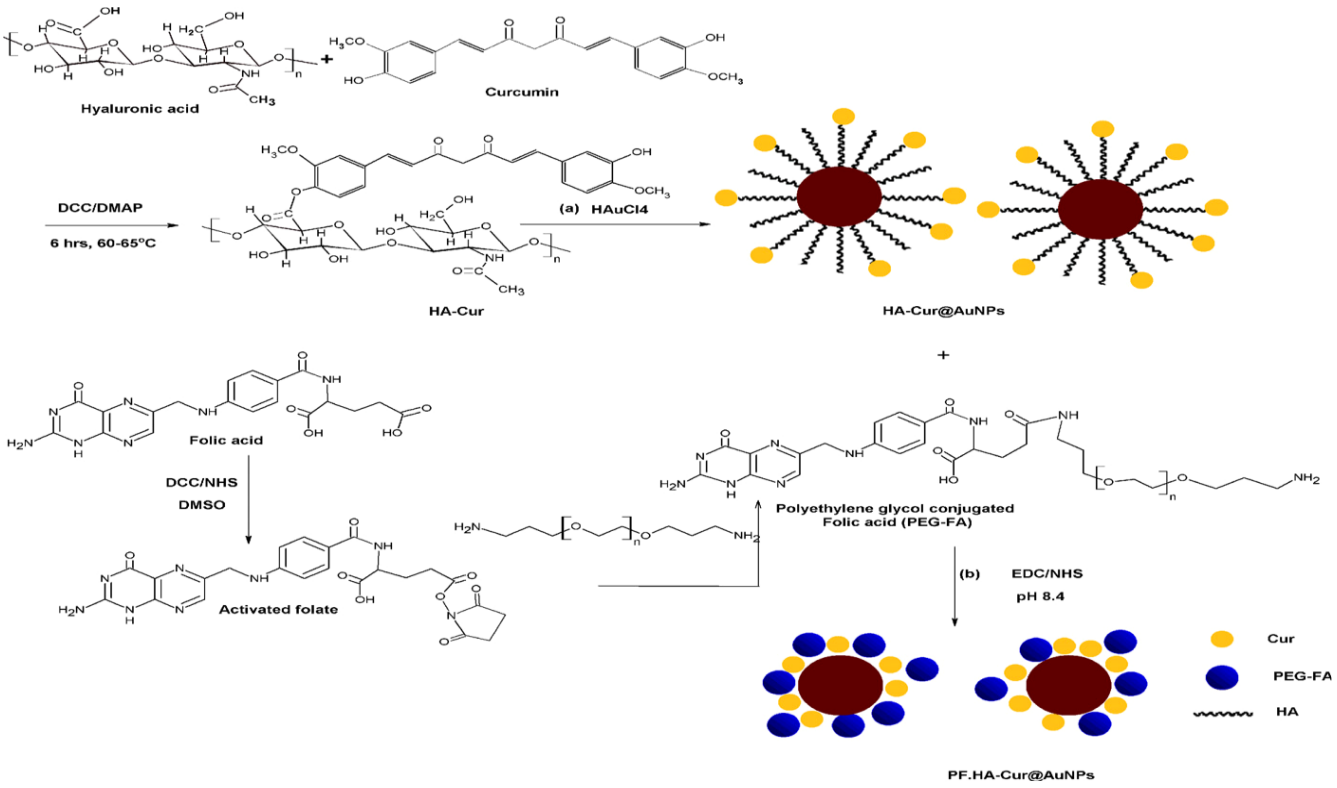

Fig. 2. Synthesis procedure of PEG-FA-Ha-Cur@AuNPs[65]

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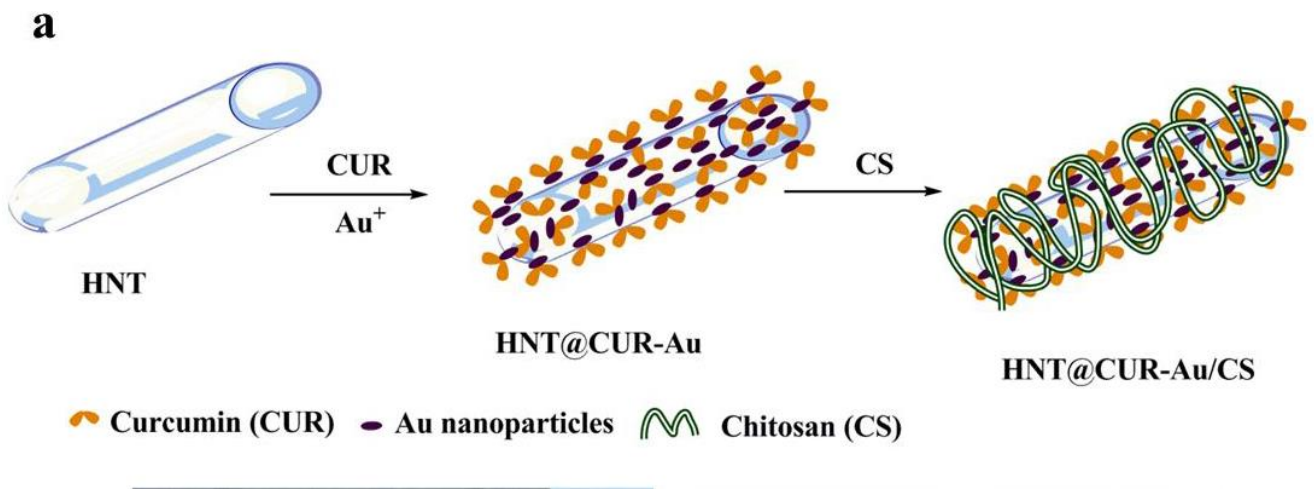

Fig. 3. Synthesis procedure of HNt@Cur-Au/CS NPs[61]

3.3. Folate-targeting nanoparticles

Folic acid (FA), known as folate and vitamin B_9, is a dietary supplement, essential for cellular biochemical pathways such as DNA and RNA synthesis, metabolize amino acids. Cellular uptake of folate is through high affinity of the receptors (FRs)[75, 76]. FRs have low expression in normal tissues but they show high expression in various tumor cells such as epithelial, ovarian, cervical, breast, lung, kidney, colorectal, and brain tumors, so it can act as a marker to detect and deliver drugs to tumor cells. This type of targeting ligands is named active targeting[77, 78]. Binding of folate to its receptors promote the NPs-FA transportation through endocytosis. After internalization of cargo-FR into the cytosol, due to acidic environment of interior side (pH~5) dissociation of FA from FA-NP will occured[77]. It is shown that FA-copolymer nanoparticles have higher cellular uptake than nanoparticles without folate conjugation[79]. Several studies about advantages of folate-conjugated nanoparticles to delivering curcumin to target cells have been published. For instance Thulasidasan et al. synthesized curcumin-loaded PLGA-PEG

nanoparticle conjugated to folic acid (PPF-curcumin) to assess its ability to improve curcumin bioavailability and tissue retention time, and PPF-Cur efficiency for inducing cancer cells towards paclitaxel as a chemotherapeutic drug[80]. PPF-curcumin did not show any significant hepatoxicity as evaluated by acute and chronic toxicity research on *Swiss albino* mice. Comparison of synergistic cytotoxicity of unmodified curcumin and PPF-curcumin along with paclitaxel represents higher synergistic cytotoxicity in HeLa cells including enhanced chromatin condensation, highly clonogenic inhibition of HeLa cells, increased paclitaxel-induced caspase-9 and caspase-3 cleavage by PPF-curcumin. In addition, they show that curcumin retention time during female *Swiss albino* mice tissue cervix and the concentration in serum of mice in the form of PPF-curcumin are higher than liposomes. It was shown that enhanced chemosensitizing effect of PPF-curcumin is due to overexpression of folate receptors (FOLR1) in cancer cells while non-tumorigenic immortalized HaCaT cells did not have many FOLR1 on their cell membranes[80].

In another study, Huong et al. provide a new drug delivery nanoparticle targeting cancer cells based on magnetic nanoparticles coated by *O*-Carboxylmethylchitosan (Fe_3O_4/OCMCS/Cur) nanoparticles attached to folic acid and evaluated efficiency of this NPs to target cancer cells. Fe_3O_4/OCMCS/Cur/Fol NPs are small and these nanoparticles can successfully target tumor tissue due to binding specifically to their receptors on the cells. *In vivo* biodistribution of Fe_3O_4/OCMCS/Cur/Fol in sarcoma-180 solid tumor- suffering mice studied at about 2 h and 5 h after intravenous injection. Curcumin amount in tumor was significantly higher than the same dose administration of Fe_3O_4/OCMCS/Cur subsequent to 2 h. Pursuing 5 h the

internalized amount of NPs folate attached was higher than the NPs without folate[81]. Previous studies have illustrated that cancerous cells in contrast to normal cells, are unstable in a range of 42-46° C and trigger apoptosis pathway[82]. On the other hand, presence of magnetic nanoparticles at tumors and being under magnetic field will induce heat and subsequently produce heat. Increased concentration of Fe_3O_4 in tumor cells due to presence of folate will cause high temperature and subsequently can trigger apoptosis in these tissues. Therefore Fe_3O_4/OCMCS/Cur/Fol nanoparticles have triple role in treating cancer cells as chemotherapy, hyperthermia and targeting[81].

3.4. Chitosans based hybrid nanoparticles

As mentioned earlier chitosan is a polysaccharide derivative of deacetylation of chitin[83]. Adding vanillin to chitosan made a reaction between amine groups on chitosan changed chitosan hydrophobically and prepare it to carry hydrophobic drugs. Application of organic and inorganic hybrid nanoparticles in environment, biomedicine, cosmetics, and water refinement has been reported. The hybrid nanoparticles containing magnetic are used to deliver drugs magnetically to target parts in controlled way[84-86]. Calcium ferrite nanoparticles (CFNP) are catalyst and because of their paramagnetic and biocompatible property, they can be used in drug delivery. Biocompatibility of CFNP is caused by the presence of calcium ions and its addition to the nanocarrier that create the hybrid materials containing the loaded drug. The modified vanillin chitosan linked to the CFNP nanoparticles enhance the curcumin encapsulation efficiency[87-89, 86].

The hybrid vanillin tailored chitosan covered with CFNP nanoparticle represents following order in the size of particle: chitosan-vanillin with CFNP > chitosan > chitosan-vanillin

NPs> CFNP. Curcumin containing hybrid NPs in size between140 to 180 nm in diameters are correspondent to parenteral drug delivery. The most curcumin release profile is obtained 97.1% for chitosan-CFNP and it is 78.3% for chitosan-vanillin-CFNP at pH 1.2 in the gastric fluid condition. In addition, drug release at pH 7.4 for chitosan-CFNP was higher than hybrid nanoparticle. Presence of vanillin increases its interaction with hydrophobic curcumin and increase the prolonged release of drug from the chitosan-vanillin-CFNP hybrid carrier. It was shown that there is a direct relationship between early loading of medication and the rate of medication discharge. VSM analysis indicated supermagnetical feature of hybrid nanoparticle. The pattern of the controlled drug release of hybrid NPs in the existence of different magnetic field showed that chitosan-vanillin with CFNP are often used to target the medication discharge at particular spot[90, 88, 91-93].

Biocompatibility assay using L929 fibroblast cell lines comparison of chitosan-vanillin and chitosan-vanillin-CUR with hybrid nanoparticle indicate the enhanced cell viability because of the presence of biocompatible CFNP. Existence of CFNP increases biocompatibility of chitosan-vanillin curcumin nanocarriers. *In vitro* cytotoxic investigation show that curcumin containing chitosan-vanillin-CFNP has more significant cytotoxicity as opposed to the unprocessed chitosan NPs and the cytotoxicity and anticancer properties of the hybrid NCs reaches above 98% at the specific amount alongside MCF-7[94, 86].

3.5. Lipid-polymer hybrid nanoparticle

Several experiments have revealed that trapping the curcumin in polymeric NPs (PNPs) and liposomes is more dominant because of evidences approved their

efficacy[13, 95-98]. Liposomes and polymeric nanoparticles are two types of main drug nanocarriers and when combine with each other they have potential to be used as a powerful hybrid nanoparticle in various therapeutic and diagnostic applications and this is refers as lipid-polymer hybrid nanoparticle (LPHNP). Most of LPHNPs consist of three different parts: the core is synthesized from biocompatible and biodegradable poly(lactide-*co*-glycolide) (PLGA) to loading hydrophobic drugs; lipid monolayer shell, composed of different lipids including phosphatidyl choline (PC), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), cholesterol, myristic acid, stearic acid, 1,2-dipalmitoylsn-glycero-3-phosphocholine (DPPC) and 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC) surrounding the core to increase stability of LPHNPs and decrease drug leakage from LPHNPs to environment; and polyethylene glycol (PEG) to protect LPHNPs from immune cells, evade recognition by reticuloendothelial system (RES) and to increase circulation of them *in vivo*[99, 41, 100]. The PEG molecules also can be modified to bind ligands targeting LPHNP for specific drug delivery to cancer cells without affecting normal and noncancerous cells and tissues[101]. Some of these targeting ligands include aptamers, peptides, antibody fragments, monoclonal antibodies and small molecules such as folic acid, which can recognize the tumor associated surface molecules[102, 101, 100]. LPNs have some advantages that make it an appropriate nanocarrier to therapeutic and drug delivery purposes which have been described in the next step.

For example, Lei et al. studied LPN containing CUR conjugated a synthetic RNA aptamer to specifically target epithelial cell adhesion molecule (EpCAM) protein (Apt-CUR-NPs) which usually overexpressed upon colorectal

adenocarcinoma cellular material (Figure 4). Both particle size of CUR-LPNs and Apt-CUR-NPs are less than 100 nm that is appropriate for targeting tumor cells. PLGA-lecithin-PEG encapsulated curcumin caused its prolonged and continuous release. in fact the hybrid LNP represent enhanced six fold half-life and three fold mean retention in comparison to free CUR in PBS with pH 7.4. It seems that LPN PEGlation is effective approach to prolong its circulation[103]. CUR encapsulated in Apt-CUR-NPs show enhanced bioavailability of CUR after 24 hours in comparison to free CUR. Apt-CUR-NPs show augmented binding to HT29 colon cancer cells and cellular uptake, through evaluation to control-Apt-CUR-NPs coupled with to EpCAM-negative HEK293T. Comparison of *in vitro* induced cytotoxicity of free CUR and Apt-CUR-NPs in HT29 cell line indicate more cytotoxicity of Apt-CUR-NPs compared to totally free CUR (cellular viabilities about 58% and 72%, respectively) and it is coincidence with attachment of EpCAM-Apt on the HT29 cells[101].

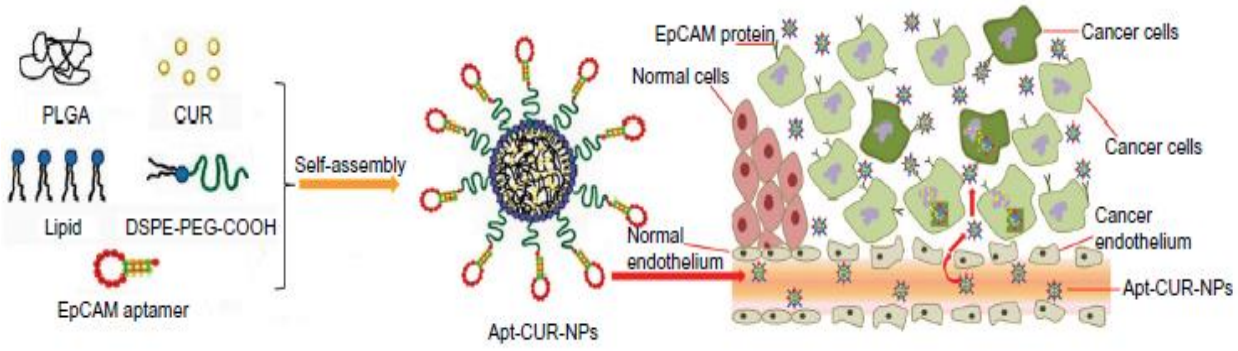

Fig. 4. Synthesis procedure of Apt-Cur-PLGA-lecithin-PEG NPs[101]

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The LPHNPs structure provides advantage that can be loaded by multiple therapeutic drugs[104-106]. For example, Changming et al. considered lipid-polymer hybrid nanoparticle as an effective drug nanocarrier for co-delivery of curcumin and cisplatin (DDP) (as a chemotherapy drug) to cervical cancer. In comparison hybrid D/C/LPNs and PNP, results represent that zeta potential of hybrid D/C/LPNs and PNPs is negative but it was lower in D/C/LPNs. Negative surface will decrease systematic toxicity and improve efficiency of target cancer therapy. Another advantage of hybrid LPNs is their high stability. The effective factors in the in vitro stability of the lipid polymers hybrid nanoparticles are nanoparticle concentration, surface charge density, and surface repulsive layer[100]. Study on the stability of LPNs and PNPs represent their constant diameter during 30 days[106]. The polymeric interior part of the LPNs can retain the hydrophobic DDP and CUR in the core on the other hand PEG shell helps to keeping drugs in the core so it will decrease the speed of drug release than PNPs nanoparticles[107, 108].

Recently lipid-polymer hybrid nanoparticles are taken into consideration as a good drug-delivery system[109]. One of the in vivo therapeutic applications of LPHNP obtained from study of the the curcumin loaded lipid-polymer nanoparticle to control the vascular deposition of circulating breast cancer tumor cells (CTCs). CTCs are able to migrate from one cancerous place to blood circulation and spread through other tissues. The CTCs residing at tumor site can release some pro-inflammatory cytokines in the circulation inducing over-expression a number of selectin molecules such as ICAM-1, VCAM-1 and E/Pselectins as receptor in vascular endothelium. Curcumin encapsulated lipid-polymer nanoparticles (NANOCurc) internalized into the CTCs and endothelial cells and triggerrelease of CUR (Fig 7). [110]. Treatment of endothelium and breast cancer cells with

mild amount of NANOCurc decreased the adhesion of CTCs to vascular endothelial cells by 70% due to decreasing number of adhering tumor cells. The NP would stop the metastatic cascade in the initial steps and restrict tumor spreading.

4. Conclusion

Curcumin has great therapeutic properties especially anticancer effects, however, low aqueous solubility and high metabolization of curcumin hamper its utility as a medicine. Development of nanotechnology and formulation of several types of nanoparticles have significant role in resolving the curcumin limitation and disadvantages. Curcumin encapsulation in nanoscale particles increased the bioavailability and decreased the dose required. They are nontoxic with any side effect when internalized into body and has advantages for chemotherapy (reduced systemic toxicity). Curcumin nanoparticles did not have tissue specificity, so besides delivering vehicles they should be safe to surrounding healthy tissues. For this reason, new generation of nanoparticles are designed as hybrid nanoparticles. They are comprised two or more components comprised each other enveloped curcumin to specific cell targeting. On the other hand, these hybrid nanoparticles show high cytotoxicity in cancerous cells compared with nanoparticles and free curcumin. In conclusion, the novel evidence suggest that curcumin-based hybrid nanoparticles are more effective in therapeutics. However further human considerations are needed to assess the efficiency of hybrid nanoparticles with clinical trials.

5. References

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