



<https://ijrps.com>

ISSN: 0975-7538

Review Article

## Curcumin nanoforms promise better therapeutic values

Heni Rachmawati\*

Research Group of Pharmaceutics, School of Pharmacy, Bandung Institute of Technology, Ganesha 10, Bandung 40132, Indonesia

### ABSTRACT

There are many reports proved great potential effects of curcumin in various diseases. Curcumin exhibits antioxidant, anti inflammation, antimicrobial and anticarcinogenic activities. It's unique ability to work through so many different pathways has a positive influence in combating almost every known disease. However, lack of its stability and solubility limits its therapeutic applications in clinic. Several approaches have been described not only in chemical modifications but also in formulation technologies to expose the therapeutic values of curcumin. This review presented an updated concise review of currently available technologies to improve the physicochemical characteristic of curcumin as well as its stability, hence showing better therapeutic effects, using different types of nanoform: nanocrystal and nanocarriers.

**Keywords:** Curcumin; dendrimer; lipid-based nanoparticle; nanocrystal; nanocarrier; polymeric nanoparticle; polymeric micelle

### INTRODUCTION

Curcumin, an active compound derived from mostly *Curcuma sp.*, is a natural hydrophobic polyphenol which has been used in Asian countries like Indonesia, India, and China to cure various diseases for centuries (Maheshwari et al, 2006; Shisodia et al, 2005). Chemically, curcumin is a bis- $\alpha,\beta$ -unsaturated  $\beta$ -diketone (commonly called diferuloylmethane, Figure 1, Anand et al, 2007), which exhibits keto-enol tautomerism having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium. Curcumin has been identified as a potent constituent for a wide spectrum of biological and pharmacological activities. It exhibits antioxidant, anti-inflammation (Sharma, 1976; Ruby et al, 1995; Sugiyama et al, 1996; Srimal and Dhawan, 1973), antimicrobial, and anticarcinogenic (Jordan and Drew, 1996; Mahady et al, 2002; Kim et al, 2003; Reddy et al, 2005; Kuttan et al, 1985) activities. Additionally, the hepato- and nephro-protective (Kiso et al, 1983; Venkatesan, 1998; Venkatesan et al, 2000), thrombosis suppressing (Srivastava et al, 1985), myocardial infarction protective (Dikshit et al, 1995; Nirmala and Puvanakrishnan, 1996a, b), hypoglycemic (Srinivasan, 1972; Babu and Srinivasan, 1995, 1997; Arun and Nalini, 2002) and antirheumatic (Deodhar et al, 1980) effects of curcumin are also well established.

Curcumin's unique ability to work through so many different pathways with its extraordinary antioxidant and anti-inflammatory attributes can have a positive influence in combating almost every known disease. In spite of these attractive activities of curcumin, it has not yet been approved by U.S FDA (Food and Drug Administration) as a drug. Applicational advancement of curcumin has been hindered by its water insolubility, degradation at alkaline pH, and photodegradation and thus extremely low bioavailability in both vascular and oral administration (Letchford et al, 2008; Anand et al, 2007). Its poor solubility and slow dissolution rate responsible are the contributing factors for its low bioavailability. The solubility or the dissolution rate of the drug is a key factor determining its rate and extent of absorption after oral administration. Curcumin's poor bioavailability within the body can be attributed to its poor absorption and high rate of metabolism in the intestines and rapid elimination from the body. This has been a major obstacle in preventing its progress from the laboratory to clinic; therefore, not much progress could be made in conducting clinical trials beyond Phase I. In view of this, curcumin's chemoprevention and therapeutic potential has not been fully exploited for the prevention and treatment of diseases. Therefore, many approaches have been investigated, including synthetic analogues, chemical modification to prodrugs, combined with other dietary components and using nanoscale drug delivery systems to overcome deficiencies. On top of that, nano-enabled drug delivery systems show good promise in overcoming the problem of low bioavailability of curcumin (figure 2). In order to assess nano-based curcumin's potential applications in the field of medicine, 254 relevant patents

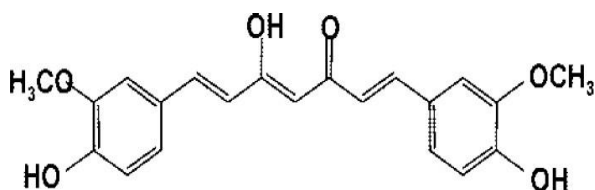
\* Corresponding Author  
Email: hrachma@yahoo.com  
Contact: +222504852  
Received on: 01-03-2013  
Revised on: 13-03-2013  
Accepted on: 15-03-2013

were analysed with segmentation based on the types of various diseases (table 1).

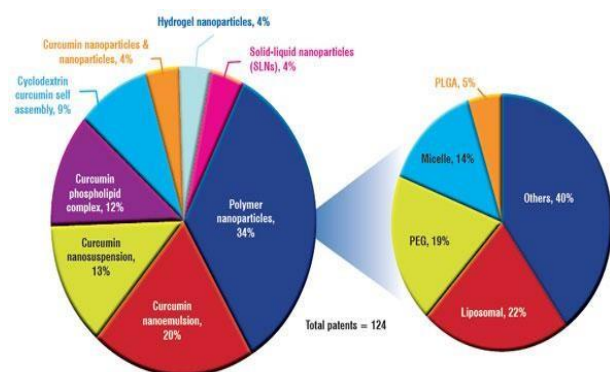
**Table 1: Segmentation of nano-based curcumin applications in different types of diseases and cancers**

Type of diseases	Percentage (%)
Dementia	1
Parkinson	4
Psoriasis	7
Gastrointestinal	9
Alzheimer	9
Arthritis	10
Diabetes	11
Inflammation	12
Cardiovascular	13
Cancer and tumor	24

This review described several nanotechnology-based attempts that have been reported to improve the bioavailability of curcumin not only through enhancing its solubility and dissolution rate, but also its stability *in vitro* and *in vivo*. A number of nano-based approaches are being developed to improve curcumin's bioavailability and reduce perceived toxicity.



**Figure 1: Chemical structure of curcumin**



**Figure 2: Various nanotechnology approaches for drug delivery of curcumin**

**Various nanoforms OF CURCUMIN**

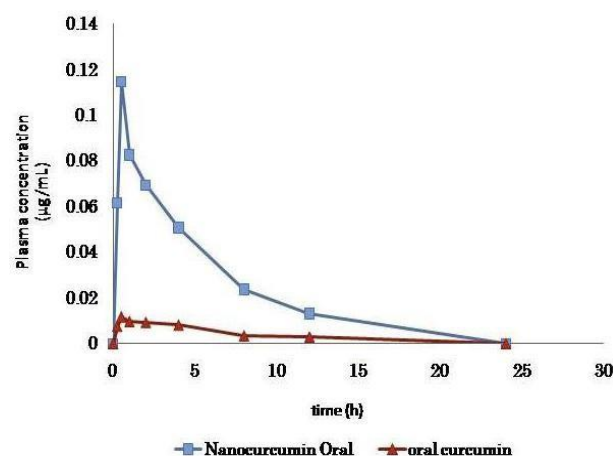
**Curcumin Nanocrystal**

Nanocrystals are nanoscopic crystals of the substance with dimensions less than 2000 nm as defined in the first patents in this field (Hovey et al, 2006; Liversidge and Jenkins, 2006; Ruddy and Ryde, 2002). Nanocrystal dispersions contain dispersion media (water, aqueous solutions or nonaqueous media), active substances and surface active agents or polymers required for stabilization (Junghanns and Müller, 2008). Preparation of drug nanocrystals is basically a nanosizing method,

which is utilized to enhance the oral bioavailability of poorly water-soluble drugs.

Development of curcumin nanocrystals has been reported (Onoue et al, 2010; Rachmawati et al, 2012). Various methods were applied to reduce the particle size of curcumin crystalline such as milling and high pressure homogenization. Onoue et al described the method of curcumin particle reduction not only to enhance bioavailability but also to prevent the photodegradation of curcumin. Nanocrystal solid dispersion (CSD-Cur), amorphous solid dispersion (ASD-Cur), and nanoemulsion (NE-Cur) were developed. CSD-Cur was prepared through wet-milled with NanoMill1-01 system using HPC (Hydroxypropyl Cellulose) and SDS (Sodium Dodecyl Sulfate) as stabilizers, followed by freeze-dried. This technique resulted flaky freeze-dried curcumin nanocrystal with size around 250 nm. They reported that all curcumin formulations exhibited marked improvement in the dissolution behavior when compared with crystalline curcumin. Significant improvement in pharmacokinetic behavior was observed in the newly developed formulations, as evidenced by 12- (ASD-Cur), 16- (CSD-Cur), and 9-fold (NE-Cur) increase of oral bioavailability. Upon photochemical characterization, curcumin was found to be photoreactive and photodegradable in the solution state, possibly via type 2 photochemical reaction, whereas high photochemical stability was seen in the solid formulations, especially CSD-Cur.

The use of high pressure homogenizer using various stabilizers to produce curcumin nanocrystal as reported previously (Rachmawati et al, 2012) clearly explained that the technique did not change the crystallinity of the curcumin. We demonstrated that the stabilizer influences the physical stability of the nanocrystal. Enhancement of the curcumin solubility is due to the reduction of particle size and not by amorphization. The pharmacokinetic parameter of this curcumin nanocrystal tremendously increased which revealed improved bioavailability (figure 3, data not published yet).



**Figure 3: The bioavailability of curcumin versus curcumin nanocrystal after oral administration in male Wistar rat**

## Curcumin Nanocarriers

Nanocarriers are nanosized materials (diameter 1–100 nm) that can carry multiple drugs and/or imaging agents. Owing to their high surface-area-to-volume ratio, it is possible to achieve high ligand density on the surface for targeting purposes (Peer et al, 2007). Nanocarriers can also be used to increase local drug concentration by carrying the drug within and controlling its release when bound to the targets. Currently, natural and synthetic polymers and lipids are typically used as drug delivery vectors. The family of nanocarriers includes polymer conjugates, polymeric nanoparticles, lipid-based carriers such as solid lipid nanoparticle (SLN), nanostructure lipid carrier (NLC), liposomes and micelles, dendrimers, carbon nanotubes, and gold nanoparticles, including nanoshells and nanocages. These nanocarriers have been explored for a variety of applications such as drug delivery, imaging, photothermal ablation of tumors, radiation sensitizers, detection of apoptosis, and sentinel lymph node mapping (Duncan, 2006; Ferrari, 2005; La Van et al, 2003).

Nanocarriers can offer many advantages over free drugs. They protect the drug from premature degradation, prevent drugs from prematurely interacting with the biological environment, enhance absorption of the drugs into a selected tissue (for example, solid tumor), control the pharmacokinetic and drug tissue distribution profile, and improve intracellular penetration.

Development of nanocarriers for better curcumin activities have been reported by many investigators. In contrast to nanocrystal, the rational reason to encapsulate curcumin in particular carrier is mainly to improve curcumin stability and to prolong the resident time in the body by against the rapid eliminated from the body. The clinical effects of curcumin are currently being investigated in human clinical trials for a variety of conditions including pancreatic cancer, colorectal cancer and multiple myeloma. The mechanisms by which curcumin is thought to inhibit tumorigenesis are diverse, and pro-apoptotic, anti-angiogenic, anti-inflammation, immunomodulation, and anti-mitogenic effects have been described in various systems (Hatcher et al, 2008; Maheshwari et al, 2006). Some of curcumin's potential molecular targets include insulin-like growth factor (IGF), Akt, mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT3), Nuclear Factor kappa B (NFkB) and Notch (Kunnumakkara et al, 2008; Ravindran et al, 2009). These pathways are all thought to be active in malignant brain tumors (Atkinson et al, 2010; Schmidt Schmidt et al, 2010), raising the possibility that curcumin could be effective in treating medulloblastoma or glioblastoma (Lim et al, 2011). They developed nanoparticle-encapsulated curcumin to treat medulloblastoma and glioblastoma cells. However, the retention time of curcumin in body is limited due to its rapid systemic elimination (Yang et al, 2007). Therefore, the therapeutic efficacy of curcumin is restricted due to its

short systemic retention in circulation. To increase the retention time of curcumin in the body, various formulation techniques have been applied. For example, curcumin-phospholipid complex can extend the retention of curcumin in rat serum (Mythri et al., 2007). In spite, development of various nanocarriers for curcumin has received a lot of attention due to their stability and ease with which their surfaces can be modified. They can be tailor-made to achieve both controlled drug release and disease-specific localization by tuning the characteristics and surface chemistry.

### *Polymer-based nanoparticles of curcumin*

Polymers are the most commonly explored materials for constructing nanoparticle-based drug carriers. Polymeric nanoparticles can be made from synthetic polymers, including poly(lactic acid) (PLA) and poly(lactic co-glycolic acid) (Hrkach et al, 1997), or from natural polymers such as chitosan (Calvo et al, 1997) and collagen (Elsamaly et al, 1983) and may be used to encapsulate drugs without chemical modification. The drugs can be released in a controlled manner through surface or bulk erosion, diffusion through the polymer matrix, swelling followed by diffusion, or in response to the local environment. Several multifunctional polymeric nanoparticles are now in various stages of pre-clinical and clinical development (Ferrari, 2005; La Van, 2003; Moses, 2003; Farokhzad and Langer, 2006). Concerns arising from the use of polymer-based nanocarriers include the inherent structural heterogeneity of polymers, reflected, for example, in a high polydispersity index (the ratio of the weight-and-number-average molecular weight (Mw/Mn)).

Various polymeric-based curcumin nanoparticles for different therapeutic targets have been presented by many groups. Feng et al synthesized biodegradable poly( $\epsilon$ -Caprolactone)-poly(ethylene glycol)-poly( $\epsilon$ -Caprolactone) (PCL-PEG-PCL) copolymers to deliver curcumin for cancer treatment. In this report, the CUR-NPs were produced from the self-assembly of the copolymer, assisted by a probe-type ultrasonic emulsion and solvent evaporation method without any surfactants (Feng et al, 2012). While, polyester nanoparticle-based delivery systems showed favorable for hydrophobic compounds and enhance the bioavailability of poorly water-soluble agents (Anand et al., 2007). Polyesters such as poly(lactic-co-glycolic acid) (PLGA) are the material generally used for nano-formulation since they are biodegradable, biocompatible, have versatile degradation kinetics (Park, 1995) and have been approved by the U.S. Food and Drug Administration for pharmaceutical application. Therefore, recent *in vitro* studies have revealed that curcumin inhibition of cancer cell growth was effected by curcumin-loaded PLGA nanoparticles due to enhanced uptake by cells (Anand et al., 2010). The therapeutic effects of curcumin on metastatic cancer cells are also increased after encapsulation with PLGA nanoparticles (Yallapu et al., 2010).

Similar study also described curcumin encapsulated in synthesized polymeric nanoparticle using micellar aggregates of cross-linked and random copolymers of N-isopropylacrylamide (NIPAAm), with N-vinyl-2-pyrrolidone (VP) and poly(ethyleneglycol)monoacrylate (PEG-A) (Bisht et al, 2011; Ray et al, 2011). The entrapment efficiency of curcumin within the nanoparticles was found to be >90%. Curcumin release occurs in a sustained manner, such that only 40% of the total drug is released from the nanoparticles at 24 hours. The potential use of N-isopropylacrylamide (NIPAAm), vinylpyrrolidone (VP), and acrylic acid (AA) as polymer composite to encapsulate curcumin. A polymeric nanoparticle encapsulated curcumin (NanoCurc™) was formulated which is completely water soluble. NanoCurc™ treatment protects neuronally differentiated human SK-N-SH cells from ROS (H<sub>2</sub>O<sub>2</sub>) mediated insults. NanoCurc™ (Ray et al, 2011) also rescues differentiated human SK-N-SH cells, which were previously insulted with H<sub>2</sub>O<sub>2</sub>. *In vivo*, intraperitoneal (IP) NanoCurc™ injection at a dose of 25 mg/kg twice daily in athymic mice resulted in significant curcumin levels in the brain (0.32 µg/g). Biochemical study of NanoCurc™-treated athymic mice revealed decreased levels of H<sub>2</sub>O<sub>2</sub> as well as caspase 3 and caspase 7 activities in the brain, accompanied by increased glutathione (GSH) concentrations. Increased free to oxidized glutathione (GSH:GSSH) ratio in athymic mice brain versus controls also indicated a favorable redox intracellular environment.

Natural polymers also show good characteristic as carriers for curcumin encapsulation (Das et al, 2010). A composite nanoparticles (NPs) for curcumin was prepared by using three biocompatible polymers: alginate (ALG), chitosan (CS), and pluronic, by ionotropic pre-gelation followed by polycationic cross-linking. Curcumin from ALG-CS-PF127 NPs showed slow release and exhibited better activities in cancer model cell line.

The most recent investigation of developing polymer-based nanoparticles for curcumin is using peptide and protein. Mulik et al described apolipoprotein-E3 mediated curcumin loaded poly(butyl)cyanoacrylate nanoparticles (ApoE3-C-PBCA) and characterized for size, zeta potential, entrapment efficiency, photostability, morphology, and *in vitro* release study. ApoE3-C-PBCA were found to be effective against SH-SY5Y neuroblastoma cells compared to curcumin solution (CSSS) and curcumin loaded PBCA nanoparticles (C-PBCA) from *in vitro* cell culture investigations.

Entrapment of curcumin in dipeptide also exerted as a great delivery system for curcumin (Alam et al, 2012). In this study, a novel self-assembled NPs, derived from the dipeptide methionine-dehydrophenylalanine (MΔF), which contains the modified amino acid α,β-dehydrophenylalanine (ΔPhe), an unsaturated analog of the naturally occurring aromatic amino acid phenylalanine was developed. Incorporation of dehydrophe-

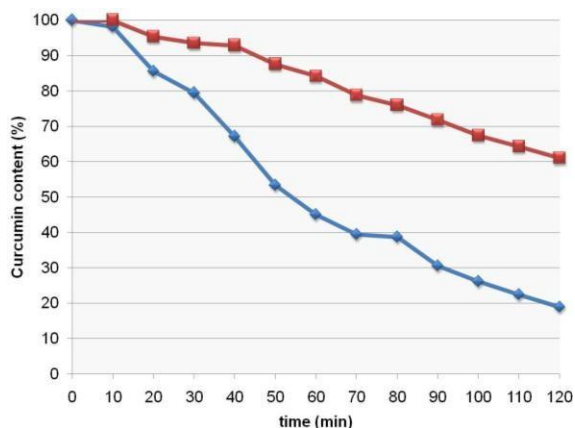
nylalanine in the peptide was expected to provide NPs with enhanced assembly properties due to less spatial freedom as well as increased stability against enzymatic degradation. MΔF nanoparticles can be assembled in a mixture of aqueous and organic phase and used for the loading and release of the hydrophobic curcumin. Curcumin-loaded MΔF nanoparticles \*(Cm)NPs+ were well-dispersed in aqueous environments and showed increased cellular availability with enhanced cytotoxicity in various cancerous cell lines as well as delayed tumor growth with enhanced survival time in a B6F10 melanoma mouse model.

### Polymeric micelle

Micelles are formed when amphiphilic surfactant or polymeric molecules spontaneously associate in aqueous medium to form core-shell structures or vesicles. They were first proposed as drug carriers about 24 years ago (Jones et al, 1999). The inner core of a micelle is hydrophobic which is surrounded by a shell of hydrophilic polymers such as poly (ethylene glycol) (Nishiyama and Kataoka, 2006). Their hydrophobic core enables incorporation of poorly water soluble and amphiphilic drugs while their hydrophilic shell and size is <100 nm. Due to this property, micelle is also potential carrier for better curcumin stability and delivery. There are several reports described the formulation of curcumin-encapsulated micelles using different materials. Cationic micelle has been described to improve curcumin stability in alkaline environment (Leung et al, 2008). They studied three types of micelles composed of the cationic surfactants cetyl trimethylammonium bromide (CTAB) and dodecyl trimethylammonium bromide (DTAB) and the anionic surfactant sodium dodecyl sulfate (SDS). Curcumin encapsulated in cationic micelles: CTAB or DTAB micelles prevented the hydrolysis at pH 13. In contrast, curcumin undergoes rapid degradation by alkaline hydrolysis in the SDS micellar solution due to dissociation of curcumin from the SDS micelles to the aqueous phase. The absence of encapsulation and stabilization in the SDS micellar solution was clearly explained the rapid hydrolysis of curcumin. This is in line with our results in which the use of micellar system composed by glyceril monooleate:chromophor RH 40:PEG 400 (1:8:1) suppressed the alkaline hydrolysis of curcumin (figure 4). This system was spontaneously dispersed in water resulted transparent solution with the average particle size was in the range of <100 nm and high curcumin loading capacity (~ 100%).

Another micellar form of curcumin in stearic acid-g-chitosan oligosaccharide (CSO-SA) polymeric micelles was reported (Wang et al, 2012). This composition was able to self-assemble forming nanoscale micelles in aqueous medium. The mean diameter of the curcumin-loaded CSO-SA micelles was 114.7 nm and their mean surface potential was 18.5 mV. Curcumin-loaded CSO-SA micelles showed excellent internalization ability that increased curcumin accumulation in cancer cells.

Curcumin-loaded CSO-SA micelles also had potent anti-proliferative effects on primary colorectal cancer cells *in vitro*, resulting in about 6-fold greater inhibition compared with cells treated with a solution containing an equivalent concentration of free curcumin. Intravenous administration of curcumin-loaded CSO-SA micelles marginally suppressed tumor growth but did not increase cytotoxicity to mice, as confirmed by no change in body weight. Most importantly, they demonstrated that curcumin-loaded CSO-SA micelles were effective for inhibiting subpopulations of CD44+/CD24+ cells (putative colorectal cancer stem cell markers) both *in vitro* and *in vivo*.



**Figure 4: Stability test of curcumin micelle versus curcumin solution in alkaline environment**

The purpose of curcumin-encapsulated micelle is not only to obtain better value of curcumin in therapeutic field but also in functional health food (Esmaili et al, 2011). Beta casein, a self-assembling protein, was used to form micellar nanostructures. The mechanism in which curcumin was entrapped in the micelle was mainly via hydrophobic interactions between beta-casein micelles with curcumin, increasing the solubility of curcumin and therefore improves its bioavailability and antioxidant activity.

#### **Lipid-based nanoparticles of curcumin**

Lipids and lipid nanoparticles are extensively employed as oral-delivery systems for drugs and other active ingredients. These have been exploited for many features in the field of pharmaceutical technology. Lipids usually enhance drug absorption in the gastrointestinal tract (GIT), and when formulated as nanoparticles, these molecules improve mucosal adhesion due to small particle size and increasing their GIT residence time. In addition, lipid nanoparticles may also protect the loaded drugs from chemical and enzymatic degradation and gradually release drug molecules from the lipid matrix into blood, resulting in improved therapeutic profiles compared to free drug. A clear advantage of the use of lipid particles as drug carrier systems is the fact that the matrix is composed of physiological components, that is, excipients with generally recognized as safe (GRAS) status for oral and topical administration, which decreases the cytotoxicity.

#### **Solid Lipid Nanoparticles (SLN)**

SLN are biocompatible and biodegradable and have been used for controlled drug delivery and specific targeting. These colloidal carriers consist of a lipid matrix that should be solid at both room and body temperatures, having a mean particle size between 50 nm and 1000 nm (Muller and Lucks, 1996). Due to their physiological and biodegradable properties, SLN have been tested for several administration routes (Tsai et al, 2011; Mukherjee et al, 2009) including the oral (Rawat et al, 2011; Luo et al, 2011) and peroral (Hu et al, 2010; Souto and Muller, 2010) routes. SLN possess a solid lipid matrix identical to polymeric nanoparticles. In addition, SLN are of low cost (Muller et al, 2005), the excipients and production lines are relatively cheap, and the production costs are not much higher than those established for the production of parenteral emulsions (Wissing et al, 2004). Different techniques to produce SLN-loaded nanocurcumin are described in this review. The superiority of SLN showed in line property i.e. improved curcumin formulation and delivery.

SLN has been used to solve the hurdles for the therapeutic use of curcumin. Transferrin-mediated SLNs were formulated to increase photostability and enhance its anticancer activity against MCF-7 breast cancer cells. The anticancer activity of curcumin is enhanced with transferrin-mediated SLNs compared to curcumin solubilized surfactant solution and apoptosis is the mechanism underlying the cytotoxicity (Mulik et al, 2010).

Plianbanchang et al (2007) demonstrated the first topical formulation of curcumin as anti aging agent encapsulated in SLN. In this study, the prominent effect of curcuminoids loaded SLN cream on the outcome measures were hypothesized to be contributed to active ingredient, i.e., curcuminoids, and its delivery carrier, SLN. The antioxidant property of curcuminoids improved skin wrinkles and exhibited skin whitening effect, while the enhancement of skin hydration, elasticity, and viscoelasticity were the result of the occlusive characteristic of SLN.

#### **Nanostructure Lipid Carrier (NLC)**

Nanostructured Lipid Carriers are the second generation of solid lipid nanoparticles and are composed of a binary mixture of solid lipids and a spatially different liquid lipid as a carrier. NLCs are consisting of a lipid matrix with a special nanostructure. This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%. However, the NLC system minimizes or avoids some potential problems associated with SLN (Mehnert and Mader, 2001).

Fang et al (2012) described nanostructured lipid curcumin carriers prepared using the ethanol dripping method. This nanostructured lipid curcumin carriers showed a significantly higher peak plasma concentration ( $564.94 \pm 14.98$  ng/mL versus  $279.43 \pm 17.21$  ng/mL,  $P < 0.01$ ), a shorter time taken to reach peak plasma concentration ( $0.5 \pm 0.01$  hour versus  $1.0 \pm 0.12$  hour,  $P < 0.01$ ), and a greater  $AUC_{0-\infty}$  ( $820.36 \pm 25.11$  mg $\cdot$ hour/L versus  $344.11 \pm 10.01$  mg $\cdot$ hour/L,  $P < 0.05$ ) compared with curcumin suspension. In the tissue distribution studies, curcumin could be detected in the spleen, heart, liver, kidneys, lungs, and brain. Following intragastric administration of the nanostructured lipid curcumin carrier formulation, tissue concentrations of curcumin also increased, especially in the brain. The nanostructured lipid curcumin carrier formulation improved the ability of curcumin to cross the blood-brain barrier, with an 11.93-fold increase in the area under the curve achieved in the brain when compared with curcumin suspension.

Bondi et al (2010) reported the preparation and chemical-physical characterization of nanostructured lipid carriers containing curcumin, based on Imwitor, Compritol or Precirol as lipid matrix. By *in vitro* experiments, they have demonstrated that these nano-systems are able to carry curcumin into LAN5 neuroblastoma cells and their effect on cell mortality is higher than free curcumin.

### Liposome

Liposomes are the small vesicle of spherical shape that can be produced from cholesterol, non toxic surfactants, sphingolipids, glycolipids, long chain fatty acids and even membrane proteins. Liposomes are the drug carrier loaded with great variety of molecules such as small drug molecules, proteins, nucleotides and even plasmids. Liposomes were discovered about 40 years ago by A.D. Bangham (1980) which has become the versatile tool in biology, biochemistry and medicine today. Liposome can be formulated and processed to differ in size, composition, charge and lamellarity. The use of liposome to formulate natural compounds has been reported to improve solubility and chemical stability (Coimbra et al, 2011).

Several reports have been shown the potential use of liposomal carrier to improve the bioactivity of curcumin. (Runghphanichkul et al, 2011; Basnet et al, 2011; Chen et al, 2012; Agarwal et al, 2012; Orr et al, 2012; Aditya et al, 2012; Rahman et al, 2012) for various routes of administration. The transdermal delivery of liposomal curcumin has been described by Chen et al. Soybean phospholipids (SPC), egg yolk phospholipids (EPC), and hydrogenated soybean phospholipids (HSPC) were selected for the preparation of different kinds of phospholipids composed of curcumin-loaded liposomes: C-SPC-L (curcumin-loaded SPC liposomes), C-EPC-L (curcumin-loaded EPC liposomes), and C-HSPC-L (curcumin-loaded HSPC liposomes). The average par-

ticule sizes of these three types of curcumin-loaded liposomes were  $82.37 \pm 2.19$  nm (C-SPC-L),  $83.13 \pm 4.89$  nm (C-EPC-L), and  $92.42 \pm 4.56$  nm (C-HSPC-L). However, the C-SPC-L showed better skin permeation and further studied for the pharmacodynamic evaluation. They demonstrated that curcumin encapsulated in liposome composed by C-SPC-L showed better deposition, and better antimelanoma activity.

More complex form of curcumin loaded  $\gamma$ -cyclodextrin liposomes with size of about 100 nm and entrapment efficiency of nearly 100% was developed by Dhule et al (2012), indicated significant potential as delivery vehicles for the treatment of cancers of different tissue origin.

### Dendrimer

Dendrimers are nanostructures showing highly branched with an inner core, produced from macromolecules such as polyamidoamine (PAMAM), polypropyleneimine and polyaryl ether. The particle size range is between 1 to 100 nm although their sizes are mostly less than 10 nm. The uniqueness of dendrimers is based on their series of branches, multivalency, well defined molecular weight and globular structure with controlled surface functionality, which enhances their potential as carriers for drug delivery (Gilles et al, 2005; Gupta et al, 2006). Their globular structures and the presence of internal cavities enable drugs to be encapsulated within the macromolecule interior. Dendrimers have been reported to provide controlled release from the inner core. However, drugs are incorporated both in the interior as well as attached on the surface. Due to their versatility, both hydrophilic and hydrophobic drugs can be incorporated into dendrimers.

Unlike other nanocarriers which have been explored to improve the property of curcumin, application of dendrimer is still in early phase. Aim is also to improve the delivery of curcumin, mainly to cancer cells. The first form of curcumin-dendrimer conjugate was described by Markatou et al (2007). A water soluble poly(amidoamine) (PAMAM) was used to improve the solubility of curcumin analog. In addition, similar curcumin-dendrimer conjugate was reported by Shi et al (2007). They reported that monofunctional curcumin derivatives retain biological activity and are efficient for labeling and dissolving amyloid fibrils. This promising function of dendrimer conjugate is suggested to initiate more investigations to improve the limitation of curcumin in therapy.

### CONCLUSION

The main problem of using curcumin for therapy is low solubility hence low bioavailability. Development of both nanocrystal and nanocarrier systems showed promising approaches to improve the efficacy of curcumin through enhancement of its bioavailability. Nanocarrier systems, particularly, such as polymeric-based and lipid-based nanoparticles, micelle and den-

dimer showed more interesting system than nano-crystals due to their ability not only improve curcumin solubility and stability, but also assisting curcumin crossing biological membranes, tissue, blood-brain barrier, and even into cells. In addition, the flexibility to functionalize the surface of the carriers, makes them possible to target the curcumin-carrier system for specific application in clinic, especially for cancer therapy.

#### ACKNOWLEDGEMENT

This work was partly funded by Bandung Institute Technology research grand 2011.

#### REFERENCES

- Aditya NP, Chimote G, Gunalan K, Banerjee R, Patankar S, Madhusudhan B (2012) Curcuminoids loaded liposomes in combination with arteether protects against Plasmodium berghei infection in mice. *Exp Parasitol* 131(3):292-299.
- Agarwal NB, Jain S, Nagpal D, Agarwal NK, Mediratta PK, Sharma KK (2011) Liposomal formulation of curcumin attenuates seizures in different experimental models of epilepsy in mice. *Fundam Clin Pharmacol* Epub ahead of print.
- Alam S, Panda JJ, Chauhan VS (2012) Novel dipeptide nanoparticles for effective curcumin delivery., *Int J Nanomedicine* 7:4207-4221.
- Anand P, Kunnumakkara AB, Newman RA, and Aggarwal BB (2007) Bioavailability of Curcumin: Problems and Promises, *Mol Pharm* 4(6):807–818.
- Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB (2007) Bioavailability of curcumin: problems and promises. *Mol Pharm* 4(6):807-818.
- Anand P, Nair HB, Sung, B, Kunnumakkara AB, Yadav VR, Tekmal RR, Aggarwal BB (2010) Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo. *Biochem. Pharmacol* 79:330-338.
- Arun N, Nalini N (2002) Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. *Plant Foods Hum. Nutr* 57(1):41-52.
- Atkinson GP, Nozell SE, Benveniste ET (2010) NFkappaB and STAT3 signaling in glioma: targets for future therapies. *Expert Rev Neurother* 10:575-586.
- Babu PS, Srinivasan K (1995) Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat. *Mol. Cell. Biochem* 152(1):13–21.
- Babu PS, Srinivasan K (1997) Hypolipidemic action of curcumin, the active principle of turmeric (*Curcuma longa*) in streptozotocin induced diabetic rats. *Mol. Cell. Biochem* 166(1–2):169-175.
- Bangham, A.D (1980) *Liposomes in Biological Systems*, John Wiley and Sons: Chichester.
- Basnet P, Hussain H, Tho I, Skalko-Basnet N(2012) Liposomal delivery system enhances anti inflammatory properties of curcumin.. *J Pharm Sci* 101(2):598-609.
- Bisht S, Khan MA, Bekhit M, Bai H, Cornish T, Mizuma M, Rudek MA, Zhao M, Maitra A, Ray B, Lahiri D, Maitra A, Anders RA (2011) A polymeric nanoparticle formulation of curcumin (NanoCurc™) ameliorates CCl4-induced hepatic injury and fibrosis through reduction of pro-inflammatory cytokines and stellate cell activation., *Lab Invest* 91(9):1383-1395.
- Bondì ML, Craparo EF, Picone P, Di Carlo M, Di Gesu R, Capuano G, Giammona G (2010) Curcumin Entrapped Into Lipid Nanosystems Inhibits Neuroblastoma Cancer Cell Growth and Activates Hsp70 Protein. *Cur Nanoscience* 6(5):439-445.
- Calvo P, RemunanLopez C, VilaJato JL, Alonso MJ (1997) Chitosan and chitosan ethylene oxide propylene oxide block copolymer nanoparticles as novel carriers for proteins and vaccines. *Pharm. Res* 14:1431-1436.
- Chen H, Wu J, Sun M, Guo C, Yu A, Cao F, Zhao L, Tan Q, Zhai G (2012) N-trimethyl chitosan chloride-coated liposomes for the oral delivery of curcumin.. *J Liposome Res* 22(2):100-109.
- Coimbra M, Isacchi B, van Bloois L, Torano JS, Ket A, Wu X, Broere F, Metselaar JM, Rijcken CJ, Storm G, Bilia R, Schiffelers RM (2011) Improving solubility and chemical stability of natural compounds for medicinal use by incorporation into liposomes., *Int J Pharm* 416(2):433-442.
- Das RK, Kasoju N, Bora U (2010) Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells., *Nanomedicine* 6(1):153-160.
- Deodhar SD, Sethi R, Srimal RC (1980) Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J. Med. Res* 71:632-634.
- Dhule SS, Penfornis P, Frazier T, Walker R, Feldman J, Tan G, He J, Alb A, John V, Pochampally R (2012) Curcumin-loaded  $\gamma$ -cyclodextrin liposomal nanoparticles as delivery vehicles for osteosarcoma. *Nanomedicine* 8(4):440-451.
- Dikshit M, Rastogi L, Shukla R, Srimal RC (1995) Prevention of ischaemia-induced biochemical changes by curcumin & quinidine in the cat heart. *Indian J. Med. Re* 101:31–35.
- Duncan, R (2006) Polymer conjugates as anticancer nanomedicines. *Nat. Rev. Cancer* 6:688-701.

- Elsamalgly MS, Rohdewald P (1983) Reconstituted collagen nanoparticles, a novel drug carrier delivery system. *J. Pharm. Pharmacol* 35:537-539.
- Esmaili M, Ghaffari SM, Moosavi-Movahedi Z, Atri MS, Sharifzadeh A, et al (2011) Beta-casein micelle as a nano vehicle for solubility enhancement of curcumin, food industry application. *Food Science and Technology, LWT* 44(10):2166-2172.
- Fang M, Jin Y, Bao W, Gao H, Xu M, Wang D, Wang X, Yao P, Liu L (2012) In vitro characterization and in vivo evaluation of nanostructured lipid curcumin carriers for intragastric administration., *Int J Nanomedicine* 7:5395-5404.
- Farokhzad OC, Langer R (2006) Nanomedicine: Developing smarter therapeutic and diagnostic modalities. *Adv. Drug Deliv. Rev* 58:1456-1459.
- Feng R, Song Z, Zhai G (2012) Preparation and in vivo pharmacokinetics of curcumin-loaded PCL-PEG PCL triblock copolymeric nanoparticles., *Int J Nanomedicine* 7:4089-4098.
- Ferrari, M (2005) Cancer nanotechnology: opportunities and challenges. *Nat. Rev. Cancer* 5:161-171.
- Gilles ER, Fréchet JM (2005) Dendrimers and dendritic polymers in drug delivery. *Drug Discovery Today* 10(1):35-43.
- Gupta U, Agashe HB, Asthana A, Jain NK (2006) A review of in vitro-in vivo investigations on dendrimers: the novel nanoscopic drug carriers. *Nanomedicine* 2:66-73.
- Hatcher H, Planalp R, Cho J, Torti FM, Torti SV (2008) Curcumin: from ancient medicine to current clinical trials. *Cell Mol Life Sci* 65:1631-1652.
- Hovey D, Pruiit J, Ryde T, inventors; Elan Pharma International Limited, assignee (2006) Nanoparticulate megestrol formulations. US patent 7,101,576:5.
- Hrkach JS, Peracchia MT, Domb A, Lotan N, Langer R (1997) Nanotechnology for biomaterials engineering: Structural characterization of amphiphilic polymeric nanoparticles by H-1 NMR spectroscopy. *Biomaterials* 18;27-30.
- Hu L, Xing X, Meng J, and Shang C (2010) Preparation and enhanced oral bioavailability of cryptotanshinone-loaded solid lipid nanoparticles. *AAPS Pharm Sci Tech* 11(2):582-587.
- Jones MC, Leroux JC (1999) Polymeric micelles—a new generation of colloidal drug carriers. *Eur. J. Pharm. Biopharm* 48(2):101-111.
- Jordan WC, Drew CR (1996) Curcumin, a natural herb with anti-HIV activity. *J. Natl. Med. Assoc* 88(6):333.
- Junghanns JUAH, Müller AH (2008) Nanocrystal technology, drug delivery and clinical applications. *Int J Nanomedicine* 3(3):295–309.
- Kim MK, Choi GJ, Lee HS (2003) Fungicidal property of *Curcuma longa* L. rhizome-derived curcumin against phytopathogenic fungi in a greenhouse. *J. Agric. Food Chem* 51(6):1578–1581.
- Kiso Y, Suzuki Y, Watanabe N, Oshima Y, Hikino H (1983) Antihepatotoxic principles of *Curcuma longa* rhizomes. *Planta Med* 49(3):185-187.
- Kunnumakkara AB, Anand P, Aggarwal BB (2008) Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett* 2008 269:199-225.
- Kuttan R, Bhanumathy P, Nirmala K, George MC (1985) Potential anticancer activity of turmeric (*Curcuma longa*). *Cancer Lett* 29(2):197-202.
- LaVan DA, McGuire T, Langer R (2003) Small-scale systems for in vivo drug delivery. *Nat. Biotechnol* 21:1184-1191.
- Letchford K, Liggins R, Burt H (2007) Solubilization of hydrophobic drugs by methoxy poly(ethylene glycol)-block-polycaprolactone diblock copolymer micelles: theoretical and experimental data and correlations. *J Pharm Sci*;97(3):1179-1190.
- Leung MH, Colangelo H, Kee TW (2008) Encapsulation of curcumin in cationic micelles suppresses alkaline hydrolysis. *Langmuir* 24(11):5672-5675.
- Lim KJ, Bisht S, Bar EE, Maitra A, Eberhart CG (2011) A polymeric nanoparticle formulation of curcumin inhibits growth, clonogenicity and stem-like fraction in malignant brain tumors., *Cancer Biol Ther* 11(5):464-473.
- Liversidge G, Jenkins S, inventors; Elan Pharma International Limited, assignee (2006) Nanoparticulate candesartan formulations. WO 074218.
- Luo CF, Yuan M, Chen MS, et al (2011) Pharmacokinetics, tissue distribution and relative bioavailability of puerarin solid lipid nanoparticles following oral administration. *Int J Pharm* 410(1-2):138-144.
- Mahady GB, Pendland SL, Yun G, Lu ZZ (2002) Turmeric (*Curcuma longa*) and curcumin inhibit the growth of *Helicobacter pylori*, a group 1 carcinogen. *Anticancer Res* 22(6C):4179-4181.
- Maheshwari RK, Singh AK, Gaddipati J, Srimal RC (2006) Multiple biological activities of curcumin: a short review. *Life Sci.* 78(18):2081–2087.
- Maheshwari RK, Singh AK, Gaddipati J, Srimal RC (2006) Multiple biological activities of curcumin: a short review. *Life Sci* 78:2081-2087.
- Markatou E, Gionis V, Chryssikos GD, Hatziantoniou S, Georgopoulos A, Demetzos C (2007) Molecular interactions between dimethoxycurcumin and Pamam dendrimer carriers. *Int J Pharm* 339(1-2):231-236.



- Mehnert M, Mader K (2001) Solid lipid nanoparticles: production, characterization and applications. *Adv. Drug Deliv. Rev* 47:165-196.
- Moses MA, Brem H, Langer R (2003) Advancing the field of drug delivery: taking aim at cancer. *Cancer Cell* 4:337-341.
- Mukherjee S, Ray S, and Thakur RS (2009) Solid lipid nanoparticles: a modern formulation approach in drug delivery system. *Indian J Pharm Sci* 71(4):349-358.
- Mulik RS, Mönkkönen J, Juvonen RO, Mahadik KR, Paradkar AR (2007) Transferrin mediated solid lipid nanoparticles containing curcumin: enhanced in vitro anticancer activity by induction of apoptosis. *Int J Pharm* 398(1-2):190-203.
- Muller RH and Lucks JS (1996) Arzneistoffträger aus festen Lipidteilchen-feste Lipid Nanosphären (SLN), Germany.
- Muller RH, Wehnert W, and Souto EB (2005) Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for dermal delivery. Hong-Kong.
- Mythri RB, Jagatha B, Pradhan N, Andersen J, Bharat MM (2007) Mitochondrial complex I inhibition in Parkinson's disease: how can curcumin protect mitochondria. *Antioxid. Redox. Signal* 9:399-408.
- Nirmala C, Puvanakrishnan R (1996) Effect of curcumin on certain lysosomal hydrolases in isoproterenol-induced myocardial infarction in rats. *Biochem. Pharmacol* 51(1):47-51.
- Nirmala C, Puvanakrishnan R (1996) Protective role of curcumin against isoproterenol induced myocardial infarction in rats. *Mol. Cell. Biochem* 159(2):85-93.
- Nishiyama N, Kataoka K (2008) Current state achievements and future prospects of polymeric micelles as nanocarriers for drug and gene delivery. *Pharmacology and Therapeutics* 112:630-648.
- Onoue S, Takahashi H, Kawabata Y, Seto Y, Hatanaka J, Timmermann B, Yamada S (2010) Formulation design and photochemical studies on nanocrystal solid dispersion of curcumin with improved oral bioavailability. *J Pharm Sci* 99(4):1871-1881.
- Orr WS, Denbo JW, Saab KR, Myers AL, Ng CY, Zhou J, Morton CL, Pfeffer LM, Davidoff AM (2012) Liposome-encapsulated curcumin suppresses neuroblastoma growth through nuclear factor-kappa B inhibition. *Surgery* 151(5):736-744.
- Park TG (1995) Degradation of poly(lactic-co-glycolic acid) microspheres: effect of copolymer composition. *Biomaterials* 16:1123-1130.
- Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R (2007) Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol* 2(12):751-760.
- Plianbanchang P, Tungpradit W, Tiyafoonchai W (2007) Efficacy and safety of curcuminoids loaded solid lipid nanoparticles facial cream as an anti-aging agent, Naresuan University *J* 15(2):73-81.
- Rachmawati H, Shaal LA, Müller RH, Keck CM (2013) Development of curcumin nanocrystal: physical aspects. *J Pharm. Scie* 102(1):204-214.
- Rahman S, Cao S, Steadman KJ, Wei M, Parekh HS (2012) Native and  $\beta$ -cyclodextrin-enclosed curcumin: entrapment within liposomes and their in vitro cytotoxicity in lung and colon cancer. *Drug Deliv* 19(7):346-353.
- Ravindran J, Prasad S, Aggarwal BB (2009) Curcumin and cancer cells: how many ways can curry kill tumor cells selectively *AAPS J* 11:495-510.
- Rawat MK, Jain A, and Singh S (2011) In vivo and cytotoxicity evaluation of repaglinide-loaded binary solid lipid nanoparticles after oral administration to rats. *J Pharm Sci* 100(6):2406-2417.
- Ray B, Bisht S, Maitra A, Maitra A, Lahiri DK (2011) Neuroprotective and neurorescue effects of a novel polymeric nanoparticle formulation of curcumin (NanoCurc™) in the neuronal cell culture and animal model: implications for Alzheimer's disease. *J Alzheimers Dis* 23(1):61-77.
- Reddy RC, Vatsala PG, Keshamouni VG, Padmanaban G, Rangarajan PN (2005) Curcumin for malaria therapy. *Biochem. Biophys. Res. Commun* 326(2):472-474.
- Ruby A J, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R (1995) Anti-tumor and antioxidant activity of natural curcuminoids. *Cancer Lett* 9 (1):79-83.
- Ruddy SB, Ryde NP, inventors; Elan Pharma International Limited, assignee. (2002) Solid dose nanoparticulate compositions. WO 666,539.
- Rungphanichkul N, Nimmannit U, Muangsiri W, Rojsitthisak P (2011) Preparation of curcuminoid niosomes for enhancement of skin permeation. *Pharmazie* 66(8):570-575.
- Schmidt AL, Brunetto AL, Schwartzmann G, Roesler R, Abujamra AL (2010) Recent therapeutic advances for treating medulloblastoma: focus on new molecular targets. *CNS Neurol Disord Drug Targets* 9:335-348.
- Sharma OP (1976) Antioxidant activity of curcumin and related compounds. *Biochem. Pharmacol* 25(15):1811-1812.
- Shi W, Dolai S, Rizk S, Hussain A, Tariq H, Averick S, L'Amoreaux W, El Idrissi A, Banerjee P, Raja K (2007) Synthesis of monofunctional curcumin derivatives, clicked curcumin dimer, and a PAMAM dendrimer curcumin conjugate for therapeutic applications. *Org Lett* 9(26):5461-5464.

- Shishodia S, Sethi G, Aggarwal BB (2005) Curcumin: getting back to the roots. *Ann N Y Acad Sci* 1056:206-217.
- Souto EB and Muller RH (2010) Lipid nanoparticles: effect on bioavailability and pharmacokinetic changes. *Handbook of Experimental Pharmacology* 197:115–141.
- Srimal RC, Dhawan BN (1973) Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. *J. Pharm. Pharmacol* 25(6):447-452.
- Srinivasan M (1972) Effect of curcumin on blood sugar as seen in a diabetic subject. *Indian J. Med. Sci* 26(4):269-270.
- Srivastava R, Dikshit M, Srimal RC, Dhawan BN (1985) Antithrombotic effect of curcumin. *Thromb. Res* 40(3):413-417.
- Sugiyama Y, Kawakishi S, Osawa T (1996) Involvement of the diketone moiety in the antioxidative mechanism of tetrahydrocurcumin. *Biochem. Pharmacol* 52(4):519-525.
- Tsai MJ, Huang YB, Wu PC, et al (2011) Oral apomorphine delivery from solid lipid nanoparticles with different monostearate emulsifiers: pharmacokinetic and behavioral evaluations. *J Pharm Sci* 100(2):547-557.
- Venkatesan N (1998) Curcumin attenuation of acute adriamycin myocardial toxicity in rats. *Br. J. Pharmacol* 124(3):425-427.
- Venkatesan N, Punithavathi D, Arumugam V (2000) Curcumin prevents adriamycin nephrotoxicity in rats. *Br. J. Pharmacol* 129(2):231-214.
- Wang K, Zhang T, Liu L, Wang X, Wu P, Chen Z, Ni C, Zhang J, Hu F, Huang J (2012) Novel micelle formulation of curcumin for enhancing antitumor activity and inhibiting colorectal cancer stem cells. *Int J Nanomedicine* 7:4487-4497.
- Wissing SA, Kayser O, and Muller RH (2004) Solid lipid nanoparticles for parenteral drug delivery *Adv Drug Del Rev* 56(9):1257-1272.
- Yallapu MM, Gupta BK, Jaggi M, Chauhan SC (2010) Fabrication of curcumin encapsulated PLGA nanoparticles for improved therapeutic effects in metastatic cancer cells. *J. Colloid Interface Sci* 351(1):19-29
- Yang K, Lin LC, Tseng TY, Wang SC, Tsai TH (2007) Oral bioavailability of curcumin in rat and the herbal analysis from *Curcuma longa* by LC-MS/MS. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci* 853:183-189.