CHAPTER-2

LITERATURE REVIEW
1. **Isabel ezpeleta et al. (1996) [160]** studied the feasibility of preparing small sized carrier from vegetal macromolecules. Gliadin nanoparticles have been prepared by desolvation method and cross linking them with gluteraldehyde as the drug carrier of all-trans retinoic acid (RA). Nanoparticles formed were of approx. 500 nm, with a yield close to 90% of initial protein. Cross linkage increased the stability of formed nanoparticles and their entrapment efficiency was found to be 75% of added drug. *In-vitro* release profiles of RA loaded nanoparticles showed biphasic system. An initial burst effect (in which about 20% of RA was released) followed by zero-order diffusion (release rate 0.065 mg RA/ h).


3. **Isabel ezpeleta et al. (1999) [109]** prepared Ulex europaeus lectin gliadin conjugates (UE- GNP). The activity of these conjugates has been tested with bovine submaxillary gland mucin (BSM). It has been observed that level of binding of conjugates (UE-GNPs) with this mucin is always higher than controls (GNPs).

4. **Kawamori T et al. (1999) [162]** studied the modulating effect of Curcumin on apoptosis in the tumors during the promotion/progression stage of colon carcinogenesis in male F344 rats. They fed all male F344 rats at 5 weeks of age on control diet containing no Curcumin and an experimental AIN-76A diet with 0.2% synthetically prepared Curcumin (99.9%). At the age of 7 and 8 weeks of age, rats intended for carcinogen treatment were given s.c injections of azoxymethane (AOM) at a dose rate of 15 mg/kg weight per week. After the second AOM treatment, rats were switched to the diet containing 0.2% and 0.6% Curcumin. Premalignant lesions in the colon would have developed by week 14 following AOM treatment. Rats continued to receive their respective diets for 52 weeks after carcinogen treatment and were then sacrificed. They found administration of both 0.2% and 0.6% inhibited colon tumorigenesis. Thus they concluded that dietary administration of Curcumin during the promotion/progression stage of AOM induced colon carcinogenesis significantly inhibits tumor development in a dose-dependent manner and increases apoptosis in the colonic tumors. They also concluded that most of chemopreventive efficacy is achieved during the promotion /progression phase in this model.
5. **Coester et al. (2000) [163]** prepared & developed a new two-step desolvation method for manufacturing gelatin nanoparticles. After the first desolvation step, the low molecular gelatin fractions present in the supernatant were removed by decanting. The high molecular fractions present in the sediment were redesolved and then desolvated again at pH 2.5 in the second step. At the end of the study it has been observed that the molecular weight of gelatin has a decisive influence on the stability of the manufactured gelatin nanoparticles.

6. **Garrett et al. (2001) [164]** reported that cancer is multifaceted disease, but a common feature of the most tumors is that they harbor one or more genetic mutation that allow them to proliferate outside their normal growth restraints. Proliferations normally restrained through control of cell division cycle.

7. **Arangoa et al. (2001) [165]** estimated carbazole (loaded in the different gliadin nanoparticles) absorption & elimination rates of both adhered and non-adhered nanoparticulate fractions within the stomach. They found that nanoparticles dramatically increased the carbazole oral bioavailability up to 49% and provided sustained release properties related to a decrease of the carbazole plasma elimination rate.

8. **Ahsan et al. (2002) [166]** studied various carrier systems, like liposomes and microspheres, that emerged to deliver drugs to macrophages. They studied the role of various physicochemical properties like hydrophilicity, surface charge, composition, concentration and presence of various ligands on particulate carriers for targeting of drugs to macrophages.

9. **Shim, J.S. et al. (2002) [167]** synthesized hydrazinocurcumin (HC) a novel curcumin derivative and examined it for its biological activities. HC potently inhibited the proliferation of bovine aortic endothelial cells (BAECs) at a nanomolar concentration \( \text{IC}_{50} = 520 \, \text{nM} \) without cytotoxicity. In vivo and in vitro angiogenesis experiments showed HC as a new candidate for anti-angiogenic agent.

10. **Bilati et al. (2002) [168]** investigated the entrapment of 3 different model proteins (tetanus toxoid, lysozyme, and insulin) into poly (D,L-lactic acid) and poly(D,L-lactic-coglycolic acid) nanoparticles and to address process-related stability issues. For that purpose, a modified nanoprecipitation method as well as two emulsion-based encapsulation techniques (ie, solid-in oil-in water (s/o/w) and a double emulsion
(w1/o/w2) method) has been used. The results showed that tetanus toxoid and lysozyme are efficiently incorporated by the double emulsion procedure when ethyl acetate has been used as solvent (80% entrapment efficiency), whereas it is necessary to use methylene chloride to achieve high insulin entrapment efficiencies. The use of the s/o/w method or the formation of a more hydrophobic protein-surfactant ion pair did not improve protein loading.

11. Jayaprakasha, G.K. et al. (2002) [169] developed improved HPLC method for the determination of Curcumin, Demethoxycurcumin, and Bisdemethoxycurcumin. HPLC separation was achieved on a C18 column using three solvents, methanol, 2% AcOH in water and acetonitrile, with detection at 425 nm. Four different commercially available varieties of turmeric, namely, Salem, Erode, Balasore and local market samples, were analyzed to detect the percentage of these three curcuminoids.

12. Orecchioni et al. (2002) [170] investigated loading capacities of lipophilic drug in gliadin nanoparticles. The vitamin E (VE) loaded gliadin nanoparticles have been characterized by their size, zeta potential, VE payload and entrapment efficiency. VE loaded gliadin particle size is approximately 900 nm and their charge is close to zero. They are suitable VE drug carriers with an optimum encapsulation rate approximately 100 VE µg/mg of gliadin with an efficiency of more than 77%. The release behaviour of VE loaded nanoparticles may be interpreted as a 'burst effect', followed by a diffusion process through an homogeneous sphere.

13. Umamaheshwari and Jain (2003) [115] prepared Gliadin nanoparticles (GNP) bearing acetoxyhydroxamic acid (AHA) by a desolvation method. Ulex Europaeus Agglutinin I (UEA I) and Conconavalin A (Con A) lectins has been bound to GNP formulations by the two-stage carbodiimide coupling technique. Lectin-agglutination assay was performed to evaluate the binding efficacy of lectin formulations to carbohydrate receptors of H. pylori strains. Strong agglutination patterns have been observed with mannose-specific Con A-GNP and alpha(L)-fucose specific UEA-GNP formulations. The inhibitory efficacy of UEA-GNP and Con A-GNP was approximately two-fold higher compared to GNP. These lectin-conjugated gliadin nanoparticles are found to be potential candidate for targeted drug delivery and are anticipated to be useful in the treatment of H. pylori.
14. **Pak, Y. et al. (2003)** [171] developed HPLC assay using three methods of plasma sample preparation in order to quantify curcumin, the main constituent in the herbal dietary supplement turmeric. The assay was developed in an effort to quantify extremely low curcumin plasma concentrations observed in preliminary in vivo studies. The most sensitive assay can reliably detect concentrations down to 2.5 ng/ml. Plasma quantitation was precise and accurate based on both intra- and inter-day validations as indicated by low values for coefficients of variation and bias, respectively (≤15%).

15. **Peppas, L.B.et al. (2004)** [172] described targeted nanoparticles system for cancer chemotherapy. This review explores recent work directed towards targeted treatment of cancer, either through more specific anticancer agents or through method of delivery. These include delivery by avoiding the reticuloendothelial system, utilizing the enhanced permeability and retention effect and tumor specific targeting.

16. **Van Erk et al. (2004)** [173] studied gene expression changes in response to curcumin exposure in two human colon cancer cell lines, using cDNA microarrays with four thousand human genes. HT29 cells were exposed to two different concentrations of curcumin and gene expression changes were observed at different time intervals (3, 6, 12, 24 and 48 hours). In addition, curcumin affected expression of metallothionein genes, tubulin genes, p53 and other genes involved in colon carcinogenesis has been observed.

17. **Yi H, Bentley W. E. et al. (2005)** [174] formulated the liposome-encapsulated 4-(N)-stearoyl derivative with improved anticancer activity in vivo, in HT-29 and KB396p subcutaneously grafted tumors in mice. In tumor bearing mice, the liposomal 4-(N)-stearoyl derivative displayed a biphasic pharmacokinetic pattern with a short distribution phase followed by a long terminal elimination phase and a high AUC.

18. **Shahar lev-Ari et al (2005)** [175] studied the effect of curcumin on the growth inhibitory effect of celecoxib (specific COX-2 inhibitor) in human colon cancer cells. HT-29 and IEC-18-K-ras (expressing high level of COX-2), Caco-2 (expressing low level of COX-2) and SW-480 (no expression of COX-2) cell lines were exposed to different concentration of celecoxib (0-50 umol/L), curcumin (0-20 umol/L) and their combination. They assessed the COX-2 activity by measuring prostaglandin E2 production by enzyme linked imunoassay. COX-2 mRNA levels were assessed by reverse transcription-PCR. It has been observed that exposure to curcumin (10-15umol/L) and physiologic doses of
celecoxib (5μmol/L) results in the synergistic inhibitory effect on cell growth. They also observed that the level of COX-1 has not been altered by treatment with celecoxib, curcumin or their combination.

19. **Chen, Xu et al. (2006) [78]** examined the molecular mechanisms underlying curcumin inhibition of gene expression of EGFR in colon cancer cells. Their results demonstrated that curcumin inhibited human colon cancer cell growth by suppressing gene expression of EGFR through reducing the trans-activation activity of Egr-1. These results provided novel insights into the mechanisms of curcumin inhibition of colon cancer cell growth and potential therapeutic strategies for treatment of colon cancer.

20. **Duncan et al. (2006) [176]** studied polymer conjugates as anticancer nanomedicines. According to them more sophisticated polymer-based vectors would be a significant addition to the armory currently used for cancer therapy.

21. **Mansouria, Cuieb et al. (2006) [131]** performed the characterization of folate-chitosan-DNA nanoparticles for gene therapy and explained that FA-nanoparticles have lower cytotoxicity, good DNA condensation, positive zeta potential and particle size around 118 nm, which makes them a promising candidate as a non-viral gene vector. Charge ratio (N/P) controlled the nanoparticles size and their zeta potential. Nanoparticles presented a mean size of 118nm and 80% cellular viability compared to 30% cell viability using LipofectAMINE2000 controls. Gel electrophoresis showed intact DNA within the carriers.

22. **Kunnumakkara et al. (2007) [177]** explained the therapeutic effects of curcumin in light of the long and established experience with curcumin as a foodstuff and as a natural medicine in humans.

23. **Anand et al. (2007) [79]** reviewed the bioavailability of curcumin and its problems and promises. To improve the bioavailability of curcumin, numerous approaches have been undertaken. These approaches involve, first, the use of adjuvant like piperine that interferes with glucuronidation; second, the use of liposomal curcumin; third, curcumin nanoparticles; fourth, the use of curcumin phospholipid complex and fifth, the use of structural analogues of curcumin (e.g., EF-24).

24. **Ramteke and Jain 2008 [178]** prepared clarithromycin and omeprazole containing gliadin nanoparticles by the desolvation method using Pluronic F-68 as a stabilizing
agent. The results showed that this method is reproducible, easy and leads to the efficient entrapment of drug as well as formation of spherical particles ranging from 400 to 650 nm. In vitro antibacterial activity of the formulations was performed on isolated culture of Helicobacter pylori, which showed greater eradication effect of dual therapy entrapped formulations when compared with single therapy containing formulations and plain drugs.

25. **Jahanshahi et al. (2008) [179]** described the protein nanoparticles as drug delivery systems. Methods of preparation of protein nanoparticles, characterization, drug loading, release and their applications in delivery of drug molecules and therapeutic genes has been discussed.

26. **Lazaro, M.L. et al. (2008) [180]** reviewed the anticancer properties of curcumin and its considerations for clinical development as a cancer chemopreventive and chemotherapeutic agent. *In vitro* studies have demonstrated that curcumin is an efficient inducer of apoptosis and some degree of selectivity for cancer cells has been observed. Both *in vitro* and *in vivo* studies had shown that curcumin might produce toxic and carcinogenic effects under specific conditions. Curcumin might also alter the effectiveness of radiotherapy and chemotherapy.

27. **Racoviţa et al. (2008) [181]** explained the polysaccharides based micro- and nanoparticles obtained by ionic gelation and their applications as drug delivery systems.

28. **Torrado et al. (2008) [182]** explained the Chitosan–carboxymethylcellulose interpolymer complexes for gastric-specific delivery of clarithromycin (CAM). The aim of this study was to investigate the influence of the molecular weight (M.wt.) of CS and the proportion CS/CMC on physical properties and drug release. Swelling was dependent on CS M.wt., medium pH and polymer/polymer proportion. A controlled-release gastro-retentive system was obtained by the novel method “tablets-in-capsule”, where mini-matrices containing CAM, CS and CMC in the proportion 80:15:5 (w/w) had demonstrated to have suitable swelling properties and the most suitable drug release profile.

29. **Milacic et al. (2008) [183]** reported that the tumor cellular proteasome is most likely an important target of curcumin. Nucleophilic susceptibility and *in silico* docking studies show that both carbonyl carbons of the curcumin molecule are highly susceptible to a
nucleophilic attack by the hydroxyl group of the NH(2)-terminal of threonine of the proteasomal chymotrypsin-like (CT-like) subunit. Consistently, curcumin potently inhibited the CT-like activity of a purified rabbit 20S proteasome (IC(50) = 1.85 micromol/L) and cellular 26S proteasome. Their study shows that proteasome inhibition could be one of the mechanisms for the chemopreventive and/or therapeutic roles of curcumin in human colon cancer.

30. Prajakta et al. (2009) [184] prepared curcumin nanoparticles coted with Eudragit S 100 by Solvent emulsion-evaporation technique. MTT assay demonstrated almost double inhibition of the cancerous cells by nanoparticles, as compared to curcumin alone, at the concentrations tested. Enhanced action may be attributed to size influenced improved cellular uptake, and may result in reduction of overall dose requirement. Results indicate the potential for in vivo studies to establish the clinical application of the formulation.

31. Majumdar et al. (2009) [185] prepared curcumin and resveratrol delivery system, to examine wether their combination inhibit the growth of transformed cells and colon carcinogenesis. In vitro studies have demonstrated that the combinatorial treatment caused a greater inhibition of constitutive activation of EGFR and its family members as well as IGF-1R. Their data suggested that the combination of curcumin and resveratrol could be an effective preventive/therapeutic strategy for colon cancer.

32. Das et al. (2009) [186] studied the encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells. A nano formulation of curcumin with a tri-component polymeric composite for delivery to cancer cells was reported in their paper. Cellular internalization of curcumin loaded composite nanoparticles was confirmed from green fluorescence inside the HeLa cells.

33. Tekmal et al. (2009) [187] designed of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake and increased bioactivity in vitro and superior bioavailability in vivo. They found that curcumin (NP) had much higher cellular uptake in vitro than that of curcumin. Curcumin (NP) was more potent in inducing apoptosis in tumor cells. One possible cause for higher activity could be higher cellular uptake of curcumin (NP). Curcumin (NP) was also more active than curcumin in suppressing the expression of TNF-regulated expression of cyclin D1, MMP-9 and VEGF.
Bing et al. (2009) [188] described the optimization of fabrication parameters to produce chitosan-tripolyphosphate nanoparticles for delivery of tea catechins. The results demonstrated that the particle size and surface charge of CS-TPP nanoparticles could be controlled by fabrication modulating conditions including contact time between CS and tea catechins, CS molecular mass, CS concentration, CS-TPP mass ratio, initial pH value of CS solution, and concentration of tea catechins on encapsulation efficiency.

Vyas et al. (2009) [189] described the encapsulation of cyclodextrin complexed simvastatin in chitosan nanocarriers (A novel technique for oral delivery). This work shows that nanocarriers encapsulating HP-β-CD complexed simvastatin can be prepared by cross-linking of chitosan with tripolyphosphate. The prepared NCs formed are able to encapsulate hydrophobic compounds designated to oral delivery. Finally, it could be interesting to study potential of dual nature of nanocarriers as possible candidates for having mucoadhesive and permeability enhancing property (because of chitosan).

Ravindran et al. (2009) [190] presented a review on curcumin and cancer cells in which they described that how curcumin selectively killed tumor cells, and not normal cells. Curcumin modulates growth of tumor cells through regulation of multiple cell signalling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways and protein kinase pathway (JNK, Akt, and AMPK).

Ganta, S. et al. (2009) [191] examined augmentation of therapeutic efficacy upon co-administration of paclitaxel (PTX) and curcumin (CUR), an inhibitor of nuclear factor kappa B (NFκB) as well as a potent down-regulator of ABC transporters, in wild-type SKOV3 and drug resistant SKOV3 human ovarian adenocarcinoma cells. PTX and CUR were encapsulated in flaxseed oil containing nanoemulsion formulations. The results showed that the encapsulated drugs were effectively delivered intracellular in both SKOV3 and SKOV3_{TR} cells. CUR administration was shown to inhibit NFκB activity and down regulate P-glycoprotein expression in resistant cells. Combination PTX and CUR therapy, especially when administered in the nanoemulsion formulations, was very effective in enhancing the cytotoxicity in wild-type and resistant cells by promoting the
apoptotic response. Overall, this cotherapy strategy has significant promise in the clinical management of refractory diseases, especially in ovarian cancer.

38. **Kalyan et al. (2010)** [192] explained the recent advancement in chitosan based formulations and its pharmaceutical application. Chitosan polymer was incorporated into hydrogels and microspheres, which demonstrated large potentials in delivery systems for drugs, proteins and genes. Chitosan has strong positive charge and this charge helps it to bind fats and cholesterol and initiates clotting of red blood cells. Chitosan have fiber like properties, which can be used to replace calories in foods. It can also be used in the pharmaceutical industry in direct tablet compression, for the production of controlled release solid dosage form or for the improvement of drug dissolution. Chitosan has been postulated in numerous areas of biopharmaceutical research such as mucoadhesion, permeation enhancement, vaccine technology, gene therapy and wound healing. Recent applications of chitosan are in nasal, ophthalmic, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal drug delivery and mucosal-vaccine.

39. **Nagpal et al. (2010)** [193] reviewed the potential of chitosan nanoparticles for controlled drug delivery, effectiveness for mucosal drug delivery, ability to improve the stability of drugs, genes or proteins when formulated as chitosan nanocarriers and better option for tissue engineering applications.

40. **Yallapu M.M. et al. (2010)** [194] reported that curcumin acts as a chemo/radio-sensitizer by modulating the expression of pro-survival proteins and increasing apoptosis in response to a low dose of cisplatin. Nanoparticle mediated curcumin delivery would further improve the sensitization and therapeutic capabilities of curcumin. This study demonstrated a novel curcumin pre-treatment strategy that could be implemented in pre-clinical animal models and in future clinical trials for the effective treatment of chemo/radio-resistant ovarian cancers.

41. **Ganta S. et al. (2010)** [195] evaluated the effect of curcumin in oral bioavailability and therapeutic efficacy of paclitaxel (PTX) administered in nanoemulsion to SKOV3 tumor-bearing nu/nu mice. Oral administration of the mice with CUR at 50 mg/kg for 3 consecutive days resulted in a down regulation of intestinal P-glycoprotein (Pgp) and cytochrome P450 3A2 (CYP3A2) protein levels. PTX, a Pgp and CYP3A2 substrate was administered orally at 20 mg/kg in solution or nanoemulsion either as single agent or
upon pretreatment with CUR at 50 mg/kg in tumor-bearing mice. Plasma AUC$_{0-\infty}$ of PTX administered in nanoemulsion to CUR pre-treated mice showed 4.1-fold increase relative to controls. Similarly, relative PTX bioavailability was increased by 5.2-fold, resulting in a 3.2-fold higher PTX accumulation in the tumor tissue. PTX administered in nanoemulsion to CUR pretreated mice also showed significantly enhanced anti-tumor activity. Preliminary safety evaluation showed that CUR+PTX combination did not induce any acute toxicity as measured by body weight changes, blood cell counts, liver enzyme levels, and liver histopathology.

42. **Jang et al. (2010) [196]** prepared & evaluated delivery vehicles of paclitaxel using low molecular weight water-soluble chitosan (LMWSC). LMWSC was modified with methoxy polyethylene glycol (LMWSC-MPEG, ChitoPEG), and then it was conjugated with cholesterol (LMWSC-MPEG-Chol). The results of a tumor inhibition test with CT26 implanted upon mouse tumor models *in vivo* indicated that the application of a dose of 10 mg/kg of LMWSC-NPT showed a superior survival rate and a slower tumor growth than when paclitaxel alone was administered, although the tumor growth and survival rate were not significantly changed at a dose of 2 mg/kg. The LMWSC-NPT dose above 10 mg/kg showed a superior antitumor activity.

43. **Mohanty Chandana et al (2010) [197]** synthesized curcumin loaded nanoparticulate delivery system showing narrow size distribution with biocompatibility (confocal studies and TNF-assay). The formulation displayed enhanced stability in phosphate buffer saline by protecting encapsulated curcumin against hydrolysis and biotransformation. They found that nanoparticulate curcumin is comparatively more effective than native curcumin against different cancer cell line under *in vitro* conditions. Molecular basis of apoptosis by western blotting revealed blockade of nuclear factor kappa B (NFkB) and its regulated gene expression through inhibition of IκB kinase and Akt activation. It has also been observed that in mice nanoparticulate curcumin is more bioavailable and has longer half life than native curcumin as revealed from pharmacokinetic study. In conclusion nanoparticulate curcumin is useful as potential anticancer drug for treatment of various malignant tumors.

44. **Duan jinghua et al (2010) [198]** synthesized poly-(butyl)-cyanoacrylate (PBCA) nanoparticles coated with chitosan. Curcumin nanoparticles with comparable *in vitro*
therapeutic efficacy to free curcumin against a panel of human hepatocellular cancer cell lines, as assessed by cell viability (3-[4,5-dimethylthiazole-2-yl]2,5-diphenyl-tetrazolium bromide assay (MTT assay) and proapoptotic effect (annexin V/propidium iodite staining) in vivo. Curcumin nanoparticles suppressed hepatocellular carcinoma growth in murine xenograft models and inhibited tumor angiogenesis. In conclusion both curcumin nanoparticles and free curcumin suppress COX-2 and VEGF expression, as well as cell proliferation/survival of hepatocarcinoma cells. Curcumin-PBCA nanoparticles provide an opportunity to expand the clinical repertoire of this efficacious agent by enabling ready aqueous dispersion.

45. **Kajal H. and A. Misra (2011)** [112] Nanoparticles (NP) incorporating tetanus toxoid and a model antigen ovalbumin were prepared for investigation as delivery vehicles for oral immunization. Gliadin, the seed storage protein of wheat, was used as the carrier because of its biocompatibility, oral bioavailability and mucoadhesive properties. NP with approximately 50% w/w of antigen were size-stable over 3 weeks of testing.

46. **Kakkar et al. (2011)** [199] prepared curcumin-loaded solid lipid nanoparticles (C-SLNs) with an average particle size of 134.6 nm and a total drug content of 92.3371.63% using a micro emulsification technique.

47. **Suwannateep Natthakitta et al (2011)** [200] prepared curcumin loaded nanospheres; fabricated through a self assembling mechanism from ethylcellulose (EC) and dipolymeric carrier made from a blend of methylcellulose (MC) and EC (ECMC). They found that both curcumin loaded ECMC (C-ECMC) and curcumin loaded EC(C-EC) particles showed in vitro free radical scavenging activity and dose dependent in vitro cytotoxic effect towards MCF-7 human breast adenocarcinoma and HepG2 hepatoblastoma cells in tissue culture. They performed the evaluation of in vivo adherence to stomach mucoasa and their ability to release curcumin. They observed improvement in the curcumin sustainability in blood attained by the use of C-ECMC nanoparticles as compared to free curcumin. They concluded that excellent mucoadhesion and sustained release of curcumin could be achieved by fabrication due to hydrophilic surface of self assembled spheres.

bound technique. CCM-HSA-NPs showed markedly greater solubility (300-fold) than CCM and this allowed them to eliminate cremophor EL and ethanol from the formulation to avoid their toxic effect. The biological activity of CCM in formulation was found to be preserved in vitro. Further in vivo tumor distribution and vascular epithelial cell transport studies demonstrate the superiority of CCM-HAS-NPs over CCM. Moreover CCM-HAS-NPs showed better in vivo antitumor activity than CCM in tumor xenograft animal model, with no observable toxicity. Thus they concluded that HAS-based nanoparticles technology offers a promising drug delivery system for CCM in treatment of cancer.

49. Gulfam et al. (2012) [202] synthesized and evaluated gliadin and gliadin-gelatin composite nanoparticles for delivery and controlled release of an anticancer drug (e.g., cyclophosphamide) by electrospray deposition system. They found that cyclophosphamide was gradually released from the gliadin nanoparticles for 48 h. In contrast, the gliadin-gelatin composite nanoparticles released cyclophosphamide in a rapid manner. Furthermore, they demonstrated that breast cancer cells cultured with cyclophosphamide-loaded 7% gliadin nanoparticles for 24 h became apoptotic, confirmed by Western blotting analysis. Thus they concluded that gliadin-based nanoparticle could be a powerful tool for delivery and controlled release of anticancer drugs.

50. Golla et al. (2012) [203] prepared & evaluated doxorubicin loaded apotransferrin (Apodoxonano) and lactoferrin nanoparticles (Lactodoxonano) by sol-oil chemistry. HCC in the rats was induced by 100 mg/l of diethylnitrosamine (DENA) in drinking water for 8 weeks. Rats received 5 doses of 2 mg/kg drug equivalent nanoparticles through intravenous administration. Pharmacokinetics and toxicity of nanoformulations was evaluated in healthy rats and anticancer activity was studied in DENA treated rats. They found that in rats treated with nanoformulations, the numbers of liver nodules were found to be significantly reduced. Safety analysis shows minimal cardiotoxicity due to lower drug accumulation in heart in the case of nanoformulation. Thus they concluded that drug delivery through nanoformulations not only minimizes the cardiotoxicity of doxorubicin but also enhances the efficacy and bioavailability of the drug in a target-specific manner.

51. Alizadeh et al. (2012) [204] investigated the preventive effects of polymeric nanocarrier-curcumin (PNCC) on colon carcinogenesis in an azoxymethane-induced rat tumor. Forty rats were divided into control, curcumin- and PNCC-treated groups. Animals received
azoxymethane (AOM) as a carcinogenic agent (15 mg/kg, s.c.) weekly for two consecutive weeks. They were given curcumin 0.2% and PNCC two weeks before till 14 weeks after the last injection of AOM. The histopathological and immunohistochemistry examinations were also performed on colon tissue. *In vivo*, curcumin nanoparticles inhibited colon cancer growth in animal model. This study demonstrated the potential anticancer effects of PNCC in a typical animal model.

52. **Madhavi et al. (2012) [205]** prepared & evaluated colon targeted curcumin microspheres using Eudragit S100. A "O/O solvent evaporation" technique was used in the preparation of microspheres. They found that colon target was affectively achieved using the optimized formulation. Eudragit microspheres delivered most of their drug load (79.0%) to the colon, whereas with plain drug suspension only 28.0% of the total dose reached the target site. This study successfully developed curcumin microspheres which can be used effectively in the treatment of the colon cancer.

53. **Kanai et al. (2012) [206]** evaluated the safety and pharmacokinetics of newly developed nanoparticle curcumin with increased water solubility (named THERACURMIN). Six healthy human volunteers were recruited and received THERACURMIN at a single oral dose of 150 mg. After an interval of 2 weeks, the same subjects then received THERACURMIN at a single dose of 210 mg. Plasma curcumin levels were measured at 0, 1, 2, 4, 6, and 24 h after THERACURMIN intake using high-performance liquid chromatography (HPLC). They found that one subject reported grade 1 diarrhea after intake of 150 mg THERACURMIN. No other toxicities were observed in this study. Thus they concluded that THERACURMIN can safely increase plasma curcumin levels in a dose-dependent manner at least up to 210 mg without saturating the absorption system.

54. **Asai et al. (2012) [207]** prepared various angiogenic vessel-targeted liposomes and evaluated them in experimental cancer models such as drug-resistant and hypovascular tumors. They indicated that increased apoptosis of angiogenic endothelial cells can be achieved by the targeted liposomes encapsulating cytotoxic drugs, resulting in enhanced anticancer effects.

55. **Roy et al. (2012) [208]** prepared & evaluated PLGA nanoparticles coated with Chitosan. Their results indicated that PLGA-nanoparticulation of andrographolide diterpenoid
enhanced its anti-cancer properties three fold. Chitosan coating of AG nanoparticles further accentuated cellular localization, induced G1 cell cycle arrest and increased cellular toxicity and apoptosis in MCF-7 cells. *In vivo* studies confirm that the nanoparticles reduce tumor weight by 68.21% as compared to 24.7% by AG, and increased the life span of mice infected with Ehrlich ascites carcinoma (EAC) by 78.08% as compared to 23.5% for AG alone.

56. **Lee et al. (2012) [209]** prepared & characterized PEG-modified lipid nanoparticles. The delivery efficiency into tumor tissue was evaluated using a biodistribution study. To evaluate antitumor efficacy, gold porphyrin or camptothecin (a DNA topoisomerase I inhibitor) was encapsulated and compared using an *in vivo* neuroblastoma (N2A) model. They found that drug encapsulation into PEG-modified lipid nanoparticles enhanced the preferential uptake in tumor tissue. Thus they concluded that specific design of a chemotherapeutic agent using nanotechnology is important in the development of a safe and effective drug in cancer therapy.