# REVIEW ARTICLE

# NANO-BASED THERAPY FOR TREATMENT OF SKIN CARCINOMA

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**ABSTRACT**

Skin carcinoma is a frequently occurring cancer caused due to ultra violet rays of the Sun. It starts from normal skin cells but later on transforms into cells which undergo uncontrolled mitosis. Skin cancer is not as deadly as other cancers and has no metastasis and is not life threatening. Conventional chemotherapy has in general failed to treat skin cancer due to non specific targeting, which is accompanied by several side effects. Novel therapeutic approach based on nanotechnology have emerged as the best alternative for skin cancer treatment. We presented current scenario of nano based particulate drug carrier approaches for effective therapy for skin carcinoma by reducing side effects. This approach also reduces frequency of administration and improves patient compliance. Nanotechnology has emerged as the best alternative for conventional therapy for the effective treatment of skin cancer. Nanoparticles can specifically target skin carcinoma and are able to sustain drug release and reduce side effects to a greater extent.

**Keywords:** Skin carcinoma, Nanoparticles, nanoemulsion, antineoplastics

## INTRODUCTION

Nanotechnology is the branch of science which deals with formulations, substances as well as devices that run in nano sized range. It deals with design, fabrication and systems by minimizing size and shape in nano range[1,2]. Nanotechnology is widely used in biomedical field such as imaging, diagnosis and therapy[3]. Due to site specific delivery potential of nanoparticles, they are widely used in the treatment of various types of cancers. Nanoparticles are also used for improving solubility of poorly water soluble drugs, bioavailability and modifying pharmacokinetic properties. Nanoparticles can enhance the biological half lives of drugs by decreasing metabolism. Combination therapy can be improved by using nanoparticles by simultaneous release of two or more drugs[4,5]. Nanoparticles also reduce the dose and side effect as well[6]. The nanoparticles can be used for potentiating anticancer therapeutic effects by combining drug delivery with energy forms such as heat, light, and sound[7]. In the United States (US) skin cancer is widespread but not considered as deadly[8].

Melanoma is a form of skin cancer which accounts for a majority of skin cancer deaths but this can be operated safely without harming the patient. The metastasized melanoma causes majority of deaths within short span of diagnosis i.e. within maximum of 5 years[9]. Apart from melanoma, other forms of skin cancers such as basal cell carcinoma and squamous cell carcinoma are frequently found types of skin cancer. Due to site specific drug delivery of nanoparticles they are used widely for improving therapeutic efficacy of anticancer drugs for skin cancer. The subsequent section deals with nanoparticles which are basically used both for systemic and transdermal delivery for effective treatment of skin cancers. The most important forms of nanoparticles which are employed for treatment of skin cancer include liposomes, dendrimers and carbon-based nanoparticles.

### Liposomes

Liposomes are the concentric bilayers of phospholipids vesicles ranging from 50-100 nm and even larger enclosing a aqueous compartment. The classification of liposomes is based on the size and the number of layers. They may be classified as multi-, oligo- or unilameller. The aqueous layer provides the entrapment drugs which

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are soluble in water whereas the lipid double layers are used for retaining hydrophobic or amphiphilic drugs. To protect from the uptake of reticuloendothelial system (RES) after intravenous administration, PEGylated liposomes, stealth liposomes were designed which may be used for reducing clearance and enhancing circulation time[10]. The drug delivery specificity can be enhanced by linking the liposomal surface with suitable ligands and or polymers[11]. Researchers found that liposomes reside in the interstitial medium of tumour cells[12]. Several, so many liposomal formulations containing several anticancer drugs for treating melanoma are in the pipeline in clinical research[13]. Advancement in cationic liposomes led to targeting small interfering RNA (siRNA)[14]. Muthu and Feng developed theranostic liposomes which can be loaded with diagnostic NP[15]. Magnetic liposomes can be developed for tracing their path within the body using MRI[16]. Entrapment of drugs involved in ultrasound-controlled drug delivery systems can be done using magnetic liposomes[17].

## Solid Lipid Nanoparticles (SLNs)

SLNs are submicron colloidal drug delivery systems which are composed of physiological lipids dispersed in water or in aqueous surfactant solution. SLNs have no potential toxicity problems as organic solvents are not used during their preparation. SLNs are highly stable and can protect drugs against degradation. The other advantages of SLNs include biodegradability and biocompatibility and reportedly less toxicity. The production and sterilization of SLNs on commercial scale is also possible easily. Docetaxel loaded solid lipid nanoparticles (SLNs) was found to boost therapeutic efficacy of chemotherapeutic[18] agents and malignant melanoma cell lines *in vitro* and *in vivo* studies[19]. Cholesteryl butyrate solid lipid nanoparticles were found effective for inhibiting HUVE (human umblilical vein endothelial cells adhesiveness to cancer) cell lines of different cancer types[20].

## Nanospheres and polymeric micelles

They can be designed by 2 chains having variable hydrophobic tendency. They have both hydrophilic blocks and hydrophobic blocks[21]. The specificity and efficacy of micelles can be increased by modifying functional groups[22-24]. Polymeric micelle systems can also be employed for co-delivery of drugs along with radiation agents[10,25,26]. B16F10 melanoma bearing mice were recently treated with polymeric micelles[27]. Gadolinium (Gd) or manganese (Mn) are paramagnetic materials. They are generally developed as pH sensitive systems for oral delivery to protect the drugs from harsh conditions of the stomach[28].

## Dendrimers

The term dendrimer is derived from a Greek word which means tree. Dendrimers are defined as molecules with repetitively branched units. Currently, the term dendrimer is internationally accepted. Dendrimers can be employed as carriers for delivering hydrophobic and hydrophilic drugs as well as, nucleic acids and imaging agents. Dendrimers possess excellent properties such as large number of surface functional groups, high number of branching and large number of internal cavities[10,28-30].

They include polyunsaturated fatty acids, oligo and polysaccharides and tumour associated antigens[31–33]. Dendrimers have also successfully been employed for radio-immunotherapy and immunotherapy of different tumors and melanoma and squamous skin carcinoma[34, 35]. Gadolinium-conjugate dendrimers have been employed for specific targeting as well as imagining of tumors[36].

## Nanotubes

They are similar to graphite like carbon found in pencils. They are very thin hollow cylindrical tubes, much smaller than human hair but much stronger than steel and prepared either as single- or multi-walled nanotubes for use as tissue repair scaffolds and carrier of drugs[37].

SWCNT i.e. single-walled carbon nanotubes, are used by covalent bonding of large number of monoclonal antibodies for specific tumor targeting, fluorescent probes and radiation ion chelates[38]. SWCNTs are used for carrying gadolinium atoms for MRI of tumors with specified receptor agonist and antagonist for targeting of tumor cells[39]. The diagnosis and treatment of melanoma have been done by application of carbon nanotubes[40].

**MSN (Mesoporous Silica Nanoparticles)** It has come out a cost effective drug delivery system in the few last decades[41-43]. MSNs are superior to conventional organic carriers due to their unique properties such as adjustable particle size, morphology, altered form, invariable and adjustable pore size, high surface area, high pore volume, high drug loading capacity and high mechanical as well as chemical stability and simple and easy functionalization[44-46].

**Quantum Dots** Semiconductor crystals of nanometer dimensions (2-10 nm) with distinctive conductive properties determined by their size are known as Quantum dots. They have narrow emission band as well as broad absorption band[47]. The middle part of quantum dots possess elements ranging from group II to VI of the periodic table[48], which are "over coated" with a layer of zinc sulphide. The photostability of quantum dots makes them

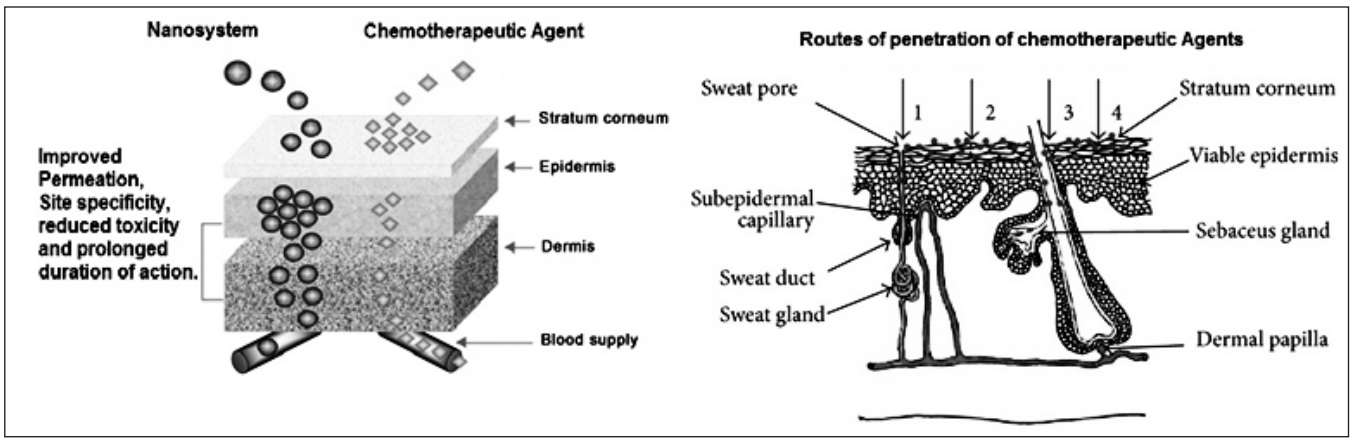


**Fig. 1: Route of penetration of chemotherapeutic agents[34]**

suitable for exceptionally sensitive, durable and multi-target bio-imaging application[49,50]. Peptides, antibodies and small molecules drugs are the possible ligands[51].

Novel approaches, such as a silica coating or a biocompatible polymer coating, have further increased the biocompatibility and reduced their toxicity.

When a magnetic field is applied externally, SPION (Superparamagnetic Iron Oxide) attains sufficient magnetic moment, for superparamagnetic behavior as they are used in biomedical fields.

In MRI, they are widely used as contrasting agents[52]. Very small quantities of SPIONs are needed for imaging therapy as they produce high contrast per unit of particles, thus able to reduce toxicity[49,50]. The SPIONs convert magnetic field into heat for selective destruction of tumor cells[53]. This generated heat can selectively destroy the cancer cells which are more sensitive to temperature as compared to normal cells[49,53]. Their biomedical applications can be enhanced by modifying their surface and increasing their biodegradability and biocompatibility[54]. The attachment of biodegradable materials to SPION, such as dextran, PLGA, PEG and cellulose, can improve their biocompatibility and bioavailability. Recently nanoparticles coated with superparamagnetic iron oxide has been developed for sentinel lymph nodes mapping in breast cancer and melanoma patients[55].

**AU Nanoparticles (Gold Nanoparticles)** are used to carry drugs and genes. They are non-toxic carriers in which Au contributes stability to the system whereas monolayer imparts surface properties such as hydrophobicity and charge. Another most interesting characteristic of gold nanoparticles is their interaction with SH groups which provides an effective and selective means of controlled intracellular release. Recent developments in biochemical applications such as gene delivery, drug and imaging agents include formulation of gold nanoparticles like nanocapsules, nanotubes and nanospheres[56,57]. The most attractive features of Au nanoparticles are excellent biocompatibility, ease of functionality, ease of preparation in nano range and their tendency to bind with different biomolecules with their original biological properties remain constant[58]. Gold nanoparticles of size less than 50 nm can improve drug targeting to brain[59], sensitization of tissues and cells and in surgical processes[60–62]. Drug targeting to tumour cells including melanoma have improved significantly by linking drugs, small molecules, proteins and DNA with gold nanoparticles. Gold nanoparticles have shown promising potential as biosensors as they can be detected by fluorescence, electrical conductivity and optical absorption[63,64]. Moreover, they are nontoxic as well as biocompatible. Au nanoparticles are neither allergic nor immunogenic[65,66]. Fig. 1 represents routes of penetration of chemotherapeutics for cure of skin carcinoma.

**Nanoparticles as transdermal patches in skin carcinoma.** Majority of the chemotherapeutic agents are commonly given parenterally. The topical application of anticancer drugs is found to be an alternative for drug targeting and therapeutic success[67]. The major challenge of topical administration is to increase penetration of the antineoplastics drug to kill tumor cells[68]. Penetration of drug through the major barrier of skin i.e. epidermis, can be improved by use of chemical permeation enhancers, sonophoresis, iontophoresis have been reported[69]. Penetration of hydrophilic anticancer drugs through stratum corneum is low because of very less o/w partition coefficient value, significant molecular weight and ionization as well. Nanotechnology coupled with new imaging techniques have shown improved therapeutics benefits in skin cancer[70,71]. The permeation of drug through stratum corneum is regulated

by Fick's 2nd law of diffusion[72]. 5-FU[73], diclofenac[73], and imiquimod are the currently used topical treatments for skin cancer as semisolid formulations. One of the most advanced and widely used treatment for skin USFDA is photodynamic therapy[74] which is used to treat non melanoma skin cancers and their precursor lesions, such as actinic keratosis. Nanoparticulate formulations could improve drug targeting and penetration into tumour cells, drug stability and reduce skin irritation[75]. Liposomes are reported to be most widely used nanocarriers for treatment of skin cancer[76]. Liposomes loaded with doxorubicin[77, 78], cisplatin[79, 80], oxaliplatin[81] and camptothecin[82], have already proven improved cytotoxicity and minimized side effects. The liposomes, such as DOXIL, are already commercially available which contain doxorubicin and was approved in the US in 1995.

Fang *et al.*[83] reported that flexible liposomes (ethosomes) increased penetration through skin and retention in skin compared to traditional liposomes[84,85] Similar results such as improved cytotoxicity and penetration was observed with 5-fluorouracil loaded niosomes[86]. Liposome based formulations showed better therapeutic effect in the treatment of acne, psoriasis and other inflammatory conditions compared to non liposomes[87-90]; solid lipid nanoparticles and polymeric nanoparticles have shown increased drug penetration and stability[91,92].

## DRUG DELIVERY FROM NANOPARTICLES IN NON MELANOMA SKIN CANCERS

There are basically three types of skin cancers i.e. melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). Among them, the incidence rate of BCC is 4 to 5 times higher than SCC[93]. Exposure to ultraviolet radiation, skin type, family history, prior history of skin tumors, and immunosuppression are the primary reasons for sporadic skin malignancies. Excision is considered as the gold standard for the treatment of localized SSC and BBC. The various approaches available for excision are surgical excision, cryosurgery and micrographic surgery[94].

Majority of SCC and BCC are locally invasive, however 1 % to 5 % of primary SCC may permeate to nearby lymph nodes and distant locations as well[95]. On the other hand, BCC can metastasize to distant sites of the body, which is considered a terminal condition[96]. Topical treatment of SCC with 5-FU(5-fluorouracil) is widely used and recommended specially in situations where postoperative healing is impaired[97]. There are many reactions for re-occurrence of tumour with typical treatment of 5-FU, such as incomplete duration of treatment, lower drug concentration in plasma, inadequate drug administration, poor penetration through epidermis[98]. In order to improve penetration of 5-FU and to reduce many negative side effects of conventionally used chemotherapy drugs and control the release of the therapeutic agent, 5-FU loaded albumin magnetic nanocomposite spheres were reported to improve penetration and reduce side effects since albumin accumulates in tumor sites due to their altered physiology and metabolism. Administering polybutyl cyanoacrylate nanoparticles containing 5-FU once a day for 35 to 40 days for local remedy of patients with basal cell carcinoma showed absolute resolution illustrating that current practice is favoured by patients who are not surgical candidates[99]. PDT (Photodynamic therapy), a nonsurgical treatment by application of a photo sensitizer (PS) in the presence of oxygen, can produce cytotoxic reactive oxygen species that oxidize subcellular organelles and biomolecules, ultimately leading to the destruction of diseased cells and tissues[100,101]. Aminolevulinic acid, a PS agent using, blue light photodynamic therapy, is officially accepted for therapy, of actinic keratoses in Brazil, Argentina, Chile, USA, Korea, Mexico and Columbia. Methyl aminolevulinate, another PS agent, is licensed in Europe for PDT of AKs (actinic keratoses), Bowen's disease, and BCC[102]. Liposomes[103], chitosan[104] based nanoparticles and complexation with folic acid modified chitosan[105] was formulated for better penetration of ALA through epidermis. PLGA i.e. Poly (lactic-co-glycolic acid) based formulations[106] have shown encouraging results in the treatment of skin SCC A431 cells[107]. For the prevention of skin carcinoma induced by UV radiation and BaP (benzo(a)pyrene) treatment in mice, Das *et al.* loaded Ap(apigenin), a dietary flavonoid having an anticancer property, with poly(lactic-co-glycolide) nanoparticles (NAp)[108-109]. Antitumour activity by exposure to UV light has been reported in *in vivo* study in mice[110]. However, the nanoformulation of apigenin exhibited better effects than free apigenin and reduced tissue damage. Cytotoxic chemotherapy has not been approved for the treatment of advanced BCC. However, with variable successes, cisplatinum-based chemotherapy regimens have been used since 3 years[111]. Recent advancements in understanding the pathogenesis of BCC lead to the development of targeting of drugs to the biological systems driving this carcinoma. Indeed, BCCs are critically dependent on a single signaling pathway, the sonic Shh (hedgehog) pathway, and the majority of BCC bearing mutations in genes in this developmental pathway[112], Sinces it has been illustrated that BCC tumor growth can be inhibited by blocking Shh-signaling[113]. Current literature reveals that nanoparticulate formulation of

inhibitor of transcription factor (Gli 1, Nano HH1) has shown excellent tumour growth inhibition and antimetabolic effects[114]. Currently decarbazine (DTIC) is approved by FDA for first line treatment of melanoma[115]. As the median survival time of metastasized melanoma patients is around 6-10 months[116-118], it has lead to the development of many particulate drug delivery systems such as liposomes[119], dendrimers, polymersomes, carbon based nanoparticles and protein based nanoparticles[120,121]. Gold nanoparticle of doxorubicin has shown improved chemotherapeutic effect beneficial against the melanoma cell lines[122].

Lo Prete *et al*. prepared a nanoemulsion enriched with cholesterol to deliver etoposide to mice for the treatment of melanoma[123]. They reported five times enhancement of maximum tolerated dose, significant decrease in adverse effects, and significant inhibition of growth of tumor by increasing the concentration of etoposide four times higher than the free etoposide at the tumor site. Nanoparticles loaded with doxorubicin conjugated with antibody against CD44, have shown significant drug targeting malignant cells[124]. The size of the tumor is reduced to 60 % as compared to not treating tumor by the nanoparticles. For the treatment of metastatic melanoma, solvent-based taxanes were found to be active but demonstrated a high toxicity and limited efficacy due to poor solubility in water, resulting less loading as well as adverse effects to the solvents used in each formulation. Using (Nab-PTX) i.e. nanoparticles albumin bound paclitaxel, Phase II clinical trials as reported by Herch *et al* and Kottochade *et al* showed that albumin based paclitaxel nanoparticles were well tolerated in patients with metastatic melanoma. The response rate was 25.6 % in the chemotherapy-naive cohort and was 8.8 % in the previously treated cohort[125]. The inclusion of bevacizumab to nab-paclitaxel and carboplatin (regimen ABC) showed encouraging results in terms of both median progression-free survival and overall survival along with side effects vis-à-vis neutropenia, thrombocytopenia, neurosensory problems, fatigue, nausea and vomiting. In another clinical test[126], VEGF (vascular endothelial growth factor) antibody increased the effect of nab-PTX[127]. Ott *et al*. found that the combination of a B cell lymphoma protein (Bcl)-2 antisense oligonucleotide, temozolomide, and nab-PTX produced a response of 40.6 %[128]. Comparable side effects were also reported in Kottschade *et al*.'s study. Generally, higher cytotoxicity is observed with nanoparticles compared to free drug. Higher cytotoxicity was observed nearly 3.6 fold with phosphatidyl ethanolamine liposomal cisplatin compared to classical liposomes and free drug[129]. Combination of vascular-disruptive drug (combretastatin phosphate, CA4P) and a liposomal formulation of doxorubicin) greatly inhibited melanoma proliferation and growth compared to monotherapy alone[130]. Glucocorticoids loaded liposomes were highly effective in suppressing tumor angiogenesis as well as inflammation simultaneously[131]. Prednisolone phosphate loaded liposome was found to strongly inhibit endothelial cell proliferation and reduce proangiogenic protein (such as bFGF) levels, which were related to tumor angiogenesis[132]. Polyinosinic-polycytidylic acid loaded cationic liposome exceptionally enhanced tyrosinase related protein (TRP-2-specific) IFN-releasing cells which boosts the antitumor immune response. It opened another door for immunotherapy for melanoma by peritumoral injection[133]. Fast build up as well as being contained within the tumor makes functionalized quantum dot-liposome hybrid a suitable approach[134,135]. *In vivo* study of liposomal siRNA showed decreased melanoma growth and metastasis[136]. Certain inhibitors of the MAPK pathway have been delivered by the most acceptable technology i.e. nanotechnology[137]. Basu *et al* prepared nanoparticles entrapped with MEK1 inhibitor PD98059 and reported improved antitumour activity to cisplatinum. The above result has given a particular direction for research in tumor cell targeting. This led to the combination of BRAF inhibitors, MEK inhibitors with drug delivery systems to target brain metastasis. RNA interference based approach opens up the possibility of tumor- selective delivery of small RNA or DNA molecules targeting anticancer drugs to transcribed gene. A chitosan nanoparticle of VEGF siRNA demonstrated improved healing effect. A plasmid-based STAT3 siRNA delivered by functional graphene oxide which exhibited markedly minimized growth of xenografted tumor[138,139]. In fact, STAT3 is regarded as one of the most important mediators in melanoma promoting brain metastasis[140]. The increase efficacy of TNF-alpha (Tumor necrosis factor) was found by Inhibiting phosphorylated STAT3 for melanoma[141]. A nanoparticle can also carry siRNA against the oncogene c-Myc to target melanoma cells B16F10 and exhibited effectiveness against melanoma[142]. Increased anticancer effect was observed with nanoparticle formulation containing both siRNAs against BRAF and Akt3[143]. Recent research revealed that inclusion complexation of 4-hydroxynonenal with ß- cyclodextrin enhanced antitumor activity[144]. Nanotechnology has been found to increase the therapeutic effect of Bcl-2 inhibition. In genetically modified i.e. mice without thymus, an antisense oligonucleotide against Bcl-2 i.e. oblimersen reduced the growth of xenografted melanoma[145]. In phase III clinical trial in patients it was observed that the effectiveness of combination of oblimersen with DTIC

was twofold as compared to DTIC alone[146]. Bcl-2 siRNA as well as Myc and VEGF loaded nanoparticle could be developed for the treatment of melanoma[147]. It leads to Bcl-2 reduction in mRNA as well as levels of protein which enhanced the *in vitro* as well as *in vivo* anticancer activity. In phase I clinical trial, oblimersen in combination with temozolamide and nab-PTX found to be more effective in patients with advanced stage melanoma[148]. Nanoformulations with immunotherapeutic agents have been found to reduce adverse effects[148,149].

Yao *et al*. developed nanoparticles with polyethylenimine linked to β – cyclodextrin and conjugated with folate, and again mixed with IL-2 plasmid. This combination reduced tumor growth as well as extended the survival of the mice with melanoma[150]. Using poly (polycaprolactone), a biodegradable polymer, a nanoporous miniature device was developed for local delivery of cytokine IFN-alpha and exhibited constant slow release of IFN-alpha[151].

## CONCLUSION

Nanocarriers have emerged as the most promising and versatile capable system as they offer multidimensional benefits, like less irritation of skin and enhanced stability of entrapped drug. The key benefit of nanocarriers as drug delivery systems is increased penetration of anticancer drug through skin. The use of nano based drug delivery systems such as liposomes, polymeric nanoparticles and dendrimers have shown tremendous potential in enhancing drug permeation through skin, antitumor activity and site specificity.

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