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Recent Nanoparticulate Approaches of Drug Delivery for Skin Cancer

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ABSTRACT

Very few drug delivery systems are potent enough to fight against cancer yet gentle enough on the body. The Nanoparticles have been successfully utilized to create a new drug delivery system for treatment of cancer. Study and application of nanoparticles is advancing rapidly within the pharmaceutical field. These nano-sized materials, e.g., “nanoparticles”, take on novel properties and functions that differ markedly from that delivery system presently available in market. The nano-size and surface improved solubility and multi-functionality of nanoparticles. This improves the quality and the biomedical applications of the nanoparticles. The skin provides a physical barrier to the harmful effects of the external environment in the body. The skin cancer appears in the upper layer of the skin. In recent years there has been an exciting increase in the prevalence of skin cancer worldwide. Non-melanoma skin cancer is the most common diagnosed cancer in the UK accounting for a quarter of all new cancer cases. It is a slow growing form of cancer and can be present many years before detection. Several obstacles frequently still encountered with the skin cancer. In general, the best way to eliminate a problem is to eliminate the cause. This article has reviewed nanoparticulate delivery system with a view as to its impact on skin cancer.

Key words: Nanoparticles, skin cancer, multi functionality, non-melanoma

INTRODUCTION

Cancer is the most challenging diseases to treat and the second leading cause of death in the society. The “war on cancer” is now in its fourth decade since the national cancer act was passed in 1971 in USA. Although, much progress has been made in cataloging the environmental causes and cellular and molecular biological basis for this dreaded disease, we still do not have a precise understanding of the differences between a cancer cell and its normal counterpart (Kawasaki and Player, 2005). Cancer harms the body when damaged cells divide uncontrollably (Raihan *et al.*, 2012) to form lumps or masses of tissue called tumors (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). There are various types of cancer. The lists of common cancer types includes cancers that are diagnosed with the greatest frequency according to American cancer society are listed in the Table 1.

According to WHO Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) in the world. Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030. Cancer incidence and mortality statistics reported by the American Cancer Society and other resources were used to create the mortality ratio in different types of cancer (Table 2).

Table 1: List of various types of cancers

Bladder cancer	Lung cancer
Breast cancer	Skin cancer (melanoma)
Colon and rectal cancer	Non-Hodgkin lymphoma
Endometrial cancer	Pancreatic cancer
Kidney (renal cancer)	Prostate cancer
Leukemia	Thyroid cancer

Table 2: Mortality ratio of different types of cancer

Cancer type	Estimated new patients	Deaths
Bladder	73510	14880
Breast (female-male)	226870-2190	39510-410
Colon and rectal (combined)	143460	51690
Endometrial	47130	8010
Kidney (renal cell) cancer	59588	12484
Leukemia (all types)	47150	23540
Lung	226160	160340
Melanoma	76250	9180
Non-Hodgkin lymphoma	70130	18940
Pancreatic	43920	37390
Prostate	241740	28170
Thyroid	56460	1780

SKIN AND SKIN CANCER

The top layer of skin is the epidermis. The epidermis is very thin, averaging only 0.2 mm thick (about 1/100 of an inch). It protects the deeper layers of skin and the organs of the body from the environment. The middle layer of the skin is called the dermis. The dermis is much thicker than the epidermis. The deepest layer of the skin is called the subcutis. Drugs are applied topically to topical route can also be used for systemic drug delivery, percutaneous or transdermal absorption of drug is generally poor and erratic the skin mainly for their local action (Gidwani *et al.*, 2010). Although, the Melanocytes cells can become melanoma, that are present in the epidermis layer. These skin cells make the brown pigment called melanin, which gives the skin its tan or brown color. Melanin protects the deeper layers of the skin from some of the harmful effects of the sun. A mole (nevus) is a benign skin tumor that develops from melanocytes. It is a fact that all the moles are not harmful, but having some types may raise your risk of melanoma (ACS, 2011).

Skin cancers that are not melanoma are called as non-melanoma skin cancers because they develop from skin cells other than melanocytes. They tend to behave very differently from melanomas and are often treated in different ways. Non-melanoma skin cancers include basal cell and squamous cell cancers.

Basal Cell Carcinoma (BCC) is the most common malignancy in the United States and comprises 75% of NMSC (Fig. 1) Squamous Cell Carcinoma (SCC) is the second most common skin cancer, accounting for 20% of cases of Non Melanoma Skin Cancer (NMSC).

Non-melanoma skin cancers are the common human cancers, most non-melanoma skin cancer develops on sun-exposed areas of the body, like face, neck, head, palm, lips etc. (Diepgen and Mahler, 2002) (Table 3). Although, UV radiation is the most important risk factor for pathogenesis of basal-cell and squamous cell carcinoma, the effect on risk of squamous-cell carcinoma is greatest (Kricker *et al.*, 1995). The melanoma skin cancer is partially driven by interleukin-6 acting as a growth factor (Kast and Altschuler, 2006).

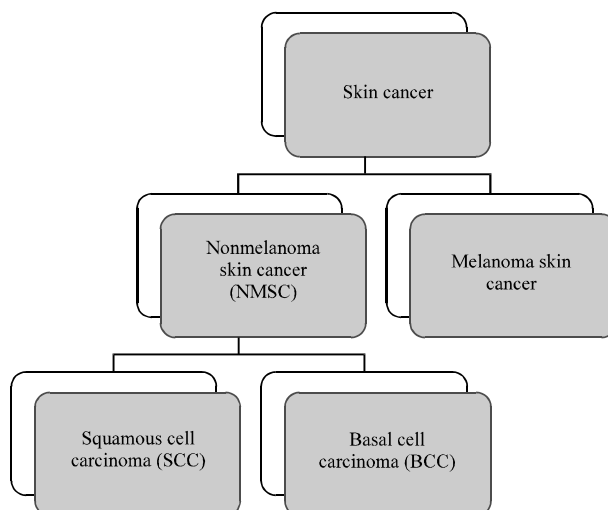


Fig. 1: Types of skin cancer

Table 3: Cause and symptom of different types of skin cancer

Type	Cause	Symptom
Basal cell carcinoma	Due to high cumulative sun exposure	Tiny blood vessels on the surface and sometime ulceration. Head, neck or shoulders are affected
Squamous cell carcinoma	Previous skin disorders, severe skin damage such as wounds, cut and exposure burns etc.	Red, scaling, thickened patch on skin. Some are firm hard nodules and dome shaped like keratoacanthomas
Malignant melanoma	Ultraviolet radiation A and B	An asymmetrical area, with an irregular border, and has color variation often greater than 6 mm diameter

Melanocytes are the main cause of the melanoma type of skin cancer. Melanocytes are the producer of the cell colour. It can be curable in early detection. It is the only serious type of skin cancer which causes death. Because of its localized nature skin cancer can possibly be best treated by local drug therapy to the skin. Conventionally it can also be treated by surgery but sometimes it can be less effective and more hazardous for the patient.

SKIN CANCER MANAGEMENT

The treatment of the skin cancer is dependent on type of skin cancer, location of the cancer, age of the patient and whether the cancer is primary or a recurrence. The treatment is also determined by the specific type of cancer. There are various chemical constituent in the market used for treatment of skin cancer (Table 4).

Surgery is the common treatment for skin cancer. But sometime surgery is not possible and there very much risk factor and limitation for the surgery (Table 5). When new skin cancers keep appearing, medicines are considered for the treatment.

NOVEL ADVANCEMENT IN THE SKIN CANCER TREATMENT

Despite the recent advancement in the therapeutic, significant challenges still present in the field of skin cancer. Commonly used chemotherapy have give unsatisfactory results, as the therapy is deleterious to patient health by making patients more susceptible to other diseases and often

Table 4: According to National Cancer Institute some FDA approved drugs for treatment of topical cancer

Type of cancer	Chemical constituent	Marketed product
Basal cell carcinoma	Fluorouracil	Efudex
	Erivedge	Vismodegib
	Imiquimod	Aldara
Melanoma	Fluorouracil	Adrucil
	Aldesleukin	Proleukin
	Dacarbazine	DTIC-dome
	Vemurafenib	Zelboraf
	Ipilimumab	Yervoy

Table 5: Strategy of treatment of skin cancer and their limitations

Type of skin cancer	Strategy	Limitations
Basal cell carcinoma	Skin grafting, surgery	Make skin more "reactive." A rash, scratch, pimple, or inflammation etc. may trigger the area, resulting in formation of new cancer on the skin
Squamous cell carcinoma	Radiotherapy, chemotherapy, Mohs surgery	Kill healthy cells and causes toxicity to the patient body, pathologist not familiar with surgery
Malignant melanoma	Chemotherapy, surgery	Dose dumping, killing of normal cell, weakening the immune system of the patient body

cause death by weakening the immune system of the patient body. The simple, soluble, biocompatible environmental friendly drug carrier systems are recently used for drug delivery (Harisa *et al.*, 2011).

Nanotechnology is en vogue. It is a relatively new but fast revolutionized field. Its potential impact on drug delivery at the field of cellular level is very high. It seems to provide means for achieving otherwise unreachable goals. This includes improving human diagnostics or therapeutics and cure (Staples *et al.*, 2006; Cevc and Vierl, 2010). Nanotechnology had an enormous impact on medical technology, significantly improving the performance of drug in terms of efficacy, safety and patient compliance (Kumari *et al.*, 2012). It can affect many of its composing disciplines in amazingly innovative and unpredictable ways. The emergence of nanotechnology is likely to have a significant impact on the drug-delivery sector and Nanoparticles (NPs) are at the leading edge, with many potential applications in clinical medicine and research (Kayser *et al.*, 2006). Depending on the effects of administration route, particle size and particle properties on biodistribution, a variety of nanoparticulate designs have been proposed for cancer therapy and diagnosis. Active intracellular delivery and improved pharmacokinetics and pharmacodynamics of drug nanoparticles depend on various factors, including their size and surface properties. Nanoparticle therapeutics is an emerging treatment modality in cancer therapy. Nanoparticles have been used to deliver drugs to target sites for cancer therapeutics (Gref *et al.*, 1994) or deliver imaging agents for cancer diagnostics (Lemarchand *et al.*, 2004). These vehicles can be engineered to recognize biophysical characteristics that are unique to the target cells and therefore minimize drug loss and toxicity associated with delivery to non-desired tissues. Lipid nanocarriers are adsorbed to the skin surface, allowing lipid exchange between the outermost layers of the stratum corneum. Several skin diseases (e.g., Leishmaniasis, actinic keratosis, non-melanoma skin cancers) have been the focus of lipid nanoparticles skin targeting. There is a need of delivery vehicles that allow localized and controlled delivery of drugs for preventing skin problem by intracellular pathogens as well as have in built natural healing property of topical cancer (Singh *et al.*, 2010).

ADVANTAGE OF NANOPARTICLES

The main advantages of nanoparticles are:

- Improved bioavailability by enhancing aqueous solubility
- Increasing resistance time in the body (increasing half life for clearance/increasing specificity for its cognate receptors)
- Targeting drug to specific location in the body (its site of action). This results in concomitant reduction in quantity of the drug required and dosage toxicity, enabling the safe delivery of toxic therapeutic drugs and protection of non target tissues and cells from severe side effects (Irving, 2007)

IMPLEMENTATION OF NANO PARTICLE IN SKIN CANCER

Colloidal carrier system has improved the characterization of diagnosis and treatment in recent years (Saraf *et al.*, 2011a). The identification of the best route of administration, the success of the pharmacotherapy is strictly related to the choice of an appropriate delivery system. The administration of drug-loaded vesicles may represent an interesting approach for both the targeting of drugs to skin and the improvement of the passage of drugs through the mucus barrier and hence of their intracellular uptake.

The effectiveness of a cancer therapeutic agent is measured by its ability to reduce and eliminate tumors without damaging healthy tissue. Therefore, a distinct capacity to target tumors is essential in the success of the therapeutic agent. The increased site specificity and internalization are the main goal for the cancer treatment and to reduce the side effect. The ultimate goal of skin cancer therapeutics is to increase the survival time and the quality of life of the patient. Nanoparticle systems offer major improvements in therapeutics through site specificity, their ability to escape from multi-drug resistance and the efficient delivery of an agent (Brannon-Peppas and Blanchette, 2004).

Nanoparticles have been used in several applications such as imaging, targeting tumors, drug delivery and in combination with other physical agents for tumor ablation, such as brachytherapy (Jain, 2008). Targeting the specific site of action for the localized action to treat skin cancer is particularly a important factor. This can be achieved by the nanoparticulate delivery only. Nanoparticles have the potential to provide benefits to the skin that no other products can currently provide. Nanotechnology has helped create sunscreens with nanoparticles of titanium and zinc that provide effective barriers to UVA and UVB light which can protect the skin cancer. New Sunscreens have been analyzed to show that they are coated to reduce reactivity, clump in aggregates, or do not enter the skin. Sunscreens containing nanoparticle also help prevent skin cancer such as melanoma and photo damage.

The drug targeting to specific skin strata may improve the use of agents which are prone to cause local unwanted effects. Recent investigations have indicated that improved uptake and skin targeting may become feasible by means of nanoparticulate systems such as Solid Lipid Nanoparticles (SLN), Nanostructured Lipid Carriers (NLC) and Nanoemulsions (NE) (Borgia *et al.*, 2005). Encouraged by rapid and promising progress in cancer nanotechnology, researchers continue to develop novel and efficacious nanoparticle for drug delivery (Semwal *et al.*, 2010).

Application of nanoparticles for skin cancer drug delivery: In general, the best way to eliminate a problem is to eliminate the cause. In cancer, the problem can be perceived differently at various stages of the disease. Most apparently, if genetic mutations are the underlying cause, then we must counteract the causes of the mutations. over the past severs years increasing

attention has focused on designing new drug dosage form in order to increase the effectiveness and decrease the side effect of the drug by drug carrier (Jun *et al.*, 2006).

Nanoparticles have been successfully utilized to create a new drug delivery system for treatment of cancer. The toxicity of currently available anticancer drugs and the inefficiency of chemotherapeutic treatments, especially for advanced stages of the disease need a carrier which is actively target the skin cancer cells. Another approach is the direct intratumor delivery of anticancer agents using NPs, which can be used in the treatment of local cancers like skin cancers. Recently, it is demonstrated that Transferrin (Tf) conjugated paclitaxel (Tx)-loaded biodegradable NPs are more effective in demonstrating the antiproliferative effect of the drug than its solution or with un conjugated Tx-loaded NPs.

Applications of nanotechnology to skin cancer have seen much effort in the design of new imaging and therapeutic approaches. The main focus has been on diagnosing and treating metastatic melanoma, which is the deadliest of skin cancers (Lev *et al.*, 2004). Most chemotherapeutics are administered systemically and are cytotoxic to healthy cells; therefore, cancer patients must endure considerable morbidity. Nanomedicine seeks to engineer nanoparticles to image (Schmieder *et al.*, 2005; Boles *et al.*, 2010) and selectively deliver the therapeutic agents or small-interfering RNA (Chen *et al.*, 2010; Davis *et al.*, 2010) specifically to melanoma cells. Many potential drugs fail clinically because of insolubility. Nanoparticles may overcome the insolubility problem as many more types and higher concentrations of drugs can be loaded into nanoparticles (Dhar *et al.*, 2011).

Size of nano particles: Particle size and size distribution are the most important parameters of nanoparticles. They determine the *in vivo* distribution, biological fate, toxicity and targeting ability of such delivery systems. Nanoparticles influence drug loading, drug release and stability of the therapeutic agents because of their unique small size. Many studies have demonstrated that nanoparticles have a number of advantages over microparticles (Panyam *et al.*, 2003). The broader concept is that because of their small size nanoparticles have unique qualities that are not found in the same material at larger size (Singh *et al.*, 2011a). Nanoparticles have relatively high cell uptake when compared to microparticles and are available to a wider range of cellular and intracellular targets due to their small size and mobility. In a similar study, nanoparticles were shown to penetrate throughout the submucosal layers of a rat intestinal loop model, while microparticles were predominantly localized in the epithelial lining (Redhead *et al.*, 2001). This indicates that particle distribution can, in part at least, be tuned by controlling particle size.

Drug release is also affected by particle size. Smaller particles have a larger surface area-to volume ratio; therefore, most of the drug associated with small particles would be at or near the particle surface, leading to faster drug release (Singh and Lillard, 2009).

Drug loading: A successful nano-delivery system should have a high drug-loading capacity, thereby reducing the quantity of matrix materials for administration. There is two method for drug loading into a carrier. (1) the incorporation method (2) the adsorption/absorption methods. Drug loading and entrapment efficiency depend on drug solubility in the excipient matrix material (solid polymer or liquid dispersion agent), which is related to the matrix composition, molecular weight, drug-polymer interactions and the presence of end functional groups (i.e., ester or carboxyl) in either the drug or matrix (Govender *et al.*, 2000; Panyam and Labhasetwar, 2003). Drug

encapsulation is also increased by different mechanism (Singh *et al.*, 2011b). Polymeric nanoparticulate system have been developed to improve the drug loading and the physicochemical stability of other carrier (Saraf *et al.*, 2011b).

Drug release: Drug release and polymer biodegradation are two most important parameters for developing nanoparticulate delivery system. In general, the drug release rate depends on: (1) drug solubility (2) desorption of the surface-bound or adsorbed drug (3) drug diffusion through the nanoparticle matrix (4) nanoparticle matrix erosion or degradation and (5) the combination of erosion and diffusion processes. Hence, solubility, diffusion and biodegradation of the particle matrix govern the release process.

One of new findings for nanoscale drug delivery in diagnosing and treating cancer is nanoshells-gold-coated silica. These nanoshells, set in a drug-containing tumor-targeted hydrogel polymer, injected into the body (Freitas, 2005), accumulate near tumor cells. When heated with an infrared light, the nanoshells selectively absorb a specific infrared frequency, melting the polymer and releasing the drug payload at a specific site. They are designed for specific targeting micrometastases, tiny aggregates of cancer cells too small to remove with a scalpel.

Membrane coating acts as a drug release barrier; therefore, drug solubility and diffusion in or across the polymer membrane becomes a determining factor in drug release. Furthermore, the release rate also can be affected by ionic interactions between the drug and auxiliary ingredients.

Different nanoparticulate carrier for skin cancer treatment: Clearly, the most current cancer nanotechnology-based treatment methods involve the use of some type of nanoparticle. Therefore, a brief description of bio-medical nanoparticles is in order. A general nanoparticle consists of a core that can have a constitution ranging from very simple to highly complex, depending on the intended application. The core can contain one or several payload drugs, as well as permeation and visibility enhancers. The surface may be bare or conjugated to targeting ligands. The nanoparticle with the size range of 100 nm has the ability to internalize the cell surface. Nanostructures have the potency to enter the cells due to their nanoscale size. Some of the leading nanostructures being used for this purpose include fullerenes, dendrimers and nanoshells (Liang *et al.*, 2010). In comparison with conventional antitumor chemicals such as cisplatin and cyclophosphamide, these nanoparticle are highly efficient at suppressing tumor growth.

One approach to improve drug efficacy is to utilize nanotechnology (10⁻⁹ m in size) to improve pharmacokinetics and reduce side effects associated with drugs (Wang *et al.*, 2007). Nanotechnologies are being explored for both drug delivery and imaging of cancer in patients (Table 6) (Cuenca *et al.*, 2006; Gullick, 1991; Kaushik *et al.*, 2001; Kawamori *et al.*, 2006). For melanoma research and treatment, nanotechnology is a relatively new and rapidly developing field with a timeline of key discoveries.

Nanoparticles are used as a base for the construction of multifunctional nanoscale carriers (Table 7). These carriers can combine with diagnostic, imaging, targeting and therapeutic agents in the same package. Thus far, several kinds of nanoparticles have been engineered and used in Skin cancer applications; these nanoparticle agents range from liposomes (De Leeuw *et al.*, 2009), oil-based dispersions (Konan *et al.*, 2002), polymeric particles (Gomes *et al.*, 2007) and hydrophilic polymer-photosensitizer conjugates (Jang *et al.*, 2005) to gold nanoparticles (Cheng *et al.*, 2008). Recently, silica-based nanoparticles have been widely developed as an efficient means for drug and gene delivery owing to their unique advantages such as small and uniform pore size, large surface area and pore volume, as well as nontoxicity and biocompatibility. The size of nanoparticles is

Table 6: Nano particulate carriers for drug delivery and imaging

Nanotechnology	Current uses	References
Liposomes	siRNA/DNA/asODN/drug delivery	Gokhale <i>et al.</i> (2002), Gray <i>et al.</i> (2008) and Merritt <i>et al.</i> (2008)
Nanoshells	Thermal ablation/imaging	Hirsch <i>et al.</i> (2003)
Carbon nanotubes	DNA/siRNA delivery/thermal ablation	Bianco <i>et al.</i> (2003) and Pantarotto <i>et al.</i> (2004)
Dendrimers	Drug delivery/imaging	Heiden <i>et al.</i> (2007)
Superparamagnetic nanoparticles	Magnetic targeting/thermal ablation/MRI contrast agent	Laurent <i>et al.</i> (2011)

Table 7: Some nanoparticulate carrier with anticancer drugs

Name of anti cancer agent	Nanoparticulate carrier	Inference	Reference
Doxorubicin	Nanospheres	Afforded a greater reduction in the number of metastases, improving its efficacy and safety, anti-inflammatory action	Minotti <i>et al.</i> (2004), Chiannilkulchai <i>et al.</i> (1989) and Steiniger <i>et al.</i> (2004)
	Solid lipid nanoparticle	Prolonged drug plasma level, low uptake of anti cancer agent to other tissue, reduced cytotoxicity	Brigger <i>et al.</i> (2004) and Muller <i>et al.</i> (2000)
Methotrexate	Dendritic polymer conjugate	Increased its antitumor activity and markedly decreased its toxicity, allowing therapeutic responses not possible with the free drug	Kukowska-Latallo <i>et al.</i> (2005)
Cisplatin	Nanoparticles	Increased the circulating half life, reduced the cytotoxicity	Barroug <i>et al.</i> (2004)
Paclitaxel	Micelles	Highly increased systemic drug exposure and a simultaneously decreased clearance, leading to alteration in the pharmacodynamic characteristics of the solubilized drug, significantly diminished drug uptake and reduced circulating concentrations	Singla <i>et al.</i> (2002)
	Nanosphere	Promote full paclitaxel efficacy, significant tumor regression and higher survival rates	Sharma <i>et al.</i> (1996)
Mitoxantrone	Nanoparticle	Reduce the volume of the tumor in melanoma	Beck <i>et al.</i> (1993)
	Liposome	Prolonged survival time	

crucial for successful delivery into melanoma tumors. Vesicles <100 nm have reduced uptake into liver tissue, while vesicles >100 nm are prone to rapid clearance rates by the mononuclear phagocytic system (De Jong and Born, 2008).

The nano-range dimensions imbue nanoparticles with advantageous unique physical properties that facilitate immense possibilities in cancer therapeutics. Several new nanotechnologies, mostly based on nanoparticles, can facilitate delivering anticancer and imaging agents to kill cancerous cells in cancer therapy and cancer diagnosis. Some nanoparticulate carrier systems used in the skin cancer treatment are discussed as under:

Solid lipid nano particles: Solid Lipid Nanoparticles (SLN) are colloidal drug carrier systems (Mehnert and Mader, 2001; Muller and Keck, 2004) that are generally containing solid lipid, emulsifier and water. SLN are composed of physiologically tolerable and biocompatible lipids

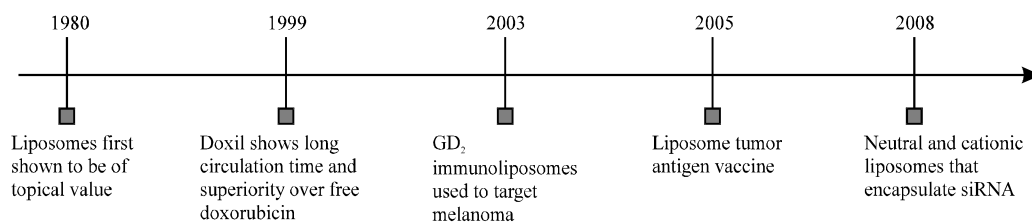


Fig. 2: Milestones for liposomal applications in melanoma (Tran *et al.*, 2009)

material that are non toxic in nature and the advantages like controlled drug release and avoiding drug leakage, low toxicity, good biocompatibility and higher bioavailability (Abbasalipourkabir *et al.*, 2012). SLN show adhesiveness, occlusion and skin hydration effects when applied topically on skin. SLN show adhesiveness by forming a monolayer on the skin when the particle size is less than 200 nm.

SLN constitute an attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. SLN's may be used for drug targeting, when reaching the intended diseased site in the body the drug carried needs to be released. So, for drug delivery biodegradable nanoparticle formulations are needed as it is the intention to transport and release the drug in order to be effective (Mathur *et al.*, 2010). Solid lipid nanoparticles, although, in its nascent stage, has a great potential to cure the cancer, with least side effects. The poorly water soluble drugs are also complexes with cyclodextrin and incorporated in SLN for targeting to the cancer cell (Vyas *et al.*, 2008).

Liposome: The concept of using a liposome as a selective drug delivery carrier for the skin was first introduced in 1980 (Mezei and Gulasekharam, 1980). Technologies currently being developed or explored for skin cancer. Liposomes have been demonstrated to be useful for delivering pharmaceutical agents. These systems use 'contact-facilitated drug delivery', which involves binding or interaction with the targeted cell membrane.

Liposomes is a good vehicles for delivery of therapeutic agents into skin because of it's associated hydrophobic lipid construction. The fatty layer on liposome confines and protects the enclosed drug until the liposome is delivered and adheres to the outer membrane of target cancer cells. By this process drug toxicity to healthy cells is decreased and its efficacy may be increased. Liposome therapy is a well-developed technology for delivery of chemotherapy drugs (Silva *et al.*, 2001; Torchilin and Weissig, 2003; Duncan *et al.*, 2005). Liposome can provide enhanced efficacy and reduced toxicity for anticancer agent. It provides stable formulation, improved pharmacokinetics and also degree of passive or physiological targeting to tumor tissue (Shaheen *et al.*, 2006).

In order for agents targeting tumor cells to be effective, the drug must accumulate in tumors and be taken up into tumor cells. An ideal drug formulation for melanoma would preferentially accumulate in tumors or if taken up by normal cells, have little or no effect on cellular function. Liposomes can be used to accomplish this objective through several approaches. For melanoma research and treatment, nanotechnology is a relatively new and rapidly developing field with a timeline of key discoveries shown in Fig. 2.

The combination therapy is very effective for melanoma treatment. One way to potentially improve drug combinations is to design a liposome containing multiple agents. This approach could be used to take advantage of liposomes to select agents that are incorporated into different locations

in liposomes such as in the inner core and the lipid bilayer itself. By combining multiple agents in one liposome formulation, cocktails of drugs could be delivered simultaneously leading to increased patient compliance.

Dendrimers: Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches (Sampathkumar and Yarema, 2007). Dendrimer-based drug delivery systems focused on encapsulating drugs. Drug encapsulation is higher in dendrimeric nanoparticle. Recent developments in polymer and dendrimer chemistry have provided a new class of molecules called dendronized polymers, which are linear polymers that bear dendrons at each repeat unit. Their behavior differs from that of linear polymers and provides drug delivery advantages because of their enhanced circulation time. Another approach is to synthesize or conjugate the drug to the dendrimers so that incorporating a degradable link can be further used to control the release of the drug (Singh *et al.*, 2011b; Singh and Lillard, 2009). Dendrimers can achieve passive enhanced permeation and retention-mediated targeting to a tumor simply by control of their size and physicochemical properties. Passive targeting, which localizes the nano-particle in the close vicinity of a cancer cell, can be immediately useful for diagnostic purposes or for the delivery of radioisotopes capable of killing any cell within a defined radius. In general, however, most delivery strategies require that the anticancer agent directly attached to, or be taken up by, the target cell (Sampathkumar and Yarema, 2007). Dendrimers can also be being applied to a variety of cancer therapies to improve their safety and efficacy.

Nanostructured lipid carriers (NLC): A new generation of nanostructured Lipid Carriers (NLCs) consisting of a lipid matrix of both liquid lipid and solid lipid with a special nanostructure has been developed (Singh and Kumar, 2010). This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by various methods like high pressure homogenization, nanoemulsions technique, aqueous dispersion method and the process can be modified to yield lipid particle dispersions with solid contents from 30-80%. Carrier system. NLC nanoparticles would provide a high incorporation capacity (due to the liquid lipid) and control of drug release (due to the encapsulating solid lipid).

Several obstacles frequently encountered with anticancer compounds, such as normal tissue toxicity, poor specificity and stability and a high incidence of drug resistant tumor cells, are at least partially overcome by delivering them using NLC. NLC were found to increase the triptolide penetration into the skin as well as the anti-inflammatory activity. This strategy improved the bioavailability at the site of action, reduces the required dose and the dose-dependent side effects like irritation and stinging at the site of action. TiO_2 , as inorganic UV blocker, could be successfully incorporated in NLC formulations. Enclosing Titanium dioxide (TiO_2) in NLC increased the UV blocking activity of this blocker. This will give a chance to reduce the concentration of the TiO_2 in the finished products while maintaining the desired high UV blocking activity.

Polymersomes: Polymersomes, hollow shell nanoparticles, have unique properties that allow delivery of distinct drugs. Loading, delivery and cytosolic uptake of drug mixtures from degradable polymersomes were shown to exploit the thick membrane of these block copolymer vesicles, their aqueous lumen and pH-triggered release within endolysosomes. Polymersomes break down in the acidic environments for targeted release of these drugs within tumor cell endosomes. While cell membranes and liposomes are created from a double layer of phospholipids, a polymersome is

comprised of two layers of synthetic polymers. The individual polymers are considerably larger than individual phospholipids but have many of the same chemical features. Polymersomes have been used to encapsulate paclitaxel and DOX for passive delivery to tumor-bearing mice (Ahmed *et al.*, 2006).

Magnetic nanoparticles: Magnetic Nanoparticles (MNPs) are the next generation of Magnetic Resonance Imaging (MRI) contrast agents Corot *et al.* (2006) used as carriers for targeted drug delivery. The magnetic nanoparticles are smaller in size; this can be beneficial for aspects of skin targeting such as cell labeling or cell targeting and can be helpful in early diagnosis of skin cancer (Baroli *et al.*, 2007). As therapeutic tools, MNPs have been evaluated extensively for targeted delivery of pharmaceuticals through magnetic drug targeting (Neuberger *et al.*, 2005) and by active targeting through the attachment of high affinity ligands. Recently, described how Superparamagnetic Iron Oxide (SPIO) nanoparticles can be used to detect cancer *in vivo* using a mouse xenograft model. MNPs have been examined extensively as MRI contrast agents to improve the detection, diagnosis and therapeutic management of solid tumors on skin. The magnetic effect of magnetic nanoparticles is due to super paramagnetic iron oxides, typically Fe_2O_3 and Fe_3O_4 , which do not retain their magnetic property when removed from the magnetic field. Their paramagnetic characteristics have made them good candidate the destruction of tumors *in vivo* through hypothermia. Polymer coating on the surface of magnetic nanoparticles prevents their cytotoxicity and allows them to move freely in the organism without any reaction or adhesion magnetic nanoparticles are also noteworthy for *in vivo* diagnostic purposes. Magnetic nanoparticles can be used to target drug delivery, as hyperthermia agents to destroy cancer cells and have potential to move the particles to specific sites in an organism and hold them until treatment is finished. Their sizes are in the range of 50-300 nm. They have applications in magnetic immunoassay and also as Magnetic Resonance Imaging (MRI) contrasts. Magnetic nanoparticles are sensitive to magnetic fields and electromagnetic radiation. This property induces hyperthermia for cancer treatment (Jordan *et al.*, 1999).

Hydrogels: There is a great effort for the preparation of environmental friendly drug carrier system to target the drug and the carrier must be biocompatible. Hydrogels have received significant attention over the past few decades because of their exceptional promise in biomedical application (Singh *et al.*, 2008). Hydrogel-nanoparticles are based on proprietary technology that uses hydrophobic polysaccharides for encapsulation and delivery of drug, therapeutic protein, or vaccine antigen. A novel system using cholesterol pullulan shows great promise. In this regard, four cholesterol molecules gather to form a self-aggregating hydrophobic core with pullulan outside. The resulting cholesterol nanoparticles stabilize entrapped proteins by forming this hybrid complex. These particles stimulate the immune system and are readily taken up by dendritic cells. Alternatively, larger hydrogels can encapsulate and release monoclonal antibodies.

CONCLUSION

Nano particulate drug delivery systems offer a great impact to overcome some of the obstacles to efficiently target a number of diverse cell types. Despite the recent advancement in the therapeutic, significant challenges still present in the field of cell cancer. Commonly used chemotherapy have give unsatisfactory results, as the therapy is deleterious to patient health by

making patients more susceptible to other diseases and often cause death by weakening the immune system of the patient body. Thus, a budding interest in nanotechnology has been generated remarkable number of advancements in recent years with a main focus on current cancer therapy.

Nanoparticulate delivery of anticancer drugs to tumor tissues can be achieved by preparing the nanodrug carrier. Nanotechnology is expected to play an increasingly important role in the diagnostics, prognostics and management of targeted cancer treatments. Nanotechnology is fast expanding area of research anticipated to lead to development of novel, sophisticated applications which recognize skin cancer cells, deliver drugs to target tissue, reporting outcome of therapy, monitor intracellular changes to help prevent precancerous cells from becoming malignant. The future remains exciting and wide open for ongoing efforts by scientists, researchers and medical personnel can sincerely ensure to do big things using the very small. The ideal delivery system would be targeted and precisely controlled. To target nanoparticles to the desired tissues, a number of methods have been developed. These include physical means such as controlling the size, charge and hydrophobicity of the particles. In addition, targeting molecules, such as antibodies and peptides, that recognize specific cell surface proteins and receptors, can be conjugated to the nanoparticle surface to specifically target specific cell types.

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