RECENT APPROACHES OF DRUG DELIVERY FOR SKIN CANCER

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ABSTRACT

The search for new drug delivery approaches and new modes of action represent one of the frontier areas which involves a multidisciplinary scientific approach to provide major advances in improving therapeutic index and bioavailability at site specific delivery. Carrier-mediated drug delivery has emerged as a powerful methodology for the treatment of various types of cancer. The therapeutic index of traditional and novel drugs is enhanced via the increase of specificity due to targeting of drugs to a specific tissue, cell or intracellular compartment, the control over release kinetics, the protection of the active agent or a combination of the above. Cancer is the most challenging disease to treat and the second leading cause of death in the society. This review article is written to provide a coverage commentary of novel drug delivery system for skin cancer. Novel drug delivery systems have been developed to improve. The present review article explores the overall study of different formulation which leads to skin cancer.

Key words: Skin cancer, liposome, noisome, dendrimers, nanoparticles.

INTRODUCTION

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect [1]. Innovations in the area of the drug delivery are taking place at a much faster pace as compared to the last two decades. Improved patient compliance and effectiveness are inextricable aspects of a new drug delivery system [2].
Drug targeting to specific organs and tissues has become one of the critical endeavors of the new century. The search for new drug delivery approaches and new modes of action represent one of the frontier areas which involves a multidisciplinary scientific approach to provide major advances in improving therapeutic index and bioavailability at site specific delivery [3-6]. The hard to target tissues such as blood-brain barrier permeation limitation can now be overcome allowing the use of therapies otherwise excluded by conventional dosage forms [7]. These new system can hinder solubility problems, protect the drug from the external environment such as photodegradation and pH changes, while reducing dose dumping by controlling the release profile [5-6]. Moreover, controlled targeting at the site of action and reduced time of exposure at non-targeting tissues increases the efficacy of treatments and reduce toxicity and side effects [8] thus improving patient compliance and convenience.

Controlled release dosage form cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administrations; however, recently such devices have also been introduced for parenteral administration, ocular insertion and for transdermal application. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance. The advantages of controlled release preparation have been summarized as following:

- Decreased incidence and/or intensity of adverse effects and toxicity.
- Better drug utilization.
- Controlled rate and site of release.
- More uniform blood concentrations.
- Improved patient compliance.
- Reduced dosing frequency.
- More consistent and prolonged therapeutic effect.
- A greater selectivity of pharmacological activity [9].

**Cancer**

Cancer is not a single disease. It is a group of more than 200 different diseases. Cancer can be generally described as an uncontrolled growth and spread of abnormal cells in the body. Cells are basic units of life. The body is made up of trillions of living cells. Normal body cells
grow, divide into new cells, and die in an orderly fashion. During the early years of a person’s life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out of control growth of abnormal cells \[10-11\].

Cancer is the most challenging disease to treat and the second leading cause of death in the society. 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 \[12\]. Cancer harms the body when damaged cell divide uncontrollably \[13\] 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).

Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues is what makes a cell a cancer cell.

Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell does not die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does \[10\].

According to WHO cancer is leading cause of death worldwide, accounting for 7.9 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 1).
Table 1: Mortality ratio in different types of cancer.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Estimated new patients</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>73510</td>
<td>14880</td>
</tr>
<tr>
<td>Breast (female-male)</td>
<td>226870-2190</td>
<td>39510-410</td>
</tr>
<tr>
<td>Colon and rectal (combined)</td>
<td>143460</td>
<td>51690</td>
</tr>
<tr>
<td>Endometrial</td>
<td>47130</td>
<td>8010</td>
</tr>
<tr>
<td>Kidney (renal cell) cancer</td>
<td>59588</td>
<td>12484</td>
</tr>
<tr>
<td>Leukemia (all types)</td>
<td>47150</td>
<td>233540</td>
</tr>
<tr>
<td>Lung</td>
<td>226160</td>
<td>160340</td>
</tr>
<tr>
<td>Melanoma</td>
<td>76250</td>
<td>9180</td>
</tr>
<tr>
<td>Non-Hodgkin</td>
<td>70130</td>
<td>18940</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>43920</td>
<td>37390</td>
</tr>
<tr>
<td>Prostate</td>
<td>241740</td>
<td>28170</td>
</tr>
<tr>
<td>Thyroid</td>
<td>56460</td>
<td>1780</td>
</tr>
</tbody>
</table>

Skin cancer

Skin cancers are named after the type of skin cell from which they arise. Basal cell cancer originates from the lowest layer of the epidermis, and is the most common but least dangerous skin cancer. Squamous cell cancer originates from the middle layer, and is less common but more likely to spread and, if untreated, become fatal. Melanoma, which originates in the pigment producing cells (melanocytes), is the least common, but most aggressive, most likely to spread and, if untreated, become fatal[14]. Skin cancers that are not melanoma are called as non-melanoma skin cancer 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 State and comprises 75% of NMSC. Squamous cell carcinoma (SCC) is the second most common skin cancer, accounting for 20% of cases of Non Melanoma Skin Cancers (NMSCs).

NMSCs 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.[15]. 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[16] (Table 2). The melanoma skin cancer is partially driven by interleukin-6 acting as a growth factor[17].
Table 2: Cause and symptom of different types of skin cancer.

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

**Novel approaches for skin cancer treatment**

Novel drug delivery systems can include those based on physical mechanisms and those based on biochemical mechanisms. Physical mechanisms also referred as controlled drug delivery systems include osmosis, diffusion, erosion, dissolution and electro transport. Biochemical mechanisms include monoclonal antibodies, gene therapy, and vector systems, polymer drug adducts and liposomes. Therapeutic benefit of some new drug delivery systems include optimization of duration of action of drug, decreasing dosage frequency, controlling the site of release and maintaining constant drug levels [18-20]. Among drug carriers one can name soluble polymers, micro particles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles (figure 1). The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest [21].

![Figure 1: Various Types of Pharmaceutical Carriers.](image)
The purpose of using these carriers is to obtain a controlled release thus maintaining therapeutic drug levels over a specified time period while reducing systemic absorption \[^{22}\]. Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties \[^{23-24}\].

**Liposomes**

Liposomes are one of the most studied nanocarriers for the treatment of cancer. They are colloidal particles and are biocompatible and biodegradable, consisting primarily of phospholipid vesicles. These vesicles are in turn composed of one or several lipid bilayers \[^{25}\].

The concept of using a liposome as a selective drug delivery carrier for the skin was first introduced in 1980 \[^{26}\]. 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 were first produced in England in 1961 by Alec D. Bangham, who was studying phospholipids and blood clotting, at the Babraham Institute, in Cambridge \[^{27}\]. It was found that phospholipids combined with water immediately formed a sphere because one end of each molecule was water soluble, while the opposite end is water insoluble. Water-soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into the phospholipid layer \[^{28-29}\].

Liposomes are good vehicles for the delivery of therapeutic agents into the skin because of its associated hydrophobic lipid concentration. The fatty layer on liposome confines and protects the enclosed drugs 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 the chemotherapy drugs \[^{30-32}\]. 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.$^{[33]}$

The combination therapy is very effective for the melanoma treatment. One way to potentially improve drug combination 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 in the inner core and the lipid bilayer itself. By combining multiple agents in one liposome formulation, cocktails of drugs could be delivered patient compliance.

**Application of liposomes**$^{[34]}$

Liposomes are used for the following range of therapeutic and pharmaceutical applications:-

1. Liposomes in the pharmaceutical industry (Table 3).
2. Liposomes as drug/protein delivery vehicles
   - Controlled and sustained drug release
   - Enhanced drug solubilisation
   - Altered pharmacokinetic and biodistribution
   - Enzyme replacement therapy and lysosomal storage disorders.
3. Liposomes in antimicrobial, antifungal (lung therapeutics) and antiviral (anti-HIV) therapy
   - Carrier for small cytotoxic molecules
   - Vehicles for macromolecules as cytokines or genes
4. Liposomes in gene therapy
5. Liposomes in immunology
Table 3: Liposomes in the pharmaceutical industry[^35].

<table>
<thead>
<tr>
<th>Liposome Utility</th>
<th>Current Applications</th>
<th>Disease States Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubilization Site-Avoidance</td>
<td>Amphotericin B, minoxidil Amphotericin B – reduced nephrotoxicity, doxorubicin – decreased cardiotoxicity</td>
<td>Fungal infections Fungal infections, cancer</td>
</tr>
<tr>
<td>Sustained-Release</td>
<td>Systemic antineoplastic drugs, hormones, corticosteroids, drug depot in the lungs</td>
<td>Cancer, biotherapeutics</td>
</tr>
<tr>
<td>Drug protection</td>
<td>Cytosine arabinoside, interleukins</td>
<td>Cancer, etc</td>
</tr>
<tr>
<td>RES Targeting</td>
<td>Immunomodulators, vaccines, antimalarials, macophage-located diseases</td>
<td>Cancer, MAI, tropical parasites</td>
</tr>
<tr>
<td>Specific Targeting</td>
<td>Cells bearing specific antigens</td>
<td>Wide therapeutic applicability</td>
</tr>
<tr>
<td>Extravasation</td>
<td>Leaky vasculature of tumours, inflammations, infections</td>
<td>Cancer, bacterial infections</td>
</tr>
<tr>
<td>Accumulation</td>
<td>Prostaglandins</td>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td>Enhanced Penetration</td>
<td>Topical vehicles</td>
<td>Dermatology</td>
</tr>
<tr>
<td>Drug Depot</td>
<td>Lungs, subcutaneous, intra-muscular, ocular</td>
<td>Wide therapeutic applicability</td>
</tr>
</tbody>
</table>

Table 4: Liposomal formulation in market.

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Payload</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunoxome®</td>
<td>Market</td>
<td>Daunorubicin</td>
<td>Cancer</td>
</tr>
<tr>
<td>Doxil®/caelyx®</td>
<td>Market</td>
<td>Doxorubicin</td>
<td>Cancer</td>
</tr>
<tr>
<td>Moet®</td>
<td>Market</td>
<td>Doxorubicin</td>
<td>Cancer</td>
</tr>
<tr>
<td>Ambisome®</td>
<td>Market</td>
<td>Amphotericin B</td>
<td>Fungal infections</td>
</tr>
</tbody>
</table>

**Liposome Formulation in Market**

Drug molecules can be either entrapped in the aqueous space or intercalated into the lipid bilayer of liposomes, depending on the physicochemical characteristics of the drug. Liposomes can be prepared with enormous diversity in structure, composition, size, flexibility, and a variety of surface modification approaches proving most intelligent carrier system for both active and passive delivery of bioactives. They have been successfully exploited in cancer therapy, carrier for antigens, pulmonary delivery, leishmaniasis, ophthalmic drug delivery etc. Some of liposome-based formulations are already in market (Table 4)[^9].
Niosomes
Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Niosomes of terbinafine hydrochloride was formulated by thin film hydration method using different ratios of non-ionic surfactants (Tween 20, 40, 60, and 80) and cholesterol with constant drug concentration [36].

Niosomes are essentially non-ionic surfactant based multilamellar or unilamellar bilayer vesicles. Niosomes are a novel drug delivery system, in which the medicament is encapsulated in a vesicle. Both hydrophilic and lipophilic drugs, entrap either in the aqueous layer or in vesicular membrane made of lipid materials. Cholesterol and non-ionic surfactants are the two major components used for the preparation for the niosomes. Cholesterol provides rigidity and proper shape. Surfactants play a major role in the formation of niosomes, such as spans (20, 40, 60, 80, 85), tween (20, 40, 60, 80) are generally used for preparation of niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale [37].

Niosomes are found mostly by cholesterol incorporation as an excipient. Other excipients can also be used. Niosomes have more penetrating capability than the previous preparations of emulsions [38]. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery.

Colloidal vesicular carriers such as liposomes or niosomes have been extensively applied in drug delivery systems due to unique advantages. These vesicles can act as drug reservoirs and the rate of drug release can be modified by changing of their composition. These lipid carriers can encapsulate both hydrophilic drugs (by loading in inner space) and hydrophobic drugs (in lipid area). Because of their potential to carry a variety of drugs, these lipid vesicles have been widely used in various drug delivery systems like drug targeting, controlled release and permeation enhancement of drugs [39]. Dermal (topical) delivery defines a targeting to the pathological sites within the skin with the least systemic absorption. Drug localization in this case is a crucial issue in the treatment of dermatological problems such as skin cancer, psoriasis, alopecia and acne, where the origin of disease is located in the skin [40].
**Method of preparation of niosomes**

Niosomes can be prepared by a number of methods which are as follows (Table 5):

**Table 5: Method of Niosome Preparation**

<table>
<thead>
<tr>
<th>Method of Niosomes Preparations</th>
<th>Micro Fluidization</th>
<th>Micro Fluidization</th>
<th>Ether Injection Method</th>
<th>Multiple Membrane Extrusion Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Micro Fluidization</td>
<td>Micro Fluidization</td>
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</tr>
</tbody>
</table>

**Dendrimers**

Drug delivery is a vital aspect of formulation as its proper choice controls the bioavailability, concentration profile and side effects (by targeted drug delivery). While the most compliant way of drug administration might be its oral, it requires that drug is stable in conditions for example: pH, enzyme activity, epithelial permeability. Example, Insulin- peptide drug will be normally degraded by the digestive enzymes. Thus, a suitable drug delivery system would protect the drug against degradation and ensure that drug reaches proper permeability properties and further provides a combined transportation and protection system against the natural barriers, as done by the dendrimers\(^{[41]}\).

Dendrimers are a new class of polymeric materials having nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches\(^{[42]}\). The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behaviour dendrimers are suitable for a wide range of biomedical and industrial applications.

Dendrimer-based drug delivery systems focused on encapsulating drugs. Drug encapsulation is higher in dendrimeric nanoparticle. Recent development 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\(^{[43-44]}\). 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 nanoparticle in the close vicinity of a cancer cell can be immediately useful for diagnostic purposes or for the delivery of the radioisotopes capable of killing any cell within a defined radius. In general, however, most delivery strategies require that the anticancer agent directly attach to, or be taken up by, the target cell \([42]\). Dendrimers can also be being applied to a variety of cancer therapies to improve their safety and efficacy.

This fascinating particle holds significant promise for cancer treatment. Researchers have fashioned dendrimers into sophisticated anticancer machines carrying five chemical tools- a molecule designed to bind to cancer cells, a second that fluorescence upon locating genetic mutations, a third to assist in imaging tumor shape using X – rays, a fourth carrying drugs released on demand, and a fifth that would send a signal when cancerous cells are finally dead. The creators of these dendrimers had successful tests with cancer cells in culture and plan to try them in living animals soon \([45-46]\).

**Nanoparticles**

Nanoparticles are defined as “particles with at least one dimension smaller than 100 nm or 0.1 µm, and with different properties than particles of larger diameters made of the same material”.

Nanoparticles (including nanospheres and nanocapsules of size 10-200 nm) are in the solid state and are either amorphous or crystalline. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles as drug carriers can be formed from both biodegradable polymers and non-biodegradable polymers. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organs/tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through the peroral route \([47-48]\).

**Solid lipid nanoparticles**

Solid lipid nanoparticles (SLN) are colloidal drug carrier systems \([49-50]\) that are generally containing solid lipid, emulsifier and water. SLN are composed of physiologically tolerable and biocompatible lipids 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. SLN show adhesiveness, occlusion and skin hydration effects when applied locally 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. 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.

Method of preparation of Nanoparticles
Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on many factors including: (a) Size of nanoparticles required; (b) Inherent properties of the drug, e.g., aqueous solubility and stability; (c) Surface characteristics such as charge and permeability; (d) Degree of biodegradability, biocompatibility and toxicity; (e) Drug release profile desired; and (f) Antigenicity of the final product.

Nanoparticles have been prepared most frequency by three methods: (1) Dispersion of preformed polymers; (2) Polymerization of monomers; and (3) Ionic gelation or coacervation of hydrophilic polymers.

CONCLUSION
From the above discussion and study of different research papers, Novel approach of drug delivery has a great opportunity to overcome skin cancer problems to efficiently target a number of diverse cell types. Despite the recent advancement in the therapeutic, significant challenges still present in the field of skin cancer. Commonly used chemotherapy for the treatment of such cancer diseases have give unsatisfactory results, as the therapy is more dangerous to the patient health by making patient more susceptible to other diseases and often cause death by weakening the immune system of the patient. Thus, now days the novel drug
delivery system has been given a great opportunity with a main focus on current cancer therapy.

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