Research Paper

An Update on Role of Vesicular Carriers in Skin Cancer

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Skin cancer is one of the leading and most significant threats to the current scenario, mainly due to global warming occurring across the world. Anticancer drugs either completely kill most cancer cells or, in some ways, modify their growth. However, the selectivity of most medications is constrained, which makes them the most toxic drugs used in therapy. However, technologies and innovations have attracted the attention of contemporary developments with the help of numerous discoveries in nearly every subject. Additionally, vesicular carriers have been explored for drug discovery in a protracted manner. These carriers improve the drug's permeability, ensure that the drug is delivered at the target site and from approaches such as gels and patches, and, for this reason, nullify the troubles related to the distribution, resistance, specificity, selectivity, and systemic toxicity of drugs. This review highlights the etiology, therapies, and briefings of various vesicular carriers for the treatment of skin cancer.

Key words: Transdermal drug delivery, carriers, vesicular, skin, cancer

Skin cancer has become a worldwide issue and a significant concern that continues to increase. Cutaneous cancer is typically divided into two primary classes: Melanomas (melanocyte dysfunction) and non-melanocytes (originating from epidermal cells).

The skin comprises two layers (primary): Epidermis and dermis. The epidermis is the topmost section, and consists of keratinocytes, Merkel cells, and Langerhans cells. If there is any enormity with the epidermis, it leads to distinct dermatological conditions and malignancies[1].

Melanoma is caused by the unnatural growth of living melanocytes, which comprise ninety, five, and one percentage of the cells in the human skin, gazes, and gut, respectively, and are responsible for pigmentation. Melanomas account for 1 % of all skin carcinomas. Melanoma, despite enduring the highest five-year survival rate of 15 %-20 %, is the most lethal type of cancer of the skin[2].

Over 95 % of all skin cancers are Non-Melanoma Skin Cancers (NMSC), which are caused by environmental and familial factors. The NMSCs also include many other cancer types, but the two major subtypes are cutaneous Squamous Cell Carcinoma (SCC) and Basal Cell Tumors (BCC), which in total account for ninety-nine of all NMSCs[3,4].

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ETIOLOGY OF CUTANEOUS CARCINOMA

Cutaneous carcinoma has surged since the very beginning and has been identified as the most prevalent and deadliest type of cancer. The two most pervasive skin cancers observed in humans are non-melanoma and melanoma, which are later categorized into Basel cell carcinoma, squamous cell carcinoma and cutaneous malignant melanoma (Table 1)[5,6].

Ultraviolet (UV) rays:

UV radiation is one of the most common environmental carcinogens. Keratinocyte Carcinoma (KC) is characterized by C>T or CC>TT dinucleotide shifts arising at bases made of pyrimidine, with a substantial transcriptional strand bias. This mutational signature, Signature 7, is a distinguishing feature of a UV brought mutations and is prevalent in all skin-related cancers. Many assumptions exist because there may be no sensible approach to determine the reasons for skin cancer (fig. 1)[7-9].

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TABLE 1: OVERVIEW ON TYPES OF SKIN CANCER

Types of skin cancer	Causative agents	Site of distribution	Description	Disease caused	Reference
Squamous cell carcinoma	Air pollution micro-organism solar radiation genetic predisposition tobacco smoking	Neck head upper aero digestive tract, lip oral cavity	The 2nd most habitual form of skin cancer Occurs *via* cutaneous dysplasia than de -novo	Bowen's disease SCC lesions in dogs and cats. Skin cancer	[4-6]
Basal cell carcinoma	Sun exposure chemical carcinogens /radiation viral carcinogens DNA repair hereditary predisposition	Skin tonsil bladder prostate uterine cervix bronchi breast	Cancer of skin Most often occur in the region exposed to sun, that is face. Limiting sun exposure prevents its occurrence	Gorlin syndrome, Rambo syndrome, Xeroderma pigmentosa	[4-6]
Cutaneous malignant melanoma	Sun exposure genetic mutations somatic mutation affected CDKN2A	Epidermis lungs liver lymph nodes	The most pugnacious and fatal form of skin cancer. Cancer of pigment-producing cells	FAMM syndrome, Superficial spreading melanoma	[4-6]

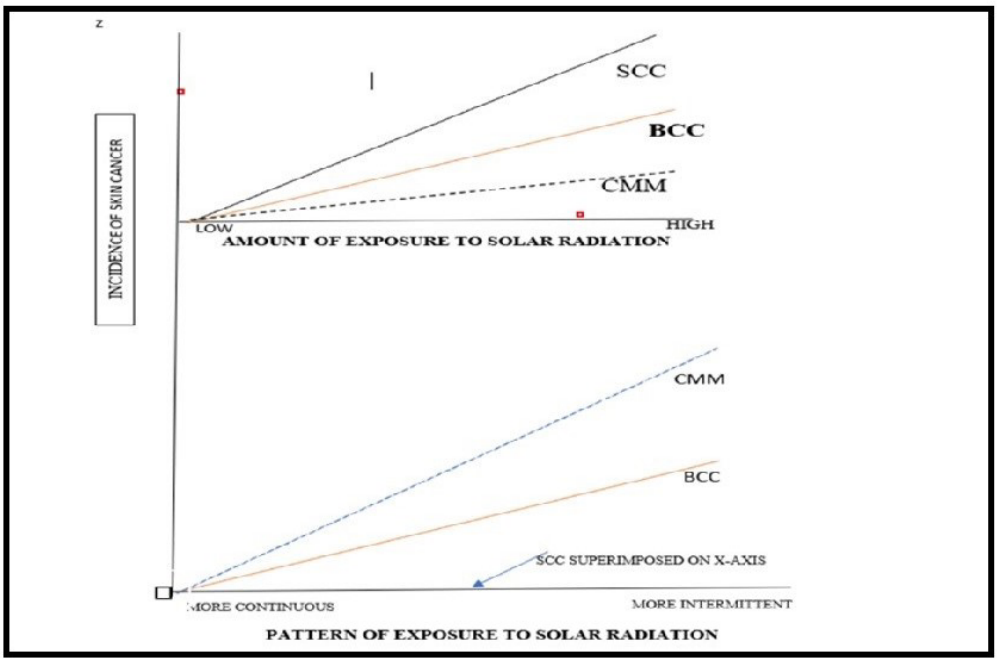

Fig. 1: Pattern of exposure of solar radiations *vs.* incidence of various types of skin cancer

Epidemiological evidences:

Relationship with ambient solar radiation: Incidence by latitude/ estimated ambient solar UV; personal residence history and effect of migration; relationship to cutaneous sun sensitivity; ethnic origin; propensity to sunburn & ability to tan; distribution on the body; relationship to personal exposure; association with benign sun related conditions; effect of reduction in sun exposure; population sun exposure and personal sun protection[10].

Immunosuppression: Another alarming aspect of KC is innate or acquired immunosuppression, mainly in the case of SCC. The maximum typically received immunodeficiency encompassing drug remedies (e.g., in stable organ transplantation), Immune-Mediated Inflammatory Diseases (IMIDs) such as Inflammatory Bowel Ailment (IBD), Rheumatoid Arthritis (RA), vasculitis, Non-Hodgkin Lymphoma/ Persistent Lymphocytic Leukemia (NHL/CLL), and Human Immune Deficiency Virus (HIV) infection are commonly associated with KC. Immunosuppression and immune suppression medicaments ' etiology usually result in dysregulation of tumor immune surveillance, but the latter can also contribute to carcinogenic outcome[11].

Human papilloma virus: Cutaneous Human Papillomavirus Virus (HPV), specifically of the beta

genus (βHPV), has been seen linked with cSCC and has been the primary one to get identified in patients having Epidermodysplasia Verruciformis (EV). This can also be seen in patients who have an immunocompetent system. Patients suffering from EV, a very uncommon autosomal recessive ailment characterized by impaired cell immunity, have additionally contributed to accelerating the risk of cSCC. It typically inhibits Deoxyribonucleic Acid (DNA) repair or apoptosis in UV-damaged cells. HPV has advanced to synchronize its infectious cycle with differentiation of the host's target cells (keratinocytes). As soon as the virus enters the epithelium through the pores and skin microlesions, it infects young basal keratinocytes and stem cells. Even in viral episomes, it persists at a low copy number in the basal cells. Finally, HPV genome replication occurs[12].

Consequently, the period vital for basal keratinocytes to achieve complete differentiation and desquamation is three weeks from contamination to virus launch. Cytolysis or cytopathic changes do not arise at some stage in virus replication due to HPV's extraordinary coordination with the epithelial improvement mechanism[13].

Furthermore, because virus-infected keratinocytes commonly die following terminal differentiation at the floor during the viral cycle, no essential threat indicators are activated in host cells. Consequently, it does not propose an inflammatory reaction was not observed. Infectious virions no longer occur till inflamed keratinocytes attain terminal differentiation[14].

Infection: Chronic skin disorders, such as psoriasis and hidradenitis suppurativa, pose altered skin microbiota that can also regulate KC development. A study by Epidermis identified that 6-N-hydroxyaminopurine could inhibit DNA polymerase in many tumor cells, including cSCC. Metagenomic evaluation of the human pores and skin microbiome prevalence of *Staphylococcus epidermidis* (*S. epidermis*) strains were visible among healthy people. For example, mice lacking immunologically good-sized genes, such as Tlr5, Il10, Tbx1, and Rag2, are especially vulnerable to colon and bowel malignant inflammation and intestinal dysbiosis. Healthful mice can inherit this tendency for most cancers using fecal transplants, cohousing, or fostering. These results apply to individuals because human microbiome composition and cancer predisposition are affected by polymorphisms in immunologically large genes. The bacteria-mediated carcinogenesis in mice were examined using a variety of microbial species, including the *Enterococcus faecalis* (*E. faecalis*) Strain, *Streptococcus gallolyticus* (*S. gallolyticus*), Enteropathogenic *Escherichia coli* (*E. coli*), Enterotoxigenic *Bacteroides fragilis* (*B. fragilis*), *Helicobacter Hepaticus*, *Salmonella enterica*, and *Fusobacterium nucleatum*. In mice suffering colon cancer, the microbe's taxa Odoribacter and Akkermansia are abundant, while the archaea, notably the phylum Methanobacteriales, are enriched in the stools of people with colorectal cancer[15,16].

Germline genetic risk factors: KC and melanoma risk types (or alleles) have been identified using Genome-Wide Association Studies (GWAS). Hereditary syndrome is rarely associated with an increased risk of cSCC. However, some of these are Xeroderma Pigmentosa (XP), epidermolysis, bullosa, Fanconi anemia, oculocutaneous albinism, and Werner syndrome (a maturing syndrome). The primary sickness linked to a greater likelihood of BCC in Basel cell nevus syndrome (Gorlin syndrome) is brought on by harmful mutations in the PTCH1 gene, with PTCH2 and SUFU occurring less frequently[17].

THERAPIES USED IN SKIN CANCER

Surgery is the most common and effective treatment for skin cancer. Some of the commonly performed surgical approaches include excision. Here, the surgeon removes the cancer tissue along with a margin of healthy skin around it; this ensures that all cancer cells are removed and aims to reduce recurrence.

Curettage and electrodessication involve scraping off the cancer tissue with a curette and later cauterizing the tissue with a curette. The same area was treated with electrical energy to stop haemorrhage. It also kills any remaining adhered malignant cells. Cryosurgery involves freezing a cancer cell with liquid nitrogen, making it die, and later scraping it[18-21].

Radiation therapy:

Radiation therapy is a long-term, successful complementary method used in the management of cancer in cutaneous oncology. In addition to resisting tumor growth, this technique provides favorable cosmetic results. Treatment includes focusing on ionizing radiation, Element beam treatment, x-ray

radiation (by employing kilovolt to megavolt beams), Radionuclide brachytherapy, and electronic brachytherapy[22,23].

Photodynamic Therapy (PDT):

The idea behind PDT is to activate photosensitizing drugs with light, creating radicals that assault malignant cells. Commonly used topical photosensitizers are 5-aminolevulinic acid and methyl 5-aminolevulinate. Many malignancies, except melanoma, directly build in the locations where many skin diseases have lesions[24].

Mohs's surgery:

It is a specialized surgery where cancerous tissue is removed layer by layer and examined under a microscope until the absolute absence of cancer cells. This procedure treats tumors larger than two cm and whose cancerous extent is difficult to determine (in the nasolabial folds or eyelid). Accomplishing a tumor-free state includes incremental lesion excision using icy portions and meticulous labelling of removed areas[25].

Laser Therapy (LT):

This involves the application of a focused beam of light to target and destroy cancer cells. Here, the laser energy is absorbed by cancer cells, which heats and kills them. LT is a precise technique which allows health professionals to target cancer cells specifically and minimize damage to surrounding healthy[26].

ANTI-CANCER DRUGS

Anticancer drugs are commonly used to kill cancer cells or to alter their growth. The selectivity and specificity, however, still perform a massive function in meeting the need of the hour, as they are one of the most poisonous agents used in therapy. Similarly, diverse endeavours exist in the most effective treatment strategies[27].

Consequently, there is a need to develop formulations that correctly supply the drug locally, have very low systemic toxicity, and achieve optimum drug release. Numerous nanotechnology-based drug carriage systems for topical formulations have been used to determine the stability between specificity and selectivity. This may overcome the inconvenience of oral administration. Nanotechnology has bridged the gap between specificity and selectivity by using nanostructures and nano stages inside the discipline. Nanomaterials are substances with diameters starting from one to a hundred nm that affect nanomedicine's frontiers[28].

BRIEF INTRODUCTION TO EVOLUTION OF DRUG DELIVERY SYSTEMS

Exploring the limitations of conventional drugs in targeting specific organs, cells, or tissues has prompted the investigation of drug transport mechanisms, leading to the development of targeted drug delivery systems for various purposes. The drawbacks of conventional drugs include their dreadful biodistribution, limited effectiveness, unwanted side effects, and absence of selectivity. Techniques, such as controlling drug transport, can overcome these limitations. Targeted Drug Delivery Systems (TDDS) magnify drug attention in target tissues, thereby lowering the drug dose. TDDS are ordinarily applied in treatments where there is a difference between the dosage of a medicine and its beneficial/harmful effects. Processes such as tissue-centric targeting have proven reliable in drug transport systems. Moreover, nanotechnology and its development have verified that nanoparticles can be used as drug carriers.

Many nanostructures with distinct physicochemical and biological features are produced using size reduction strategies and technologies. This makes them favourable for biomedical packaging and is crucial in the pharmaceutical sciences. Nanotechnology no longer improves but enhances performance in each dosage form. The benefits of nanosizing are that it complements target specificity, solubility, dissolution price, and bioavailability of medicines, lowers the dose, and reduces systemic toxicity. It also decreases patient-patient variability[29].

VESICULAR APPROACHES IN SKIN CANCER

Vesicular delivery structures achieve a wide range of goals, including drug concentration, high bioavailability, and balance in drug delivery. These are designed in a way that consists of an aqueous core adjoined with a lipid bilayer aid. The lipophilic drugs are enclosed in the membrane bilayer, while the water-loving drugs are enclosed in the interior liquid core[30].

These carriers help target the affected site in a predetermined manner over a present period. Vesicular networks display characteristics including

considerable capture of drugs, extended retention intervals, and localized drug concentrations. These systems have several advantages such as the capacity to encapsulate hydrophilic and lipophilic moieties. It aims to extend drug half-lives by increasing the period in the systemic circulation, focusing on organs for drug transport, and since these carriers are biodegradable, they lack toxicity[31,32].

LIPOIDAL BIOCARRIERS FOR SITE SPECIFIC TARGETING

Liposomes:

Liposomes are microscopic vesicles wherein the lipid bilayer makeup in an aqueous volume is enclosed by a membrane filled with lipids. It mainly consists of phospholipids (phosphoglycerates, sphingolipids) and cholesterol (as shown in fig. 2). Simple additives in liposomes include lipids and fatty acids. As lipids are a natural component of cell membranes, they are biocompatible and biodegradable. They entrap lipophilic drugs into bilayer membranes and hydrophilic drugs into valuable aqueous centers of vesicles[33-34].

The mechanism of liposome movement encompasses attachment to the cell membrane and simultaneous fusion with the release of its content material. Liposomes display amphiphilic behaviour, which allows them to accommodate drug molecules with various polarities. They target Mononuclear Phagocytic System (MPS) cells, specifically macrophages. Therefore, they can deal with diverse infections, cancers, and atherosclerosis. The nanoparticle-loaded liposome suggests a reaction to diverse environmental stimuli, such as pH and temperature, which helps vesicles cause destabilization of the liposomal membrane and simultaneous drug release into target cells. Those external stimuli can control drug release time in response to outside stimuli[35-37].

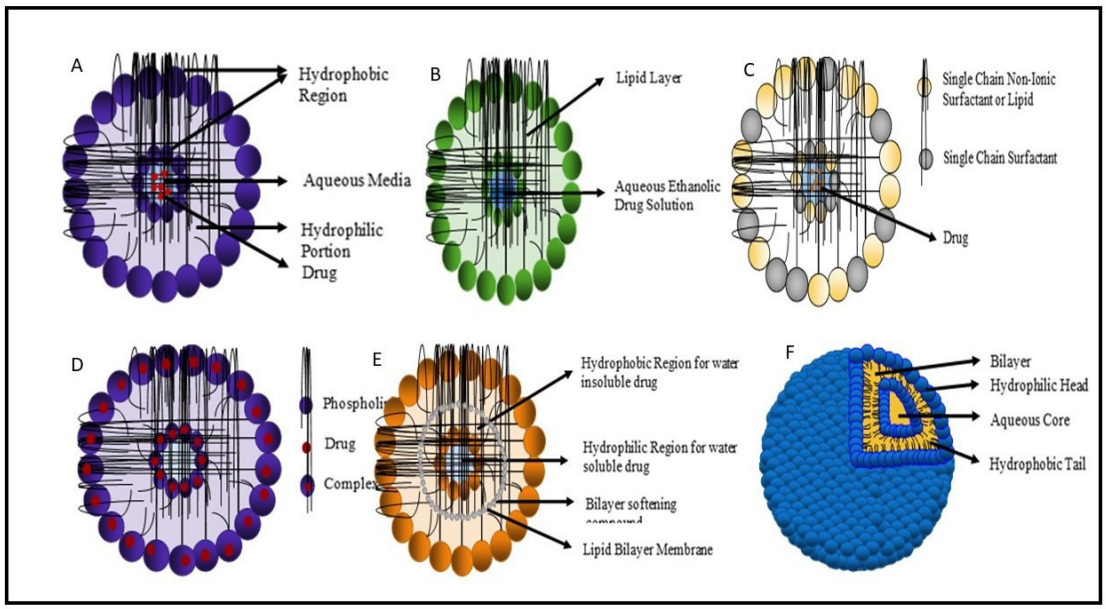

Fig. 2: Various vesicular carriers in skin cancer, (A): Liposomes; (B): Ethosomes; (C): Pharmacosomes; (D): Phytosomes; (D): Transfersomes and (D) Niosomes

A study on docetaxel liposomal formulation revealed that the encased form of the medicine has a five–six times higher rate constant of cell destruction than the conventional form. Liposome drug encapsulation decreased the systemic toxicity and improved the tolerable drug dose. Liposomes are consummates related to protecting the drug, its release rate, and its uptake from the endocytosis process. The all-around nature of liposomes gives them a unique behaviour and makes them ideal carriers for a wide range of therapeutic and clinical applications. It reduces off-target toxicity, prolonged toxicity and prolonged blood circulation[38,39].

Ethosomes:

Ethosomes are soft, flexible lipid vesicular carriers of nanometers to microns, having hydro-alcoholic or glycolic phospholipids, and alcohol (ethanol and isopropyl alcohol) with a higher focus within. These carriers deliver drugs with very low skin permeability. Ethanol acts as a penetration enhancer.

Ethanol, cysts, and skin lipids all exhibited

synergistic behaviour, increasing skin penetration better than ethanol alone. They can disturb the lipid bilayer of the skin. It fluidizes the stratum corneum bilayer and upgrades the easy transfer of drug-loaded vesicles into a disorganized bilayer. Their net charge was negative and facilitated a reduction in vesicle size. Although they have the same stability, they are packed more freely than other vesicular forms. Its flexible, malleable structure allows it to squeeze itself through tiny pores formed in the disturbed SC lipid bilayer. Therefore, stratum corneum lipids are multilayer and densely packed at average physiological temperatures. Ethosomes interact with lipids in the polar head group, increasing the fluid rush into the SC, thus increasing the inter-and intracellular permeability of these agents. Finally, it forges the way into a disorganized SC and releases all of its drug content. Compared to conventional liposomes, liposomes, including aqueous and lipid-based drugs, have increased permeation. One of the essential features is that it can also be formulated in a sustained release[40-42].

Pharmacosomes:

They are amphiphilic lipoidal colloidal dispersions of drugs covalently bonded to lipids to boost the absorption of lipophilic and hydromedicines that are not readily soluble. A pharmaceutical substance (pharmakon) and an envelope (soma) were joined to build the framework. An amphibious prodrug can be generated by esterifying a drug's liberated carboxylic domain or by adding a free hydrogen ion (OH, NH2) to the hydroxyl bond of a lipid structure. The newly formed form becomes metamorphosized to pharmacology upon dilution with water, thus engulfing mesomorphic behaviour. This action reduces friction while raising the effective vicinity area and increasing the systemic availability of drugs form[43].

Furthermore, because they are securely bound, there is no loss from therapeutic spillage, which maximizes the effectiveness of entrapment. There is no need to unfasten free entrapped drugs from the formulation. Unlike liposomes, there is no room for interaction between the encapsulated volume and drug bilayer. Pharmacosomes have emerged as viable substitutes for traditional cysts owing to their distinct benefits over liposomes and niosomes. Pharmacosomal components include drugs, solvents, and lipids. Pure and volatile solvents were used. The lipids used include sphingolipids and phosphor-glycerides[44].

Pharmacosomes obtain polymers through covalent van der Waals and hydrogen bonding and thus achieve the preferred dose of drug focused on in a controlled release fashion. They reduce the toxicity and different systemic manifestations of drugs alone. The biodegradable micelle accurately conjugates with drugs, which will increase its hydrophilicity[45].

The advantages include the absence of leaching drugs bound to lipids by covalent bonds, drug-lipid complex formation depending on the phase transition temperature rather than the rate of drug release, the capability of delivering the drug at the target site accurately, leakage issues, drug incorporation, and problems in shelf life can be nullified here; there will be significantly less interfacial tension as prodrugs with hydrophilic and lipophilic properties acquire amphiphilic behaviour and no need to remove unentrapped drugs, which are necessary for liposomes, thus improving the bioavailability of poorly soluble drugs. However, storage is a problem because it undergoes fusion or aggregation. Lipophilic agents are encapsulated in a less hydrophobic interior membrane bilayer instead of a larger floor region, and the drug being covalently bonded to lipids is a compulsory factor that is difficult under all conditions. Floor and Bulk interactions may be seen and also amphiphilicity is a mandatory requirement in the compound[45,46].

Phytosomes:

The drawback of allopathic medicines is their adverse reactions, which many researchers have endorsed as formulating or expanding medicinal herbs and phytochemicals as therapeutic options for many medical disorders. Phytosomes are novel lipophilic drug transport systems with hydrophilic bioactive phytoconstituents of herbs surrounded and bound by phospholipids. They are complexes of phospholipids and herbal phytochemicals formed by responses among plant extracts in aprotic solvents and phosphatidylcholine (polar hydrophilic head). The unpaired constituent of the herbal product binds to phosphatidylcholine, which yields better absorption. Phytosomes are formulated using natural products such as Ginkgo biloba, milk thistle, green tea, and curcumin. Currently, they are applied for cosmetic usage to supply water-soluble substances because phospholipid interacts with any product and adheres to it at molecules of cell systems[47,48].

When contrasting phytosomes with liposomes, the

critical distinction is that the phytoconstituents are chemically bonded to the polar head of the surfactant phospholipid in the former. In contrast, in the latter, phytoconstituents first dissolve in the cavity medium and exist without any chemical bonds between them.

Phytosomes offer the advantage of a solid as a robust chemical bond between phospholipids and phytoconstituents. Drug entrapment efficiency is ideal, as drugs bind with lipids to form blisters, and greater bioavailability is visible because the supply of medicines into deep tissues is assured. Phytosomes are advantageous over Liposomes for cosmetic utilization, and the presence of phosphatidylcholine will nourish the skin; they may be less soluble in aqueous media, so they retain their shape as emulsions or creams[49].

Transfersomes:

When contrasting phytosome with liposome, the critical distinction is that phytoconstituent is chemically bonded to the polar head of surfactant phospholipid in the former. In contrast, in the latter, phytoconstituents first dissolve in the cavity medium, and transferosomes are specifically optimized ultra-flexible lipid supramolecular clusters that can penetrate the intact mammalian skin. It stems from the Latin phrase for the word meaning "to hold across the frame." They can be squeezed through pores that might be smaller than their length, accounting for their flexibility and elasticity in penetrating cells. As they are tremendously deformable, they stand out as promising candidates for the non-invasive shipping of all-sized drugs[50-53].

Each transferosome encompasses at least one internal aqueous compartment, which is blanketed by a lipid bilayer and incorporates "aspect activators" inside the vesicular membrane. Part activators like Tween 80 and sodium deoxycholate destabilize lipid bilayers and cause them to be exceptionally flexible[54,55].

The passage of drugs through the pores and skin occurs because of the flexible nature of the vesicle bilayer and the improvement of the osmotic gradient across the skin. The transpire hydrostatic pressure difference makes drugs input into the stratum corneum[56].

Transferosomes have the ability to improve targeted drug delivery by increasing specificity and promoting standard safety. They possess true penetrability and flexibility, allowing the drug to remain at the therapeutic site for an extended period. Additionally, drug incorporation is not an issue, resulting in high drug entrapment, making them superior to other forms like liposomes and niosomes, which are not suitable for Transdermal Drug Delivery System (TDDS) due to decreased skin permeability, vesicle breakage, clumping during storage, and drug leakage[57].

Despite all these advantages, they are chemically unstable as they are vulnerable to oxidative degradation and are, without a doubt, expensive to formulate[53-56].

The unique characteristics of transferosomes stand out compared with those of other vesicular carriers. If applied non-occlusively, the novel form generates trans-epidermal osmotic gradients, which act as energizers to smooth the transfer of drugs loaded into it. The difference in the water concentration between the skin surface and interior induces a gradient of osmosis. This highly flexible feature allows rapid access to the intercellular lipid pathway of the subcutaneous tissue. (Virtual channel)

Transferosomes reduce skin obstruction by opening extracellular pathways and deforming themselves to accommodate passage. This property makes it possible to diagonally carry drugs in a more reproducible manner. We can say; the self-optimized, motorized property of transferosomes permits them to reach the target invasively. Owing to their stretchy attributes, they can pass through thinner skin than the vesicles themselves. As transferosomes entrap drugs of variable size, they can be used as a controlled-release formulation[58].

NON-LIPOIDAL BIOCARRIERS FOR SITE-SPECIFIC TARGETING

Niosomes:

The diligence required to handle liposomes at low temperatures has led to the development of new noisomes. They are nonionic surfactant vesicles of the unilinear or multilamellar type and polyhedral vesicles in water fluids. They are minuscule lamellar membrane structures with dimensions of 10 nm and 100 nm. Nontoxicity contributes to the nonionic nature of niosomes and thus holds the name niosomes. Along with a surfactant, cholesterol is also present, providing rigidity and stability. Here, the aqueous solution is covered with a highly ordered bilayer made from a nonionic surfactant, where the hydrophobic tail of the surfactant makes up the bilayer. The core had an aqueous space and hydrophilic head in contact.

Niosomes are user-friendly when it comes to storing and transporting substances. They are ideal for drug delivery because they are osmotically active solids with a long shelf life, allowing for sustained and controlled release through the depot system. Additionally, niosomes improve drug permeation, which enhances the drug's effectiveness. Furthermore, surfactants used in the preparation of niosomes are biodegradable and non-immunogenic, reducing the risk of immunogenic reactions[59-60].

The disadvantages of these systems include hydrolysis of drugs within an aqueous suspension of niosomes. Subsequently, it destabilizes medications and may get leaked from entrapped sites, forming aggregates. Sterilization of niosome, such as heat and membrane sterilization, is difficult because the district lipid and membrane method's warmth technique needs help concerning pore size; this may cause inhibition of human keratinocyte cell growth through unique niosome formulations[61]. Niosomes can be of various types, as mentioned below

PH-Responsive niosome:

Various approaches have been used to address the limitations of niosomes and improve drug levels inside target cells. One such example is the pH-responsive niosome. It encompasses proteins or small peptide chain molecules that interact with the target mobile membrane to disrupt it at a low acidic pH. As the pH of the extracellular tissue is acidic at some point in a diseased situation, it was used to formulate drug-loaded liposomes to launch the drug in an acidic environment.

Magnetic niosomes:

Here, entrapped magnetic nanoparticles were included in the niosomes. Because an external magnet assists drug delivery by interacting with the inner magnet, it generates a magnetic area and improves drug activity. These magnetic materials are implicated in most cancer therapies using extracorporeal magnets to direct drug-loaded magnetic niosomes into the target

Immuno-niosomes:

They are specialized forms of niosomes designed to enhance immune reactions and boost the transport of immunomodulatory vaccines. They can potentially increase the balance between immunomodulatory markers and growth immune reactions in opposition to cancer. This is essential in vaccine development and immunotherapy, optimizing immune gadget interplay, and leading to more powerful remedies.

Thermoresponsive niosomes:

The call says that Thermos-responsive niosomes are specialized lipid-based nanocarriers that respond to temperature modifications by undergoing structural changes in response to temperature alterations. At lower temperatures, they exist in a firm or gel state, making it possible to release the drug at a prolonged fee. In contrast, it undergoes a section at an elevated threshold temperature and fluidization (turning into a managed launch). Niosomes, being relatively smooth to produce and inexpensive, can be used in the veterinary, cosmetic, and pharmaceutical fields. They beautify the attainment of medication by increasing entrapment efficiency and suited drug targeting. Unique niosomes, being more beneficial than regular niosomes, should go through sizable research, potentially driving innovation closer to production marketplace-equipped and capturing market-ready products[62-65].

Examples of few successfully incorporated Anti-cancer drug loaded vesicular systems are shown in Table 2[66-70].

TABLE 2: DIFFERENT VESICULAR SYSTEMS USED IN SKIN CANCER

Sl.no	Vesicular form	Ingredients	Problems with conventional products	Results	Reference
1	Carvedilol loaded Transferosome	Drug, soy phosphatidylcholine, and Tween-80	Cardiovascular disturbances	Prolonged time and mitigated systemic effects.	[66]
2	5-Flurouracil loaded Noisome Gel	Drug, sorbitan monostearate (Span 60), sorbitan monolaurate (Span 20) cholesterol, sodium deoxycholate.	The hydrophilic nature of drug makes it poorly permeable and there is a need to maintain it at for high dose at site as its rate of metabolism is quick.	A higher entrapment efficiency and permeability to skin	[67]
3	Curcumin Loaded Ethosome	Drug, soya lecithin, ethanol, cholesterol.	Poor oral bioavailability limits its use as oral dosage form.	High permeability to skin	[68]

4	Peptide-modified vemurafenib-loaded liposome	Drug, Sodium cholate, calcein, cholesterol.	Oral route causes damage to major organs with limited antitumor efficacy and bioavailability.	Reduced side effects, enhanced antitumor efficacy	[69]
5	Phytosome formulated from aloe vera extract	Drug, Aloe vera extract-phospholipid complex	Low solubility of traditional herbal products.	Promising cytotoxic and anti-oxidant effects.	[70]
6	Cyclophosphamide loaded noisome topical gel.	Drug, Dichloromethane, Span60, cholesterol.	Mild to moderate use cause severe cytopenia, hemorrhagic cystitis, neutropenia, alopecia and GI disturbance	Prolonged drug release and reduced systemic effects Melanoma treatment.	[60]

REGULATORY CONSTRAINS

There is very little information on connecting drug-loaded vesicular carriers to skin cancer in the clinical phase. Complement Activation-Related Pseudo-Allergy (CARPA) is observed among patients with skin cancer using liposome-based formulations during their first exposure. Hence, antihistamines should be administered. A slight modification in vesicular composition may diverge the drug action. In addition, the stability and scalability of vesicles are major issues. In particular, hydrophilic drugs may leak from vesicles after storage. No vesicle till date show storage time above 3-4 mo. Pre-clinical studies indicate that vesicular carriers have high penetration, but proof to address their ability to penetrate clinical studies should be validated.

CONCLUSION

Skin cancer is one of the leading health issues in the current scenario, and the mortality rate is increasing rapidly. Although various treatment strategies are available, the prospect of treating skin cancer using vesicular carriers is promising. Anti-cancer drugs can be easily and conveniently loaded into different vesicular carriers to treat basal cell carcinoma, SCC, Melanoma, KS, and other types of skin cancer. These carriers overcome stability issues, drug loading, optimize kinetics, and direct access to cancer cells, thus improving the therapeutic efficacy of drugs. They act as transporters of drugs into the skin barrier and effectively deliver the drug dose.

As there are relatively fewer vesicular-based drugs available in the market, many dermal and transdermal applications treating cancer should be developed in the near future. There is always scope to improve the drug loading and release kinetics. Future research can extend to multiple agents, multifunctional approaches, and personalized customized approaches.

Conflict of interests:

The authors declared no conflict of interests.

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