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Localized topical drug delivery systems for skin cancer: Current approaches and future prospects

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Topical drug delivery presents a novel substitute to the conventional drug-distribution routes of oral delivery and injection. Apart from the simplicity and non-invasiveness, the skin also serves as a "reservoir" that sustains administration over a period of days. Nanocarriers provide new potential for the treatment of skin disease. The skin's barrier function offers a considerable obstacle for the potential nanocarriers to infiltrate into the tissue. However, the barrier is partially weakened in case of damage or inflammation, as in the case of skin cancer. Nanoparticles may promote the penetration of the skin. Extensive research has been done into producing nanoparticles for topical distribution; nevertheless, relatively little progress has been achieved in transferring them to the clinic for treating skin malignancies. The prior art features the critical concepts of skin malignancies and techniques in current clinical care. The present review gives a complete viewpoint of the numerous nanoparticle technologies studied for the topical treatment of skin malignancies and outlines the hurdles that hamper its advancement from the bench to the bedside. The review also intends to give knowledge of the routes that control nanoparticle penetration into the skin and their interactions inside the tissue.

KEYWORDS

melanoma, nanocarriers, stratum corneum, nanoparticles, noninvasiveness

Introduction

Skin cancer is the most common disease in Americans and European countries; one in five Americans is impacted by skin cancer, making it the most frequent disease in the United States and did not account for nonmelanoma skin cancer (NMCS) in the last of 2020 (Katalinic et al., 2003). One million new cases are accounted for in the United State. Although melanoma accounts for only 1% of all skin cancers, it causes the majority of deaths, and it is expected that almost 7,000 people will die from melanoma by the end of the year (Sigmundsdottir, 2010). Over 5.4 million cases of NMSC are treated in the U.S. each year. Basal cell carcinoma (BCC) is the most common form and is usually slow growing and locally invasive (Jain et al., 2020). Squamous cell carcinoma (SCC) is the second most common form of non-melanomatous skin cancer, accounting for approximately 20%–30% of new cases (Leiter-Stöppke et al., 2014). Skin is the largest organ of body it is a potential alternative route of administration for topical and

transdermal delivery of many drugs (Rogers et al., 2012). Skin can be used to deliver drugs locally in skin cancer because it offers several advantages like avoidance of the problems associated with stomach emptying, pH, deactivation due to enzymes, and avoidance of first-pass metabolism, which are generally associated with oral administration (Kosmadaki and Gilchrest, 2002; Simões et al., 2015). Another major advantage of topical products is the ease of termination of therapy simply by removing the formulation from the skin surface. Novel topical formulations can be used to manipulate the barrier function of the skin (Lewis and Weinstock, 2007).

Nanocarriers are colloidal drug carrier systems having submicron particle sizes typically <500 nm in the range (Guy et al., 2015). It is a nanomaterial being used as a transport module for another substance, such as drug nanoparticles are promising materials used to deliver biologically active molecules at the desired rate, and the desired time. Nanocarriers can increase solubility, stability, and bioavailability, decrease toxicities, and site-specific drug delivery *via* different routes and different types of nanomaterial used as a nanocarrier (Lewis and Weinstock, 2004). In the recent decade, topical carriers have provided a unique mode for improving skin penetration across the skin surface. Hence for localized drug delivery, topical carriers favour much more attention to attending desired plasma concentration for a longer period of time and its benefits in chronic conditions. Thus, the prior art features critical appraisal in various nanocarrier along with the literature survey, recent advances and future prospects. The aim of the present review focuses on recent advances in localized topical drug delivery for skin melanoma.

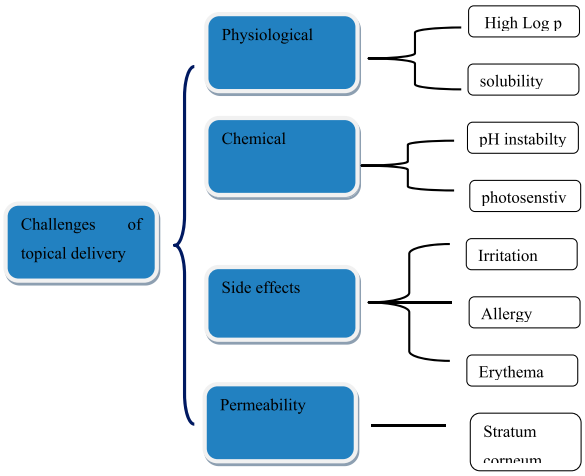

FIGURE 1
Challenges in delivering drugs through the skin.

Anatomy of the human skin

The skin comprises three layers, epidermis, dermis, and hypodermis (Andrews et al., 2013). The skin of an average adult covers a surface area of approximately two sq. m. and receives about one-third of the blood circulating through the body and serves as a permeability barrier against the topical absorption of various chemical and biological agents (Bouwstra and Honeywell-Nguyen, 2002). The outermost layer of the epidermis, stratum corneum (SC), is approximately 10–20 μm thick and is non-viable. It is formed by stratified, squamous epithelium composed mainly of keratinocytes, melanocytes, Merkel cells, and Langerhans cells (Jensen et al., 2011). Each cell is approximately 40 μm in diameter and 0.5 μm thick, and the intercellular space between adjacent cells is not more than 0.1 μm. Thus, the drug must pass through the intact SC layer for dermal availability. Once a medication has crossed the SC, it may build up in the nearby fatty tissues, leading to higher tissue concentration for a longer period of time (Prochazka, 2000). To have the edge over alternative delivery methods, tissue localization of medicines applied topically can be investigated. Cancer, vaccines, pain relief, and hormone therapy are just a few of the many possible applications for targeted medication delivery. Systems for delivering drugs *via* the skin can lower the dosage necessary for a therapeutic effect, minimizing side effects. Drug penetration into specific areas without considerably entering the bloodstream, resulting in improved efficacy due to high local concentration, is one benefit of localized drug delivery utilizing skin (Bogner and Wilkosz, 2005).

Challenges in transdermal delivery of drugs

Skin delivery of actives has many benefits, but it also acquired some drawbacks regarding effective permeability and therapeutic effect. The stratum corneum (SC) is impermeable to active pharmacological substances with molecular weights >500 Da, having drugs with very high or low partition coefficients, and high melting temperatures (Bos and Meinardi, 2000). Although, applying a formulation to the skin seems simple, SC is the main barrier that causes the skin impermeability, which is the rate-limiting step for epidermal drug transport and can help achieve therapeutic drug concentration at the target site with low adverse effects (Donnelly et al., 2005; Calin et al., 2013). Passive skin-to-skin diffusion of compounds occurs during percutaneous absorption (Kleinpenning et al., 2006). The process of permeation can entail dispersion through shunts, notably those provided by the very widely dispersed hair follicles and eccrine glands, or transit through

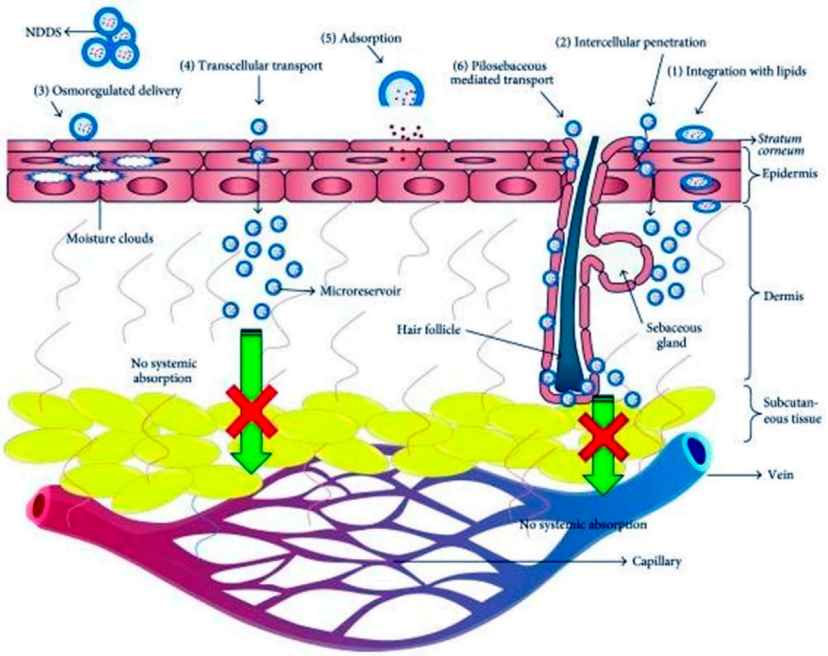

FIGURE 2
Mechanistic pathways to deliver drugs through novel carriers.

the epidermis itself that collectively called transepidermal absorption or transfollicular or shunt pathway (Benson and Watkinson, 2012). Drug molecules may enter the skin through sweat ducts or hair follicles during the initial transitory diffusion stage before being absorbed through the follicular epithelium and sebaceous glands (Kleesz et al., 2012). The predominant channel for topical penetration becomes diffusion *via* the intact stratum corneum, once a steady state has been established. Another restriction is the potential for allergic reactions to the medications or excipients used in the formulations. Figure 1 illustrates the difficulties in drug administration through cutaneous route. Figure 2 shows the mechanistic pathways for drug delivery using new carriers. New delivery systems interface with skin elements to efficiently distribute the loaded medicine to the different skin layers.

These carriers can deliver the topically applied actives to different skin layers depending on their compositional characteristics (Barua and Mitragotri, 2014). Dissolution within and release from the formulation are generally acquired two steps process by which a medicinal substance is released from a topical formulation and transported to the systemic circulation dividing up into the (SC) diffusion primarily by the lipidic intercellular route through the SC by partitioning into the viable aqueous epidermis.

The viable epidermis gets diffused into the upper dermis, papillary dermal layer and finally uptaken by microcirculation.

Summary on melanoma

Basal cell carcinoma (BCC), cutaneous malignant melanoma, and squamous cell carcinoma (SCC) are the three types of skin cancer (Zhang et al., 2012). In contrast to melanoma skin cancer, an aggressive form and one of the most chemotherapy-resistant malignancies, BCC and SCC are categorized as nonmelanoma skin cancers (Apalla et al., 2017). It results from repeated exposure to sunlight and is made up of pigment-producing cells called melanocytes, found in the deepest epidermis or basal layer (Stockfleth et al., 2008; Calzavara-Pinton et al., 2015). Since most melanocytes are found on the skin, melanoma tends to develop there; however, it can also affect the eyes and, less frequently, the mucous membranes of the nasal passages, mouth, pharyngeal cavity, vagina, and anal cavity. Melanoma, which makes up only 5% of all skin malignancies, is responsible for over 80% of all deaths brought on by skin cancer. Five phases are used to classify melanoma (Schulman and Fisher, 2009). Stage I is in the dermis without ulceration, while Stage 0 is non-invasive and visible in the epidermis. Melanoma in stage II is ulcerative and invades deeper dermal layers. Stages III and IV signify metastases to various bodily locations. Early melanomas can develop slowly and only appear on the skin's surface for several months or even years.

When melanoma is identified and treated before it spreads to the lymph nodes, the 5-year survival rate is 99 percent (Armstrong and Kricker, 1994; Amini et al., 2010). It can be

fatal if it spreads to other body parts unchecked. Malignant melanoma is brought on by melanin-containing melanocytes found in the basal epidermal layer. Most melanomas start in or close to an already present mole or skin-colored area. Normal moles are uniformly colored, have clearly defined edges, and have a round or oval shape, but melanomas look erratic and are typically larger than normal moles. Early melanomas can develop slowly, and only appear on the skin's surface for several months or even years. Later, lesions thicken and penetrate the skin further. After then, melanoma has a propensity to grow quickly, invade lymph nodes, and spread *via* the bloodstream to the liver, lungs, bones, and brain. Men can acquire melanomas on their chest and back, while women are more likely to develop them on their legs, face, and neck (MacLennan et al., 1992). There are four different forms of melanoma exists in the biological science. The most prevalent kind, superficial spreading melanoma, affects the trunk and limbs. Lentigo maligna melanoma affects elderly adults. A rare variant of lentiginous melanoma that affects the palms of the hands or soles of the feet and is not related to Sun exposure is acral lentiginous melanoma. The rate-regulating membrane of the skin is called the stratum corneum (SC), composed of dead keratinized cells in a lipid matrix with hair follicles and sweat glands intermingled permeation. Drug penetration is hampered by several major factors, including hyperkeratinization of the stratum corneum (SC) brought on by Sun exposure (Diepgen and Mahler, 2002).

New topical formulations required for the treatment of melanoma

Since, melanoma is a progressive condition, chemopreventive therapies are appropriate. This can be accomplished by concentrating on the molecular pathways and processes involved in the disease's progression (R Khan et al., 2015). Chemopreventive treatments for melanoma fall into three categories: those that prevent the development of the disease, secondly, those that stop premalignant lesions from becoming malignant, and thirdly, those that stop recurrence after primary melanomas have been successfully treated (Safwat et al., 2018). Immunotherapy, targeted therapy, and chemotherapy is given as injectables, such as ipilimumab and oral forms of vemurafenib are all approved treatments for melanoma. Numerous novel anticancer medicines have unfavourable pharmacokinetics, lack stability, have limited water solubility, and are irritating by nature. Conventional nanoformulations have several unfavourable impacts, including sub therapeutic effectiveness, dose-limiting side effects, and low patient quality of life. The inability to identify the protein targets that cause the disease, the absence of successful combination therapy and the inability to get active ingredients into tumor cells specifically are reasons for the ineffective treatment of melanoma. Studies for the chemoprevention of melanoma by medicines that prevent, stop, or reverse its development are being investigated because of the information that is currently known regarding the biology of pigment cells and the neoplastic changes found in melanoma. Sporn et al. first suggested the concept of chemoprevention, which is the use of synthetic or natural medicines to reverse, inhibit, or prevent molecular and histological premalignant lesions that develop with the advancement of invasive cancer (Mukherji et al., 1995). Researchers are looking into melanoma chemoprevention studies using substances that can stop, slow down, or even reverse the disease's progression. Cancerogenesis can be prevented sensibly and cost-effectively by preventing tumor initiation, development, and advancement. Topical delivery with encapsulated actives can be a promising strategy for melanoma chemoprevention because these formulations can protect anticancer drugs from deterioration, allow for increased tumor penetration, improve drug stability, and lessen skin irritation by preventing the drug from coming into direct contact with the skin's surface. Tyrosinase activity can be inhibited, which is advantageous because it promotes melanin overproduction in tissues and the serum.

A topical product for the treatment of melanoma has not yet received approval. The approved topical therapies for basal cell and squamous cell carcinoma are creams and solutions containing 2% and 5 % imiquimod, and 2% and 5% 5-fluorouracil (5-FU), respectively. The findings of *in vivo* testing of topically applied 1% cream of apomine for melanoma chemoprevention showed a significant decrease in tumor incidence (Kuehl et al., 2009). Additionally, apomine has been shown to prevent melanoma growth by 55%, and a topical formulation is currently undergoing clinical testing (Chinembiri et al., 2015). According to reports, actinic keratosis has been linked to melanoma when left untreated (Lebwohl et al., 2013). Precancerous actinic keratosis can be treated with commercially available topical formulations of diclofenac, 5-fluorouracil, ingenol mebutate, and imiquimod (Cornwell and Barry, 1993). Actinic keratosis can also be treated with photodynamic therapy using topical aminolevulinic acid, which works by having a photosensitizer convert a medication or a prodrug intracellularly. The process hurts because aminolevulinic acid makes the skin extremely sensitive (Alvi et al., 2011; Chinembiri et al., 2015). Resiquimod is a more recent medication that is 10–100 times more effective than imiquimod and regulates the immune system when given topically (Alvi et al., 2011). There is an increasing need for additional novel topical formulations that can address the severe side effects of conventional topical products like solutions and creams used to treat actinic keratosis, such as skin irritation, burning, redness, dryness, pain, swelling, and tenderness at the site of application (Kumar and Sinha, 2016). The inability to identify the protein targets that cause the disease, the absence of successful combination therapy and the inability to get active ingredients into tumor cells specifically are the collective reasons for the

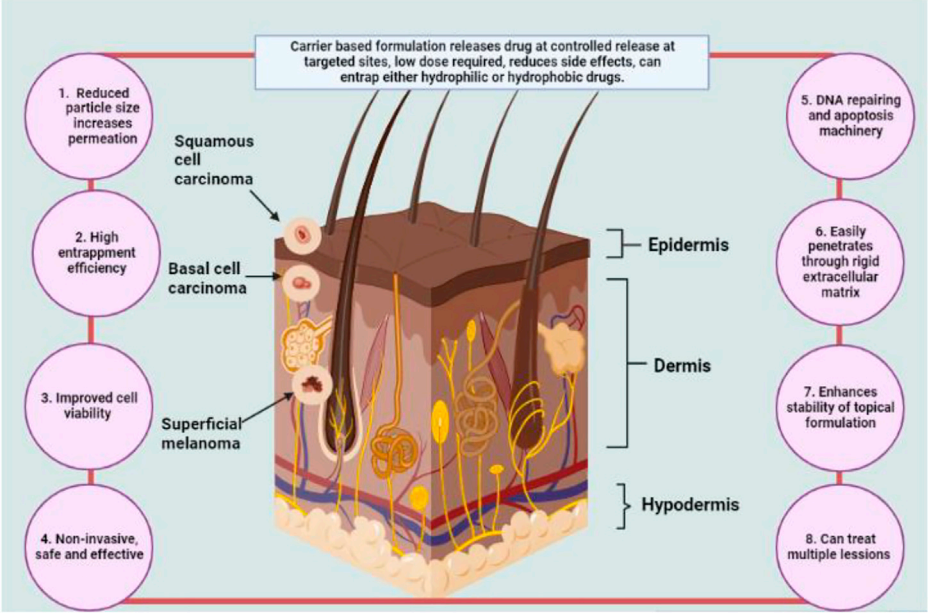

FIGURE 3
Possible therapeutic effects in skin after loading to actives into topical nanocarriers.

ineffective treatment of melanoma (Boakye et al., 2016). Additionally, Sun exposure-induced stratum corneum hyperkeratinization is a significant component that prevents drugs from penetrating the skin (Palmer and DeLouise, 2016).

Encapsulated drug-loaded topical formulations to treat melanoma early on and offer chemoprevention are promising strategies (Anselmo and Mitragotri, 2016). Additionally, as high levels of tyrosinase in the serum and tissues promote melanin overproduction reducing tyrosinase activity may help prevent melanoma (Bos and Meinardi, 2000; Fahradyan et al., 2017). Drug-loaded nanosized formulations have several benefits, including the capacity to boost tumor penetration, improve drug stability and lessen skin irritation by preventing direct drug contact with the skin's surface. Figure 3 describes possibly changes in skin physiochemical properties after incorporating actives into topical nanocarriers.

Numerous biophysical methods have been employed to pinpoint the principal skin penetration route (Ishii, 2017). Using methyl nicotinate as a probe, Albery and Hadgraft reported that, the area around the corneocytes, experienced intercellular penetration (Guy and Hadgraft, 1980; Hadgraft, 2004). Three pathways exist for substances to enter the skin, i.e., first the intercellular pathway (between the corneocyte), second the intracellular pathway (through cells and the lipids separating them) and the third pathway worked through skin appendages like hair follicles and sweat glands (Shah et al., 2007). Iontophoresis, sonophoresis, and electroporation are a few examples of physical enhancers that can be used and chemical enhancers like terpenes, flavonoids are utilized to increase bioavailability. Electricity is used in iontophoresis and electroporation to increase penetration. Using a greater voltage during electroporation, the stratum corneum lipid bilayer might have its structural integrity disturbed. When compared to passive delivery, this method can boost the transport of actives through the skin by 60 times. Sonophoresis, on the other hand, uses ultrasound to create tiny cavitations in the skin to help drugs diffuse. However, due to their high cost, adsorption of these physical penetration procedures uses is restricted. Applying chemical penetration enhancers that temporarily disrupt SC bilayers and restore them to function for enhanced skin penetration is quite simple. As a result of better partitioning between the formulation and (SC), this phenomenon increases actives penetration into tumors cells quite rapidly. Penetration promoters include substances like oleic acid, azone, ethanol, propylene glycol, transcutol, monoolein and dimethylsulfoxide (DMSO). DMSO and monoolein are the most widely used and researched chemical enhancers for topical chemotherapy. Compared to DMSO, monoolein is less harmful and biodegradable. Following are the few instances that support the importance of newer excipients in novel formulations in delivering enhanced efficacy compared to conventional systems.

According to published research, ceramides resemble SC lipids they are inactive components in innovative microemulsion formulations that facilitate medication administration into skin compartments and enable deeper

TABLE 1 Advantages and limitation of different types of nanocarriers for topical delivery.

Nanocarrier	Features	Advantages	Limitations
Nanoemulsions	Nanoemulsions (NEs) are oil in water dispersions with an average diameter of 20–200 nm which are thermodynamically stable	Having high surface area and free energy with the potential of effective dermal delivery. Low-toxicity and low-irritancy	Disruption of stratum corneum lipids integrity due to the presence of permeation enhancers Need for large amounts of surfactants and/or energy for nanoemulsion preparation
Liposomes	Liposomes consist of one or more lipid bilayers with an embedded aqueous phase in their structure and form a vesicle. Liposomes usually comprise phospholipids and cholesterol	High drug deposition in skin layers and prevention of systemic drug absorption by acting as a rate-limiting barrier Non-toxic and non-invasive nature	• Stability problems • Difficulties with scale-up process • Variable purity of phospholipids • High cost
Transferosomes	Transferosomes have an aqueous core surrounded by a phospholipid bilayer and an edge activator	Ethanol is commonly used as a solvent activator during the formulation of transferosome	Difficulty in loading hydrophobic drug Formulation are expensive
Ethosomes	These are elastic vesicles composed of phospholipids, cholesterol, water, and large amounts of ethanol	Ethanol helps in improving the solubility of lipophilic drugs and aids in disrupting the SC ethosomes were more stable and achieved superior antifungal activity with controlled-release attributes in the clinic	Predisposition to oxidative degradation. Purity of natural phospholipid formulation may be expensive
Niosomes	Niosomes are nonionic surfactant vesicular drug delivery systems that are introduced as an alternative for conventional liposome	Higher chemical stability. Reduced systemic drug absorption and related adverse reactions	Lower trans-dermal permeation in comparison to liposomes. Difficulties in large-scale production
Solid lipid nanoparticles	Solid lipid nanoparticles (SLNs) are the first generation of lipid-based nanocarriers formed from solid lipids and emulsifiers SLNs have size ranges between 40 and 1,000 nm	• Occlusive properties • Biocompatibility and skin tolerability • Reducing skin irritation • Sustained drug release possibility	• Limited drug encapsulation • Low Physical stability • Initial burst drug release followed by controlled release • Limitation in transdermal drug delivery
Polymeric nanoparticles	Polymeric nanoparticles are colloidal nanocarriers with an average diameter of less than 1,000 nm	• Potential of gene delivery • Active pharmaceuticals stabilization • The potential of macromolecules delivery	• Not suitable for trans-dermal purposes • The necessity of purification processes for natural polymeric nanoparticles 89

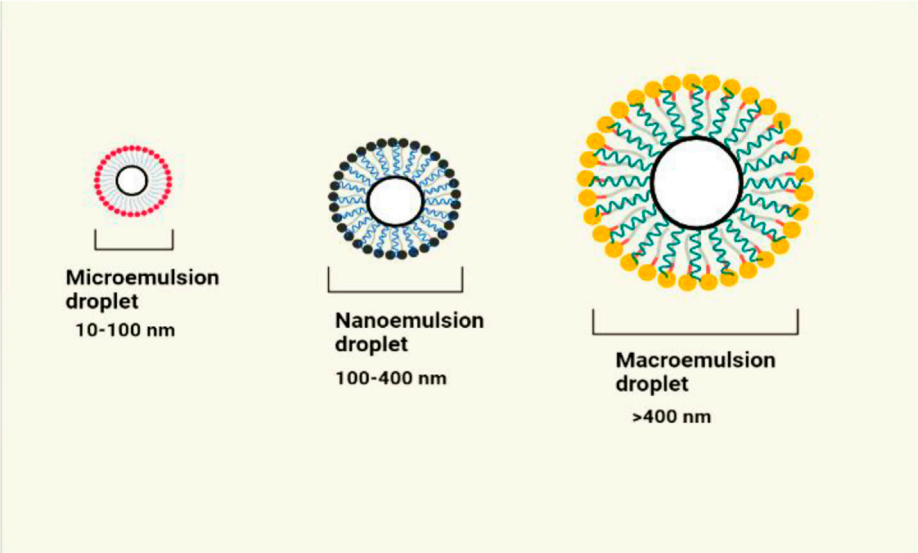

FIGURE 4
Depiction of structural properties of emulsion based systems.

penetration than a traditional hydrophilic cream. Similarly, phospholipid-based liposomes containing cholesterol, palmitic acid, ceramides, and cholesterol sulphatesmight show higher drug accumulation in the epidermis and dermis. Additionally, due to the flexibility of the vesicles and the changed membranes, modified liposomes containing oleic acid demonstrate high deposition in the skin and boost the diffusion coefficient of a medication. Published research supports drug delivery methods based on nanotechnologies, such as polymeric and lipidic nanoparticles, nanoemulsions, dendrimers, and liposomes, to improve medication penetration through the skin. Encapsulated 5-fluorouracil and doxorubicin are two examples of the formulations that reduced toxicity, avoided the reticuloendothelial system, and improved tumor uptake. The compiled advantages and disadvantages of topical nanocarriers are enlisted in Table 1.

Suggested methods for topical delivery of drugs

Microemulsions and nanoemulsion based systems

Microemulsions (MEs) are clear, colloidal, isotropic, and thermodynamically stable liquid dispersions of oil and water (Figure 4) (Subramanian et al., 2004). Surfactants and co-surfactants are used to create stable liquid dispersions of water and oil, known as MEs and NEs. Nonionic surfactants are preferred because of their cutaneous tolerability and balanced hydrophilic-lipophilic properties. The most widely used emulsifiers and co-emulsifiers are naturally occurring or modified lecithin, block copolymers that contain polyethylene oxide (PEO), castor oil derivatives with PEG conjugation (Cremophore EL), glycerides, and positively charged lipids for skin delivery. A multiphase system made up of water, oil, a surfactant, and a cosurfactant like alcohol that primarily serves as a cosolvent and demonstrates transparency by supplying globule size below 140 nm was the first to be referred to as a ME by Schulman in 1959 (Grampurohit et al., 2011). MEs provide various benefits for topical distribution, including the capacity to dissolve lipophilic medicines effectively, improved skin permeability, and a longer release of both lipophilic and hydrophilic medications for skin melanoma.

According to reports, oleic acid MEs exhibit a greater capacity for solubilizing drugs and a greater concentration of drug retention in the skin. MEs have a high capacity for drug loading. Because they have a high capacity for solubilizing drugs, they can get through the stratum corneum barrier and partition the medication into the skin. Polyoxyl castor oil derivatives like Cremophor EL and Cremophor RH 40, polysorbates, sorbitan monooleate, and different polyglycolyzed glycerides like Labrafils and Labrasol are nonionic surfactants used in topical formulations (Subramanian et al., 2005). According to conventional insight, surfactants with low HLB values of 3-6 are employed to create w/o ME, whereas those with high HLB values of 8–18 are favoured to create o/w ME for skin application. Co-surfactants are necessary for generating microemulsions when surfactants with HLB larger than 20 are % (Sharma et al., 2021). Conversion of microemulsion to emulgel favors improved topical permeation, better skin retention and deposition and less drug irritation. Moreover, ME based emulgel systems acquires improved drug loading capacity which further increases targeatibility and improved therapeutic effect. There are number of scientific reports published which potentiates the ME based emulgels for skin melanoma.

To combat the poor solubility and instability of a prodrug called temozolomide acid hexyl ester (TMZA-HE), created microemulsions of the substance. Oleic acid or isopropyl myristate was used to create microemulsions, and tocopheryl (vitamin E) polyethylene glycol 1,000 succinate and isopropyl alcohol were used as the co-surfactant and surfactant, respectively. In all systems, the microstructures were examined using freeze-fracture electron microscopy. In permeation trials, isopropyl myristate microemulsion showed enhanced drug permeability through rat skin, leading to decreased drug retention in the skin. In contrast, oleic acid microemulsion showed higher solubilizing capacity and higher concentrations of drug retention in the skin. Tagne et al. investigated dacarbazine nanoemulsions and their topical application in a nude mouse xenograft model of a human melanoma cell line. The prepared nanoemulsion's mean particle size was 131 nm, showing less negative charge, suggesting improved skin permeability. Comparing the formulation to the medication suspension, the Formulation showed a tenfold reduction in tumor growth. This may be explained by (a) the smaller particle size of the nanoemulsion (111 nm) compared to the suspension (6,000 nm) and (b) the smaller zeta potential of the nanoemulsion (−3.2 against −89.1 mV, respectively). Leflunomide (LFD) nanoemulgel's effectiveness for targeted therapy of skin damaged by melanoma was validated by Pund et al. permeation in *ex vivo* demonstrated a considerable improvement in flux, apparent permeability coefficient, steady-state diffusion coefficient, and drug deposition through rat abdomen skin. LFD nanoemulgel demonstrated increased therapeutic responses in melanoma A375 and SK-MEL-2 cell lines when tested *in vitro*. The soy isoflavone genistein, which is useful in treating a variety of cancers, was examined by Chen and Babu concerning several formulation parameters impacting physical *and chemical stability. Different oil phases (Labrafac WL1349, Ethyl Oleate, and Soybean Oil), surfactants (Cremophor EL,

TABLE 2 Summary of reported specialized emulsion systems for skin cancer.

Carrier/Drug	Formulation components	Size nm	Outcome of study	References
Leflunomide	Capryol90, cremophor EL, Transcutol HP, Pluronic F127	123.7	*In vitro* cytotoxicity of Leflunomide nano emulgel in human HaCaT, melanoma A375 and SK-MEL-2 cell lines showed enhanced therapeutic response	Pund et al. (2015)
5-FU Nanoemulsion	5-FU, propylene glycol monolaurate, Methanol, isopropyl alcohol, gattefose	68.2–124.3	5-FU in optimized nanoemulsion is much more productive than free 5-FU	Shakeel et al. (2015)
Nanoemulsion loaded with zinc phthalocyanine	Zn- phthalocyanine, phosphate buffer, saline solution, polaxamer 188, Soya phospholipid, HPLC grade DMSO	144–255	Magnetic nanoemulsion increases the drug release on the deeper skin layers when compared with a classical formulation in the absence of magnetic particles	Primo et al. (2008)
Andrographolide-loaded nanoemulsion	Andrographolide, fetal bovine serum, phosphate buffer saline, dimethyl sulphoxide, propylene glycol, soya lecithin	176.6 ± 1.8	Op-AG-NE could reduce melanin index and heal UVB irradiation exposed skin	Asasutjarit et al. (2021)
Apigenin nanoemulsion	Apigenin, tamurind gum, castor oil, olive oil, cotton seed oil, ground nut oil	138.31	The carbopol-based nanoemulsion gel formulation of apigenin possesses better penetrability across goat skin than the commercialized formulation	Jangdey et al. (2017a)
Dacarbazine nanoemulsion	Dacarbazine, ethanol, soyabean oil, polysorbate -80, HPLC grade water	131	Better stability of the drug (dacarbazine) in nanoemulsion as compared to suspension	Tagne et al. (2008)
Acai oil-based emulsion	Tween -80, acai oil, nanoure water		Acai oil in nanoemulsion was an effective photosensitizer, representing a promising source of new photosensitizing molecules for PDT treatment of melanoma	Monge-Fuentes et al. (2017)
Daidzein nanoemulsion	Daidzein, ethyl oleate, tween -80, lipoid s-100, dimethyl sulfoxide, sodium dodecyl sulfate, isopropyl alcohol	191.48 ± 5.26	It has antioxidant, and anti-inflammatory activities and also inhibits the growth of cancer cells	Kaplan et al. (2019)
Betulin nanoemulsion	Betulin, flax seed oil, α–Linolenic acid, phosphatidylcholine, dimethyl sulphoxide	—	The optimized betulin-loaded NE formulation demonstrated higher cytotoxicity than placebo liposome and BRC suspension ($p < 0.05$)	Falamas et al. (2018)
Temozolomide acid hexyl ester	Oleic acid, isopropyl myristate, tocopheryl polyethylene glycol 1,000 succinate, isopropyl alcohol	—	Isopropyl myristate ME exhibited increased permeation of drug through rat skin resulting in less drug retention in the skin, while oleic acid ME demonstrated higher solubilizing ability and a higher concentration of drug retention within the skin	Liu and Zhang (2010), Sigmundsdottir (2010)

Poloxamer188, Lecithin, and Solutol HS-15), and co-surfactants were used to create ternary phase diagrams (ethanol and propanediol). The Formulation showed the maximum cytotoxicity toward the B16BL6 melanoma cell line67 and exceptional physical and chemical stability. A list of documented specialized emulsion systems for cutaneous usage in the treatment of melanoma is presented in Table 2.

Thermosensitive gel spray formulation

At 200°C, thermosensitive gel spray formulations behave Newtonian (like a liquid), and at 37°C, they behave non-Newtonian (like a gel). Poloxamer is the thermo-responsive polymer that is utilized the most frequently. Poloxamers, which come in different grades, are synthetic triblock copolymers consisting of poly (ethylene oxide), poly (propylene oxide), and poly (ethylene oxide). They display great compatibility with other excipients used in topical preparations and are typically considered non-toxic. Reported research has shown that these systems can increase therapeutic efficacy, prolonged drug release, and high drug retention at the site of action. The gel can be administered as a liquid formulation conveniently sprays across larger afflicted areas of skin thanks to its thermo-responsive nature. Due to their ease of administration, aesthetic appeal, optimal drug release characteristics, and superior physicochemical stability, these gels may provide various advantages over conventional gels for skin melanoma. These gels comprises of several polymers like Poloxamer 407,

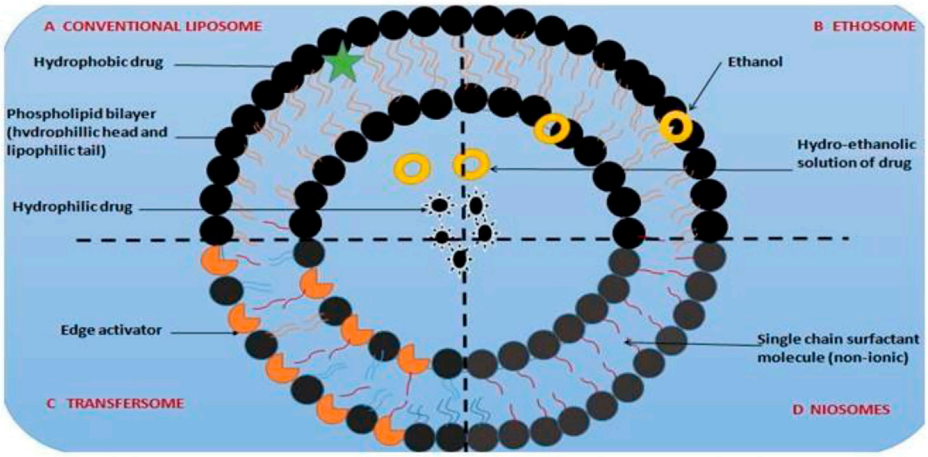

FIGURE 5
Schematic representation of vesicular drug delivery systems.

Chitin which showed controllable size and high loading capacity. Thermal gelation properties allow to form a depor at the target skin cancer cells and able to prolong the pharmacological action. Katas et al. developed topical thermosensitive gel formulation containing DsiRNA and showed reduced size of 146 nm with excellent stability. Moreover, the optimized formulation observed with improved cell viability of 88%–93%, as compared to pure gene.

Vesicular delivery systems

Vesicular drug delivery systems consist of one or more concentric bilayers and are highly organized assemblies. These vesicles are created when amphiphilic building components self-assemble in the presence of water (Tamilvanan et al., 2008; Vanniasinghe et al., 2009). These systems can localize the medication to the site of action, reducing the concentration of the drug at other places in the body, making them effective for targeted drug delivery for skin melanoma (Mezei and Gulasekharam, 1980). Since, conventional topical solution and cream formulations containing 5-FU have been sed to treat several skin cancers, 5-FU has attracted the interest of numerous researchers in developing abundant topical innovative formulations (Kirjavainen et al., 1996). According to studies, vesiculation of 5-FU enhances topical administration by achieving smooth and spherical nanovesicles (Maghraby et al., 2006). Compared to other nonvesiculized dosage forms, the optimized spherical nanovesivles provided decreased cytotoxicty by reducing the expression of biomarkers by achieving improved skin permeability and retention. Some of the most popularly studied vesicular systems include liposomes, transfersomes, ethosomes, and niosomes are examples of vesicular systems for topical delivery (Tabbakhian et al., 2006). A schematic illustration of vesicular systems is shown in Figure 5.

Liposomes

An aqueous core is encircled by a hydrophobic lipid bilayer membrane that contains phospholipids and cholesterol in liposomes, which are biocompatible and biodegradable vesicles (Trapasso et al., 2009; Cui et al., 2016). They allow for better active ingredient absorption through the skin. Although they are simple to prepare, they are prone to structural failure and oxidation (Sinico et al., 2005). The design, content, size, and drug release properties of liposomes are flexible. According to published clinical research, liposomal anticancer medication has less toxicity and better tolerance. For *in vitro* skin permeation and *in vivo* antineoplastic effect (Hsueh et al., 1995). Liposomes are versatile lipidic carriers observed with high cellular uptake, escaping reticuloendothelial system and provide enhanced anti-cancer activity, as evident from numerous case studies. In recent decade, the potential of liposomes in improving anti-cancer activity against skin was deeply studied. The potential components of liposomes imparts greater skin retention, selective effect on the potential biomarkers and allows easy pay load against melanoma cells. Recent literature findings displayed curcumin-loaded liposomal formulations comprising soybean phospholipids, egg yolk phospholipids, and hydrogenated soybean phospholipids. Curcumin-loaded soybean phospholipids demonstrated the best penetration and has largest ability to suppress the proliferation of B16BL6 melanoma cells, according to a comparative *in vitro* skin penetration investigation. Liposomal and 5-ALA

formulations demonstrated that the DPPC liposomal formulation had improved protoporphyrin accumulation in tumor tissue, which aided in photodynamic cell killing and better skin penetration ability [Ref].

Transfersomes

Transfersomes are extremely flexible, self-assembled, and ultra deformable vesicles with an aqueous core and a complex lipid bilayer on each side (Cevc, 1996). These vesicles are self-regulating and self-optimizing because of their structure and composition (Honeywell-Nguyen and Bouwstra, 2005). Transfersomes can spontaneously penetrate the SC because they can efficiently cross various transport barriers (Boinpally et al., 2003). They have better efficacy in sustained release applications for topical medication administration and are more elastic than liposomes. A study comparing several vesicular formulations found that 5-FU-loaded transfersomes had a more lethal effect on cancer cell types than liposomes and niosomes (Cevc and Blume, 2001). Characterization of particle size and shape, zeta potential, viscosity, entrapment effectiveness, deformability, *in vitro* drug release, kinetics, and drug retention (Trotta et al., 2002; Elsayed et al., 2006). The transfersome was created using the solvent evaporation, whereas the reverse-phase evaporation method was employed to create the liposomes and niosomes (Touitou et al., 2000; Maghraby et al., 2001).

Ethosomes

Ethosomes are stretchy phospholipid-based vesicles that contain 20–45 percent ethanol. The polar head group area of the lipid molecules can interact with ethanol, a known permeation enhancer, to lower the melting point of the SC lipid and increase lipid fluidity and cell membrane permeability (Touitou et al., 2000). The additional ethanol makes the vesicular membranes extremely flexible, which enables the elastic vesicles to force their way through the pores (Liu and Hu, 2007). According to published research, ethosomal systems are more effective than traditional liposomes or hydro-alcoholic solutions at delivering chemicals through the skin in quantity and depth. The ability of 5-aminolevulinic acid (ALA)-containing ethosomes to boost skin formation of protoporphyrin IX (PpIX) in contrast to liposome was investigated (Barry, 2001). Confocal laser scanning microscopy was used to detect PpIX in live animal skin (CLSM).

In comparison to ALA in an aqueous solution, the enhancements of all the formulations ranged from 11 to 15 fold in terms of PpIX intensity. Additionally, ethosomes had better penetrating power than liposomes (Godin and Touitou, 2004). A 5-fluorouracil (5-FU) ethosomal formulation that Puri and Jain created was the subject of a comparison investigation (Paolino et al., 2005). It was possible to achieve a six-fold increase in drug deposition, decreased skin irritancy, and improved anti-tumor activity.

Niosomes

Niosomes are composed of nonionic surfactant vesicles and are similar to liposomes in structure (Keservani et al., 2010). These formulations are becoming more and more significant for cutaneous drug administration because they have traits such as improved drug penetration, prolonged drug release, increased drug stability, and the capacity to transport both hydrophilic and lipophilic drugs (Kumar and Rao, 2012; Marianecci et al., 2014; Dwivedi et al., 2018). Cholesterol, Span 80, and Bola-containing 5-FU niosomes were made and tested (Marianecci et al., 2014). In SKMEL-28 (human melanoma) and HaCaT (nonmelanoma skin cancer) cell lines, 5-FU-loaded bola-niosomes were reported to demonstrate favourable cytotoxic activity and four to eight fold increases in drug penetration compared to the free drug (Dwivedi et al., 2018). Furthermore, effectiveness of artemisinin in nanovesicular niosomes and solid lipid nanoparticles against human melanoma A-375 cells and human keratinocytes (HaCaT)as studied. The created formulations showed very low toxicity to healthy skin cells while exhibiting extremely selective cytotoxicity towards melanoma cells (Hamishehkar et al., 2013). Table 3 is a compilation of published anti-melanoma vesicular dermal formulations.

Microparticulate drug delivery systems

Major particulate drug delivery systems for topical application are represented by polymeric microspheres and lipid-based formulations like solid lipid nanoparticles and nano lipid carriers. Microcapsules, microspheres, and micro sponges are microparticulate systems of solid polymeric particles with sizes ranging from 0.1 to 1,000 nm. Numerous formulations of polymeric nanoparticulate materials have been created employing polymers, including polycaprolactone, poly-dl-lactic acid, and poly-lactic-co-glycolic acid (PCL). According to published research, polymeric and solid lipid nanoparticles facilitate prolonged drug release by favoring drug accumulation in the skin for several hours and preventing drug degdradation which prolonging the effect against melanoma. For such formulations to be optimized, it is crucial to characterize elements such as the nanoparticle's mean diameter, flexibility, and surface charge. Solid lipid nanoparticles are more stable, have a longer drug release time, are simpler to sterilize, and can be produced in larger quantities than liposomes. Solid lipid nanoparticles have a significant advantage over polymeric nanoparticles in that organic solvents are not necessary for

TABLE 3 Literature review of vesicular dermal formulations for skin cancer.

Carrier/Drug	Formulation components	Size nm	EE%	Outcome of study	References no.
Liposomes/Curcumin	Soybean phospholipid, egg yolk phospholipid, hydrogenated Soybean phospholipid	82.37 ± 2.19	82.32 ± 3.91	Soybean phospholipids of curcumin exhibited the best inhibition of growth of B16 BL6 melanoma cells	Alinezhad et al. (2017)
Transfersomes, liposomes, and niosomes/5-fluorouracil	Soya phosphatidylcholine, cholesterol, sodium deoxycholate, Span 80, carbopol 941	153.2 ± 10.3	82.4 ± 4.8	Transfersomes of 5-FU exhibited maximum cytotoxicity when compared to 5-FU liposomes and niosomes	Alvi et al. (2011)
DPPC Liposomes and ethosomes/5-Aminolevulinic acid (5- ALA)	1,2-dipalmitoyl-sn glycerol-3-phosphocholine (DPPC), cholesterol, phosphatidyl ethanolamine, sodium stearate	89.80 ± 2.40; 126.4 ± 2.8	66.42 ± 0.34	DPPC liposomes and ethosomes of 5–ALA exhibited increased skin penetration facilitating photodynamic therapy	Fukuda et al. (1992)
Plumbagin-loaded glycerosome gel	Glycerol, rhodamin B, cholesterol, phospholipid 90G, plumbagin	119.20 ± 15.67	76.42 ± 9.9	The novel PLM containing GM-loaded gels shows high EE and antioxidant effects in treating skin cancer. They exhibited sustained release and give excellent flux across various stratum of the cutaneous layer	Shadab et al. (2021)
Curcumin loaded ethosome	10% soya, Lecithin, 4.5% ethanol, 10% cholesterol	—	81.2 ± 3.12	The optimized formulation holds the greater drug disposition on the skin i.e. >60% in 12 h for the better curability of the melanoma	Li et al. (2021)
Apigenin loaded transferosome	Apigenin, tween 80, rhodamine, phospholipid	35.4	84.24	The %EE of optimized formulation increased significantly with increasing surfactant concentration, as compared to pure drug	Jangdey et al. (2017b)
Brucin loaded transliposome	Brucine, cholesterol, trietnolamine, carbapol 940, PEG 400	136.20 ± 2.87	86.01 ± 1.27	BRC-TL gel shows better penetration and has higher cytotoxicity as compared to suspension	Alhakamy et al. (2021)
Carvedilol-loaded nano transferosome	Carvedilol, tween -80, sodium cholate, DSPC, α–Phosphatidylcholine	115.6 ± 8.7	93.7 ± 5.1	F18 was released through the dialysis membrane and penetrated the skin of the pig ear at a slower rate than the free drug did, but it nonetheless equally deposited the drug in the skin's dermis and epidermis	Chen et al. (2020)
Liposomes/Artemisone	Phosphatidylcholine, polyvinyl alcohol, span 60, cholesterol	295 ± 1	79 ± 5	In comparison to free drugs, nanovesicles of artemisone inhibited melanoma cells	Van Zyl et al. (2019)
Paclitaxel loaded transferosome	Paclitaxel, phospatidyl choline, ethanol, chloroform, Span 80	200 ± 2.1	68.2 ± 1.5	The steady-state flux (Jss), permeability coefficient (Kp), and enhancement ratio were all significantly higher in the SLN-loaded gel formulation. The results of the histopathological investigation unambiguously demonstrate the effectiveness of SLN-F3 3G in treating skin cancer	Raahulan et al. (2010)
Nobiletin-loaded vesicular systems	Nobiletin soybean phosphatidylcholine transcutol- P sodium acetate	126.70 ± 11.80	93.50 ± 3.60	Nobiletin-loaded composite PEVs displayed the lowest IC50 value, thus was selected for the *in vivo* study, where it restored skin condition in DMBA induced skin carcinogenesis mice	Bayoumi et al. (2021)
Colloidal(-) epigallocatechin-3-gallate vesicular systems	Epikuron 200 (soybean lecithin containing 92% PC) (-)-epigallocatechin-3-gallate (EGCG), tween 80, polyethylene glycol 400, acetonitrile and acetic acid (HPLC grade)	200–400	57–83	The prepared vesicles preserved the antioxidant activity of EGCG as well as its photostability as it is known to exhibit low bioavailability and liability to auto-oxidation by sunlight and air	El-Kayal et al. (2019)
Colloidal indocyanine green transferosomal system	Indocyanine green, cholesterol, soybean phosphatidylcholine PC (Epikuron 200) HEPES buffer and Sephadex G-100	123.9 ± 1.04	53.29 ± 5.04	Transfersomes were also able to sustain the release of ICG 42 h. Upon incorporation of transfersomal ICG in gel form, it was found to maintain the normal histology of mice skin post-irradiation with diode laser 820 nm. Moreover, ICG transfersomal PDT achieved 80% clearance rate for BCC patients with minimal pain reported during treatment	Fadel et al. (2017)

EE, entrapment efficiency.

their preparation which imparts green synthesis and reduced toxicity towards skin (Desai et al., 1997).

According to Levy et al., the flux and percutaneous absorption of H-labelled 5-fluorouracil from formulations containing 0.5% fluorouracil porous microspheres were 20–40 times lower than those from commercial formulation (Jorizzo et al., 2002). The study also showed that, compared to 54% of the marketed 5% product, 86%–92% of the absorbed fluorouracil from the 0.5 %t microsphere formulation was still present in the skin after 24 h. The prolonged period of activity at a concentration one-tenth that of the standard formulation is made possible by the innovative microsphere formulation's which observed with better skin retention (Zafrani et al., 2012).

Drug delivery methods utilizing lipid nanoparticles

Solid lipid particles with surfactants display the best *in vivo* tolerability, good physico-chemical stability, and prolonged drug release. Solid lipid particles are made up of isotropic lipids having FDA regulatory status which prepared in a lowe energy thermodynamically state and acquires Smicrometer size range (Gupta et al., 2013). Compared to liposomes, they have been described as lipidic drug carrier systems for topical applications that can replace polymers and enable large-scale manufacture at a relatively lower cost (Mandawgade and Patravale, 2008). Solid lipid microparticles (SLMs) have the potential for topical and transdermal medication delivery, although having received less research attention than solid lipid nanoparticles (SLNs) for skin applications (Fang et al., 2008). Several techniques, including solvent evaporation, melt dispersion, hot and cold homogenization, spray drying, and spray congealing, can be used to create SLMs (Štecová et al., 2007).

Since of their small size and intimate contact with the stratum corneum, lipid nanoparticles are ideal for dermal administration because they increase the amount of medication absorbed through the skin. An effective and safe substitute for colloidal emulsions, liposomes, and polymeric nanoparticles is the family of lipophilic particle-based colloidal drug delivery systems that include solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Solid lipid nanoparticles are more stable, have a longer drug release time, are simpler to sterilize, and can be produced in larger quantities than liposomes.

NLCs are made by combining solid and liquid lipids, whereas SLNs use solid lipids in place of the oils in an oil/water emulsion. Because solid lipid has reduced drug mobility. Thus, sustained medication release can enhanced by using nanoparticles. Since NLCs have a matrix with lower water content, they can improve drug loading, stability, bioavailability, and targeted administration in addition to reducing side effects, which is the main disadvantage of SLNs. Alkylating agent dacarbazine is utilized as a preferred medication for treating melanoma skin cancer. Cream with dacarbazine-loaded stearic acid nanostructured nanoparticles was examined by Hafeez and Kazmi (2017) According to the study, encapsulation efficiency is around 70%, and the spherical particles can penetrate cancer cells because they are between 10 and 20 nm in size. A higher rate of drug release than drug suspension was discovered, demonstrating the possibility of efficient melanoma treatment. Lecithin and poloxamer-188 were used to create highly penetrating shell-enriched solid lipid nanoparticles (SLN) that contained the hydrophilic medication 5-Fluorouracil (5-FU). The creation of inverted micelles within SLN was demonstrated by using 5-FU nanogold particles as a tracer. In comparison to the free drug the SLN formulation quadrupled the mobility of 5-FU *via* a hydrophobic membrane. Resveratrol-loaded SLN and NLC particles were created by Gokce et al. (2012). Utilizing high shear homogenization with ingredients such as compritol 888ATO, miglyol, poloxamer188, and tween 80. Particle size, polydispersity index, drug entrapment effectiveness, yield, and zeta potential were the metrics used to assess the drug-loaded solid lipid nanoparticles and nano lipid carriers. Nanostructured lipid carriers were more effective at transporting resveratrol through the epidermis, according to *ex vivo* skin studies.

Geetha et al. demonstrated the requirement for sesamol-loaded solid lipid nanoparticles to treat skin cancer by observing a sizable flow through mice's skin after topical administration of sesamol. The *in vivo* skin retention and *ex vivo* skin permeation investigations supported the considerable retention in the skin with low flux across the skin after topical application of sesamol-loaded solid lipid nanoparticles in a cream base. The *in vitro* antiproliferative MTT assay and DNA fragmentation investigations in HL 60 cell lines supported the apoptotic nature of sesamol. Bharadwaj et al. used high-speed homogenization and ultrasonication techniques to generate paclitaxel solid lipid nanoparticles, which were then injected into a carbopol gel. It was discovered that the drug's *in vitro* release from solid lipid nanoparticle dispersion was biphasic, with an early burst effect and then a gradual release.

Chen et al. have investigated solid lipid nanoparticles containing podophyllotoxin for topical use. Podophyllotoxin-loaded solid lipid nanoparticles enhanced the cumulative amount of podophyllotoxin in pig skin, i.e., 3.48 times over a standard tincture, according to an *in vitro* penetration investigation. Images of the formulated formulation showed robust Podophyllotoxin's regulated release and localization in the epidermis can result in epidermal targeting. Using the solvent evaporation method,

TABLE 4 Summary of published particulate dermal delivery systems for skin cancer.

Carrier/Drug	Formulation components	Size nm	*Entrapment Efficiency%	Outcome of study	References
Solid lipid nanoparticles (SLN) and nanostructure d lipid Carriers (NLC)/ Resveratrol	Compritol 888ATO, myglyol, poloxamer188 and tween80	RSV-SLN 287.2 ± 5.1 RSV-NLC 110.5 ± 1.3	18% greater in NLC.	NLCs are more efficient in carrying resveratrol to the epidermis	Teskač and Kristl (2010)
SLN/Sesamol	Glyceryl monostearate, cetyl alcohol, egg lecithin, tween	127.9	88.21	Minimal flux of sesamol-loaded SLN's indicating significant skin retention	Geetha et al. (2015)
Paclitaxel	Stearic acid, triethanolamine, pluronicF68, egg lecithin	78.82–587.8	68.3	Histopathologycal study reveals efficacy of the paclitaxel-loaded solid lipid nanoparticles in skin cancer treatment	Bharadwaj et al. (2016)
Doxorubicin lauroyl ester	Poloxamer, precirol, stearic acid glyceryl behenate	92	86	Superior cytotoxicity with doxorubicin-loaded solid lipid nanoparticles in comparison with in a solution	Taveira et al. (2014)
Podophylloto xin	Poloxamer 188, Soybean lecithin, polysorbate 80	71.67	—	Podophyllotoxin-loaded SLN increased by 3.48 times the accumulative amount of podophyllotoxin in porcine skin compared to a conventional tincture	Meyer et al. (2013)
Itraconazole combined azole di decyl dimethyl ammonium bromide (DDAB)	Suppocire NB (c-10C-18) cetyl palmitate, Brij 98 tween 80, DDAB(di decyl dimethyl ammonium bromide)	41–47	89	DDAB-coated solid lipid nanoparticle increase 30% amount of drug release	Carbone et al. (2018)
5-fluorouracil	5-FU, lecithin, polaxamer -188, Hpmc, NaCmc chitosan, phosphate buffer	137.5–800	47.92	Diffusion of the drug-loaded SLN was double as compared to free drug	Khallaf et al. (2016)
Aluminum chloride-loaded solid lipid nanoparticle	Glyceryl behenate, Stearic acid, aluminum chloride, span-80 castor oil, polyoxyethylene -40 phthalocyanine	100–200	Approx 100	Over 24 months, the ClAlPc/SLN formulations kept their physicochemical stability without releasing the medication. ClAlPc/SLN displayed exceptional phototoxic effects *in vitro* compared to free ClAlPc	Kakkar and Kaur (2011)

Chen et al. (2006) produced cationic, anionic, and neutral tripterine-loaded NLC. They assessed how the surface charge of nano lipid carriers affected *in vitro* skin permeability. Compared to pure tripterine, cationic tripterine-loaded NLC may have improved percutaneous penetration and anti-melanoma efficacy. Taveira et al. created cationic SLNs carrying doxorubicin and investigated how these particles affected the drug's cytotoxicity and cellular absorption in B16F10 murine melanoma cells using a 32 factorial design-based model (Gratieri et al., 2017). Higher concentrations of stearic acid resulted in 97 percent entrapment efficiency. This demonstrated the interaction between the cationic charges on the molecules of doxorubicin and the negative charges in stearic acid. Doxorubicin's cytotoxicity was considerably boosted by doxorubicin encapsulation in melanoma culture cell experiments. The effectiveness of doxorubicin-loaded solid lipid nanoparticles for topical administration against melanoma was examined (Tupal et al., 2016). An MTT assay and mice induced melanoma were used to test the *in vitro* and *in vivo* cytotoxicity of the optimized formulation on murine melanoma cells (B16F10), respectively. The results showed that doxorubicin-loaded solid lipid nanoparticles performed more cytotoxically than a doxorubicin solution. According to Peira et al., doxorubicin amide and lauroyl ester are lipophilic derivatives that can be trapped in spherical nanosized particles with drug entrapment efficiencies of 80%–94% w/w. MTT and colony-forming assays were used to examine the effect on cell proliferation in four different tumor cell lines (Ribeiro et al., 2017). The development of nanoparticulate drug delivery systems using a variety of biodegradable polymers is currently the research subject. In this regard, PLGA deserves special notice for its use in drug encapsulation since it is readily biodegradable, non-toxic, and exhibits a controlled release profile of its medication. Examples of reported particle topical administration systems for treating skin cancer are shown in Table 4.

Future prospects on topical formulations for skin cancer

Numerous studies on encapsulated formulations for enhanced cutaneous medication delivery for the treatment of melanoma have been published in the past 10 years. Chinembiri et al. looked at the impact of Pheroid TM technology, a different colloidal drug delivery system, on the skin permeability and anti-melanoma effectiveness of 5-fluorouracil. With Pheroid TM formulations, statistically significant amounts of 5-fluorouracil diffused into and through the skin, resulting in improved *in vitro* skin permeation and, as a result, medication getting to the intended place. Topical delivery of therapeutic peptides, proteins, and nucleic acids utilising such delivery vehicles has advanced alongside the use of small molecule medications, even though nanoparticulate systems produced employing lipids, polymers, and surfactants have grown considerably. In addition, more recent biological techniques that use biologicals as drug carriers, such as proteins and peptides, antibodies, and nucleic acids, have developed. Framework nucleic acid (FNA) and protein- or peptide-drug conjugates are two examples of these uncommon systems. Spherical nucleic acids are a novel nucleic acid-based nanoparticulate delivery technology that has demonstrated significant promise for topical application. The core of SNAs, which can be siRNA, mRNA, or oligonucleotides, is a gold nanoparticulate core that is densely covered in nucleic acid molecules. Similar ideas of using nucleic acids for topical drug administration as well as nucleic acids acting as a carrier for other pharmaceuticals were stimulated by advancements in the field of SNAs. FNAs, which represent a 3D network of single-stranded deoxyribonucleic acid molecules to produce nanoparticulate structural characteristics that can be used for drug administration, serve as an excellent illustration. The use of cell-penetrating peptides (CPPs), which provide safer choices for drug administration over skin, is another area that has experienced tremendous expansion (so-called SPPs, i.e., skin penetrating peptides). These peptides typically share the characteristics of being cationic and having an arginine-rich structure.

Conclusion

Melanoma is a progressive carcinoma disorder and devastates livinghood worldwide. A limited number of medications and delivery vehicles are available to combat this disease. Currently, topical drug delivery is a developing and challenging field in procuring skin cancer. There is a number of carriers available, like microemulsions, solid lipid nanoparticles, and nanostructured lipid carrier that produces marked therapeutic efficacy on the skin cancer. Hence, we highlighted the important properties of carriers along with mechanistic insignts and applications in the developing field. The outcome of this article produces insights on the skin cancer mediated drug delivery system.

Author contributions

DS conceptualized the idea; DS, NG, and GG, approved the final draft and submitted to the journal.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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