

Review Article

Non-melanoma skin cancers: physio-pathology and role of lipid delivery systems in new chemotherapeutic treatments



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Abstract

Non-melanoma carcinoma has high incidence rates and has two most common subtypes: basal cell carcinoma and squamous cell carcinoma. This type of carcinoma is usually not fatal; however, it can destroy sensory organs such as the nose, ears, and lips. The treatment of these injuries using non-invasive methods is thus strongly recommended. Some treatments for non-melanoma carcinoma are already well defined, such as surgery, cryosurgery, curettage and electrode section, and radiotherapy; however, these conventional treatments cause inflammation and scarring. In the non-surgical treatment of non-melanoma carcinoma, the topical administration of chemotherapeutic drugs contributes for an effective treatment with reduced side effects. However, the penetration of anticancer drugs in the deeper layers of the skin is required. Lipid delivery systems (liposomes, solid lipid nanoparticles, nanostructured lipid carriers) have been developed to overcome epidermal barrier of the skin and to allow the drugs to reach tumor cells. These lipid nanoparticles contribute to control the release profile of the loaded chemotherapeutic drugs, maintaining their stability and increasing death of

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tumor cells. In this review, the characteristics of non-melanoma carcinoma will be discussed, describing the main existing treatments, together with the contribution of lipid delivery systems as an innovative approach to increase the effectiveness of topical therapies for non-melanoma carcinomas.

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Keywords: basal cell carcinoma, squamous cell carcinoma, liposomes, solid lipid nanoparticles, nanostructured lipid carriers

Introduction

Non-melanoma skin cancer is a current public health problem worldwide. Based on the most recent statistic report, there are annually recognized about 5.4 million cases of basal cell carcinoma and squamous cell, while in the United States among 3.3 million patients are diagnosed [1, 2]. Although most non-melanoma skin cancers are reported to be treatable and are not deadly, they can destroy facial sensory organs, such as the nose, ears, lips, and eyelids, as late diagnosis and treatment may result in the growth of tumour cells and their expansion, requiring greater excisions, resulting in a greater cosmetic impact and loss of motor functions [3, 4]. Therefore, prevention, early diagnosis, as well as the development of non-invasive treatments are in demand.

Certain characteristics, such as age, light skin and light-coloured eyes, freckles, and family history of skin cancer, are risk factors for the development of non-melanoma skin cancer [5]. Among these, excessive exposure to ultraviolet (UV) radiation is regarded as the main risk factor for the development of this type of cancer [6, 7], mainly due to the decrease in the stratospheric ozone layer, which consequently increases human exposure to unfiltered ultraviolet radiation in the ozone layer [8–10].

The intake of certain nutrients can also contribute to the development and progression of skin cancer, but may also interfere with its prevention and treatment [11–14]. This is the case of excessive intake of fats, which can increase the carcinogenic effect of UV radiation, as lipid peroxidation gives rise to unsaturated aldehydes α and β , which are mutagenic and carcinogenic [15, 16]. Another example is folate, one of the B vitamins, which at high levels may increase the risk of non-melanoma skin cancer [17]. On the other hand, vitamin A is essential for the proliferation, differentiation, and maintenance of epithelial cells and for reducing the amount of ultraviolet radiation that reaches the strata below the epidermis, by increasing its thickness [18]. Retinoids thus contribute to normal cell differentiation and inhibit the growth of malignant cells [19]. Carotenoids may play a role in inhibiting tumours, converting the human body to retinol, or acting as an antioxidant and reducing deoxyribonucleic acid (DNA) modifications caused by sun exposure [20, 21]. Vitamin D shows a protective effect against non-melanoma skin cancer, by inhibiting strong carcinogens such as 7,12-dimethylbenzanthracene, exercising a photoprotective function against exposure to UV radiation [22]. The polyphenols existing in black tea may also contribute to the inhibition of tumours derived from UV radiation, through chemoprotective mechanisms, such as the elimination of reactive oxygen species (ROS) or the increase in apoptosis of cancer cells [23, 24]. However, no nutrient has conclusively been shown to prevent or reduce the risk of non-melanoma skin cancer. The reduction of fats and the use of retinol in a diet may contribute to small health benefits for patients with non-melanoma skin cancer [25, 26].

Non-melanoma skin cancer has 82 types of tumours, with different diagnoses, many of which are difficult to detect and diagnose [27, 28]. This review addresses the most common types of non-melanoma skin cancers,

focusing on the main characteristics of each type, as well as their molecular mechanisms. Thus, current treatments for non-melanoma carcinoma, and the role played by lipid delivery systems (namely, liposomes, solid lipid nanoparticles and nanostructured lipid carriers) to overcome some limitations of existing treatments, will be highlighted.

Non-melanoma carcinoma

Non-melanoma skin cancer has two most common types, basal cell or basaloid carcinoma and squamous cell or squamous cell carcinoma, with the former having a higher incidence than the latter [29, 30]. Other less common types of non-melanoma skin cancer are Merkel's carcinoma, Kaposi's sarcoma, and T-cell lymphoma [31, 32].

Basal cell carcinoma

Basal cell carcinoma is the most common malignant skin tumour, the lesions of which occur more frequently in areas subject to greater sun exposure, particularly on the head and neck [33, 34]. Its designation is related to the fact that the carcinoma is similar to the basal layer of the epidermis, its origin is associated with the germ cells of the hair follicle [35, 36]. This type of carcinoma has certain common characteristics, such as the presence of small and round basaloid cells, an oval or elongated nucleus with condensed chromatin, and little cytoplasm [37]. At the tumour boundary, cells tend to line up perpendicularly to the peripheral layer [3].

The histology of basal cell carcinoma, as well as the risk of recurrence and metastasis [38], provides the basis for its categorization into subtypes [39, 40], shown in Figure 1, allowing a more detailed and effective diagnosis and treatment [41].

Nodular basal cell carcinoma is the most common subtype and is histologically well defined [42]. The peripheral nucleus cells are palisaded, and this subtype of basal cell carcinoma is characterized by the formation of cracks that result from the contraction of mucin during tissue fixation and staining [41, 43]. Nodular basal cell carcinoma has a low risk of recurrence because it is well known clinically and consequently the tumour boundary for further treatment is well delineated [44].

Superficial basal cell carcinoma is a subtype that affects the trunk and extremities of the body more, compared to the other subtypes [45]. This subtype of basal cell carcinoma is characterized by a smooth or red stain and irregular proliferation of tumour cells in the epidermis with little or no penetration into the dermis [41]. Recurrence is common, as the lesions of this subtype of basal cell carcinoma are difficult to define clinically [46].

The infiltrative and micronodular basal cell carcinoma are two subtypes of basal cell carcinoma with a high risk of local recurrence [46]. The infiltrative basal cell carcinoma is an aggressive subtype, the definition of which refers to the fact that it expands peripherally as well as deeply, penetrating the dermis [40]. The micronodular basal cell carcinoma is similar to the infiltrative one, however, these neoplasms are constituted by aggregates of small and round basaloid cells, unlike the other subtypes that present large aggregates [47, 48].

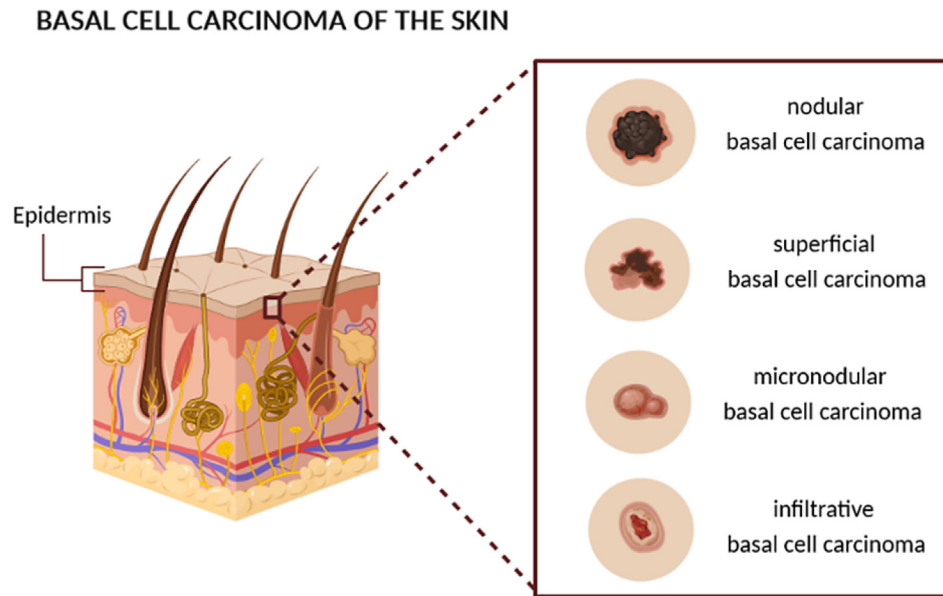


Figure 1. Schematic representation of the different subtypes of basal cell carcinoma [authors' own drawing].

Squamous cell carcinoma

Squamous cell carcinoma, the second most common type of skin cancer, is more invasive than basal cell carcinoma and has a greater predisposition to develop in certain cervicofacial regions compared to basal cell carcinoma, such as in the ears and lower lip [49, 50]. This type of carcinoma is more common in the older population; however, young people are not immune to this disease. As with basal cell carcinoma, the main cause of squamous cell carcinoma is excessive exposure to ultraviolet radiation [6]. However, other factors such as chemical carcinogenesis and human papillomavirus can lead to the development of squamous cell carcinoma, in this case in regions other than those caused by sun exposure, such as the endometrium [51, 52].

Squamous cell carcinoma corresponds to actinic keratoses, which involve only a part of the epidermis [53]. However, in addition to actinic keratosis, it is possible to differentiate squamous cell carcinoma *in situ*, which occupies the entire thickness of the epidermis, and invasive squamous cell carcinoma, which penetrates the basal layer of the epidermis [54]. All of these lesions present a disorderly maturation of the cells as they progress from the basal to the superficial layer, as well as variation in the size, shape, and colour of the nucleus and an abnormally high mitotic activity.

The pathological characteristics related to the aggressiveness of squamous cell carcinoma include the size, depth, location, and differentiation of the lesion, that is, tumours larger than 2 cm in diameter are more likely to recur and metastasize, as well as tumours more than 4 mm deep have a high probability of metastasis [55]. Regarding differentiation, the well-defined squamous cell carcinoma presents a differentiated cytological appearance, irregular infiltration of the dermis by neoplastic keratinocytes, and different degrees of inflammation and fibrosis under the lesion. Moderately defined squamous cell carcinoma has a deeper invasion and greater mitotic activity, and blood vessel invasion is also possible. Squamous cell carcinoma with little differentiation usually infiltrates the hypodermis and has little keratinization [56].

The existence of a neoplasm with intermediate histology between basal cell carcinoma and squamous cell carcinoma defines basal squamous cell carcinoma. Despite presenting an ambiguous definition, the term “basal squamous cell carcinoma” refers to basal cell carcinoma with areas made up of squamous cell carcinoma cells [57, 58]. This type of carcinoma is more common in the head and neck than in the trunk and it is argued that

it is related to the collision of primary lesions of the basal cell carcinoma and squamous cell carcinoma that are nearby [59, 60]. On the other hand, it is argued that basal squamous cell carcinoma corresponds to basal cell carcinoma capable of forming keratoses. The histological definition that brings together greater consensus argues that basal squamous cell carcinoma corresponds to the infiltrative growth of basaloid cells larger than cells of the common basal cell carcinoma, presenting little cytoplasm and large, uniform, and pale nuclei [61]. These cells form a cluster, in which aggregates of squamous cell carcinoma cells can form, either in the centre or spread over the lesion [62].

Other Non-Melanoma Carcinomas

T-cell lymphoma, Merkel's carcinoma as well as Kaposi's sarcoma refer to different types of skin cancers of the rarer non-melanoma type [31, 63]. The predominant cells of the adaptive immune system are lymphocytes, which divide into B cells and T cells [64]. With advancing age, several changes occur in the immune system, which is responsible for the state of immunosuppression, the most significant change being related to T cells, in that there is a marked decrease in T lymphocytes and inability to respond to some signs of activation [65]. This decrease in T lymphocyte response is caused by the permanent loss of CD28 protein expression, an important receptor, the absence of which makes T lymphocytes unable to undergo clonal expansion [66]. The decrease in CD28 protein on the surface of T cells and the increase in CD95 expression contribute to a greater tendency for cells to undergo apoptosis. These changes increase the occurrence of a certain type of non-melanoma skin cancer called T-cell lymphoma, which belongs to a rare group of lymphomas, being quite biologically heterogeneous [67]. T-cell lymphoma represents the second stage of aggressive non-Hodgkin lymphoma, having been categorized according to the immunophenotyping of T cells and their pathological characteristics, which allowed the definition of a wide spectrum of the different types of T cell neoplasms [68, 69].

Merkel's carcinoma is a rare but very aggressive neuroendocrine carcinoma, for which excessive sun exposure appears once again as the main risk factor for its development [58]. The histological features of Merkel's carcinoma include neuroendocrine granules and intercellular junctions, presenting fast-growing painless nodules. Merkel's carcinoma also has a high incidence in individuals with immunosuppression of T lymphocytes, such

Table 1

Target molecules of non-melanoma type carcinoma based on the most recent scientific reports.

Protein	Type of non-melanoma carcinoma	Reference
p53	Squamous cell carcinoma, Basal cell carcinoma	[82–86]
Ras	Squamous cell carcinoma, Basal cell carcinoma	[86–89]
E-cadherin	Squamous cell carcinoma	[90, 91]
Sonic hedgehog (Shh)	Basal cell carcinoma	[92–94]

as patients with human immunodeficiency syndrome (AIDS), leukaemia, or recipients of an organ transplant [58, 70]. These factors indicate the existence of an infectious agent, and a polyomavirus integrated into the genome of Merkel's carcinoma cells has recently been discovered. The then-called Merkel cell polyomavirus was detected in several Merkel carcinomas, suggesting that this polyomavirus may be the origin of this type of non-melanoma carcinoma in immunosuppressed patients [71, 72]. Kaposi's sarcoma is an antiproliferative disorder that is characterized by neoangiogenesis, inflammation, and oedema and can be classified in four main ways: classic, endemic (Africa), associated with immunosuppression, and associated with aids. Classic Kaposi's sarcoma typically affects elderly men of European origin and presents with paranodular lesions on the skin [73]. Endemic Kaposi's sarcoma, as well as aids-associated Kaposi's sarcoma, have a higher incidence in Africa, among young men and children, the latter presenting in a more aggressive form, with skin lesions and viscera [74]. Kaposi's sarcoma-associated with immunosuppression develops due to immunosuppressive therapies in transplant patients and the use of immunosuppressive pharmacologically active substances (PAS) [74, 75]. Kaposi's carcinomas result from the transmission of human herpesvirus type 8, saliva being the main source of transmission. In the case of transplanted patients, Kaposi's sarcoma may occur due to the reactivation of human herpesvirus type 8 [76, 77]. Kaposi's sarcoma is classified as an intermediate neoplasm, as it does not have the conventional characteristics of malignant disease [78]. Since basal cell carcinoma and squamous cell carcinoma are the most common, this chapter will focus on the topics covered in these two types of non-melanoma carcinoma.

Molecular mechanisms of non-melanoma carcinoma

Sun exposure is, as already mentioned, the main factor for the development of non-melanoma carcinoma [79–81]. Mutations caused by ultraviolet radiation cause the development of neoplasms, by altering the genes responsible for regulating cell growth and development [79]. These mutations are common in tumour cells of basal cell carcinoma as well as squamous cell carcinoma, although some changes are specific to each type of carcinoma (Table 1).

Ultraviolet A radiation (320–400 nm) is 10,000 times less mutagenic than ultraviolet B radiation (290–320 nm), the latter having a wavelength that is strongly absorbed by the nitrogenous bases of DNA and a spectrum of mutations distinct from those caused by other types of mutagenesis [95–97]. Mutations caused by ultraviolet B radiation tend to occur in two or more consecutive pyrimidines, consisting of the replacement of nitrogenous bases, most often in the transition Cytosine (C) → Thymine (T) and the formation of thymine dimers (CC → TT) [96, 98, 99].

DNA changes caused by solar radiation only progress to skin cancer if they are consecutive and repeated, moving on to a phase of replication [100, 101]. Mutations can occur in two alleles of a tumour suppressor, in two different proto-oncogenes, or a proto-oncogene and a tumour suppressor gene. Proto-oncogenes are normal genes that, when mutated, become active oncogenes or encode proteins with new functions. Tumour suppressor genes, when

mutated or eliminated, lose their negative influence on controlling tumour growth [100].

The evolution of squamous cell carcinoma is associated with different stages in which cellular and molecular changes occur, which, in turn, are related to the transition from keratinocytes to papilloma and consequently to carcinoma [102, 103], as shown in Figure 2.

In an initial phase, a mutation in a proto-oncogene occurs, with clonal expansion into pre-malignant cells. The progress of the neoplasia is characterized by an increase in cell proliferation resulting in a benign squamous cell papilloma [104]. The evolution to malignant squamous cell carcinoma corresponds to the last stage and occurs in a spontaneous process associated with aneuploidy and chromosomal aberrations [105, 106]. Regression means the partial or complete disappearance of a malignant tumour confirmed by microscopic examination in the absence of treatment, however, this phenomenon occurs infrequently. Among the most common neoplasms to regress are melanoma, renal cell carcinoma, and neuroblastoma [107].

Most cancers have mutations in the p53 tumour suppressor gene [108], with non-melanoma carcinoma being one of them, with this type of mutation being observed in basal cell carcinoma and a large percentage in squamous cell carcinoma. This protein plays a fundamental role in the cellular response to DNA damage, rapidly accumulating in the nucleus of damaged cells and causing a delay in the G1 phase of the cell cycle, allocating more time for DNA repair or elimination of the cell by apoptosis [84, 109]. The p53 protein is essential for inducing apoptosis of epidermal cells, whose DNA has been altered by ultraviolet radiation [82, 86]. Since ultraviolet radiation is a promoter of non-melanoma carcinomas and the fact that the death of your cells is dependent on the p53 protein [84], it then works as a mechanism to prevent the development of the carcinoma [110]. Mutations of the p53 protein in squamous cell carcinoma are predominantly transitions of type C → T and CC → TT, proving the origin of mutagenesis in ultraviolet B radiation [82]. Basal cell carcinoma also presents a mutation of the p53 protein in about 50% of the cases examined [111]. While squamous cell carcinoma loses one p53 allele and isolated mutations in another, basal cell carcinoma tends to mutate in two p53 protein alleles [112].

Ras protein mutations are also associated with the early development of neoplasms in humans [113]. The Ras protein is responsible for regulating proliferation, angiogenesis, apoptosis, and cell morphology, encoding the G protein that is responsible for the hydrolysis of guanosine triphosphate (GTP). Ras oncogene encodes the Ras protein, which prevents the hydrolysis of GTP from occurring [114]. The Ras oncogene acts together with other oncogenes, such as the Fos oncogene, and when introduced into normal keratinocytes, they cause their transformation [86]. The Ras oncogene plays a crucial role in the evolution of non-melanoma carcinomas, with mutations provoked in the Ras gene by ultraviolet B radiation, observed in basal cell carcinoma, as well as squamous cell carcinoma [89].

E-cadherin is a membrane protein involved in cell adhesion, which is expressed in epithelial tissues and with the important function of maintaining epithelial stability [115]. The inactivation of this protein is associated with the invasion of tumour cells and the metastasis of several cancers,

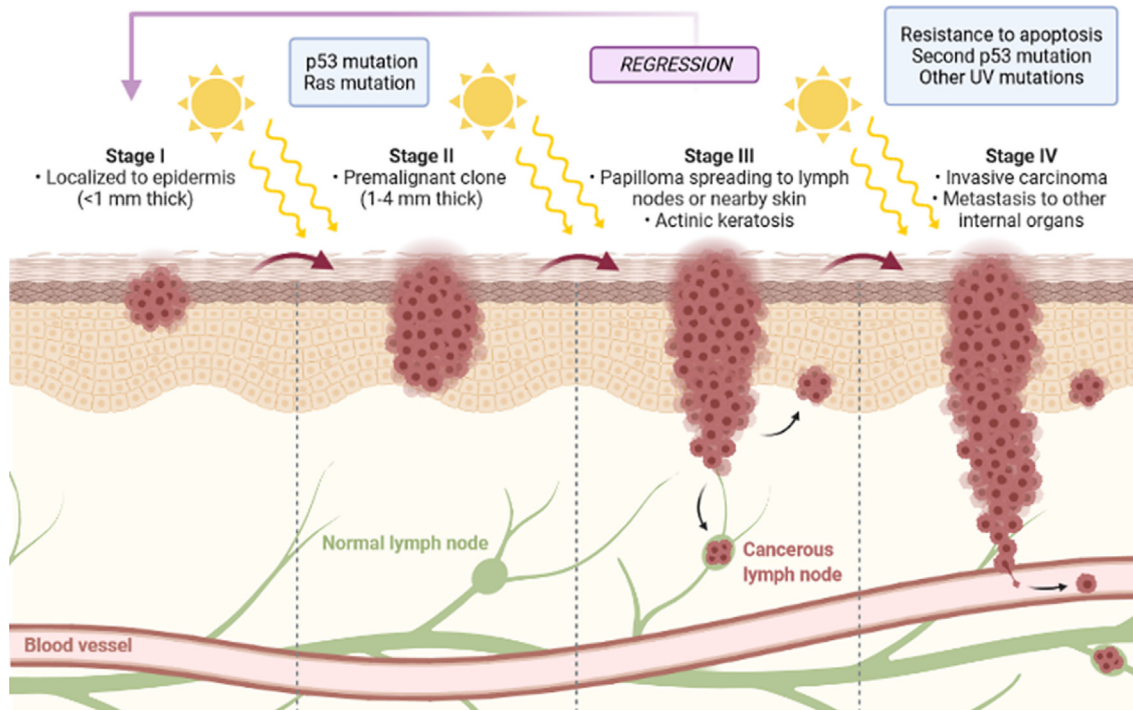


Figure 2. Schematic representation of the different stages of evolution of squamous cell carcinoma [authors' own drawing].

including squamous cell carcinoma [116]. The inactivation of E-cadherin occurs through its mutation and by hypermethylation of the E-cadherin gene promoter, a mechanism related to gene silencing [90, 117]. The increase in E-cadherin hypermethylation is directly related to the greater invasive character of the tumour [117].

The expression of the Sonic hedgehog (SHH) glycoprotein in human skin contributes to the acquisition of characteristics of basal cell carcinoma [30, 118]. Activation and changes in the SHH signalling pathway and loss of function of the receptor of the gene encoding the SHH protein (PTCH1) are relevant to the development of basal cell carcinoma, resulting in abnormal gene expression [30].

Treatments of non-melanoma carcinomas

Several surgical and non-surgical treatments have been developed over the last few years for non-melanoma carcinoma [28], with the main objective of obtaining the highest possible percentage of carcinoma elimination, with minimal tissue destruction and with acceptable cosmetic results [119]. Treatment must be individualized, based on the characteristics of the tumour, the patient, and the dermatologist's experience with the various existing techniques. The traditional treatment of non-melanoma carcinoma includes surgery, cryosurgery, curettage and electrode section, and radiotherapy [119, 120]. However, alternatives to the traditional treatment of non-melanoma carcinoma have been developed, with different levels of effectiveness, such as lasers, topical pharmacotherapy, and photodynamic therapy.

Surgery emerges as the most effective treatment for non-melanoma carcinoma, as it allows a histological assessment of the tumour margins, both in its extension and depth, and has a low percentage of recurrence. The surgery consists of excising the tumour with a safety margin, with the application of local anaesthesia in most cases, even though the treatment is individualized, it may require surgery with general anaesthesia [121].

Other treatments, such as cryosurgery and curettage, and electrode section, also have a high cure rate for the disease. In cryosurgery, biological changes in the skin are caused by freezing and thawing, causing tissue necrosis. Generally, this technique involves the use of an aerosol or a cryoprobe, and its main advantages are being safe, fast, effective, low cost, and with satisfactory cosmetic results [120]. Curettage and electrodissection are recommended for the treatment of well-defined, low-risk carcinomas [122]. This technique consists of curettage followed by electrodissection of the site to be treated, with repetition of the procedure as many times as necessary. It is a simple technique, of low cost and with satisfactory cosmetic results. However, these techniques have some disadvantages, as they do not allow the histological evaluation of the tumour margins, increase the risk of pigmentary changes and despite satisfactory cosmetic results, the use of these techniques can lead to the formation of hypertrophic or atrophic scars [123].

When the patient is not a candidate for surgery and when the tumour is more than 15 mm in diameter in high-risk areas or more than 20 mm in diameter in medium-risk areas, radiotherapy appears with the technique used for the treatment of carcinoma basal cell and squamous cell carcinoma [124]. The typical patient for this type of treatment is an elderly individual with an advanced stage of the disease. Radiotherapy has a high cure rate, as well as a low recurrence rate of basal cell carcinoma, however, the results are not as satisfactory and effective as those obtained by surgery [125]. Squamous cell carcinoma does not have as high success rates with radiotherapy treatment as basal cell carcinoma, and it can reoccur quickly after radiotherapy, being a technique that also does not allow the histological evaluation of the tumour margins [50, 126]. These factors together with advances in surgical techniques have contributed to the use of radiotherapy only in very specific situations, as previously mentioned [127].

Despite the surgical procedure emerging as the standard treatment for non-melanoma carcinomas, presenting low rates of recurrence and allowing histological studies of the tumour, in certain circumstances alternatives to surgery and less invasive options, are needed for the treatment of non-

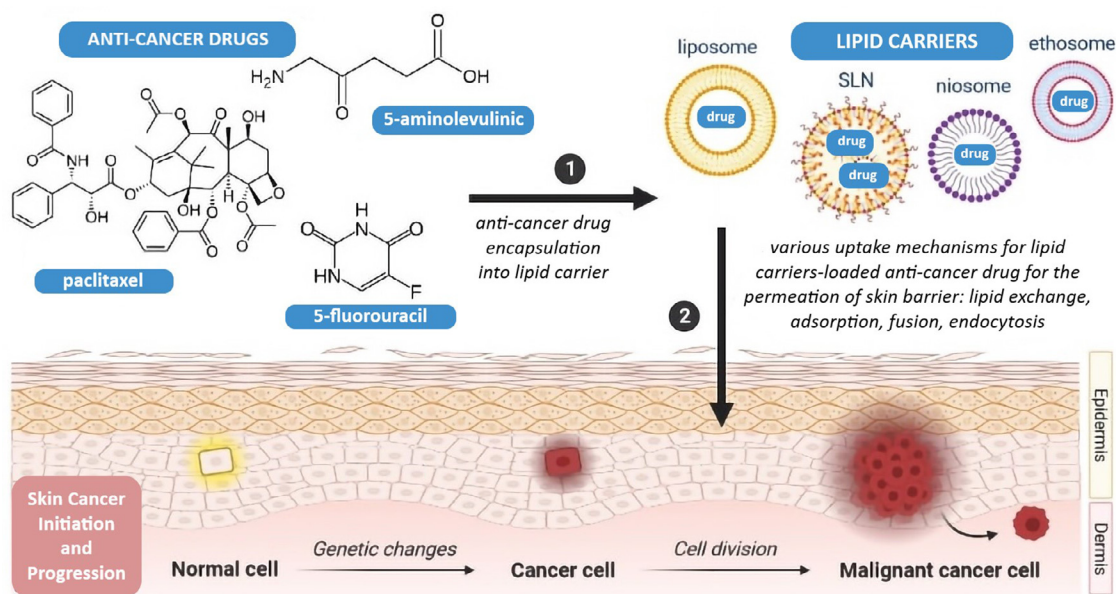


Figure 3. Schematic illustration of non-melanoma skin cancer treatment using lipid delivery systems for chemotherapeutic drugs [authors' own drawing].

melanoma carcinoma [128]. In the last decade, new techniques have been developed and improved, emerging as more recent non-surgical treatments, laser therapy, topical pharmacotherapy (5-fluorouracil and imiquimod), and photodynamic therapy [28, 129].

Laser therapy appears as an alternative treatment for low-risk skin tumours and consists of applying a light source to eliminate the tumour [130–132]. The improvement of laser technology has resulted in small and portable lasers suitable for the removal of skin lesions, with reduction of thermal diffusion and unwanted thermal necrosis, contributing to the minimization of tissue damage, ease of recovery, and less formation of scars [133]. The carbon dioxide laser and the pulsed contrast laser are the most used in the treatment of non-melanoma carcinomas [134], more specifically for basal cell carcinoma, revealing very high cure rates and satisfactory cosmetic results, with the disadvantage of not allowing to perform histological assessments [135, 136].

The treatment of non-melanoma carcinoma by topical pharmacotherapy has been reported to use semi-solid formulations of 5-fluorouracil and imiquimod [137]. 5-fluorouracil is a chemotherapeutic agent used in the treatment of basal cell carcinoma and squamous cell carcinoma topically, with a concentration of 5% [138–140]. This anti-cancer is structurally similar to thiamine and inhibits the enzyme thymidylate synthase, blocking DNA synthesis in proliferative cells. The main side effect of 5-fluorouracil is the development of serious inflammatory reactions. Another disadvantage is related to the fact that it is recommended only for the treatment of superficial carcinomas and when patients cannot undergo surgery, it is not effective for the treatment of lesions in deeper layers of the skin [141]. This limitation makes it necessary to use alternative methods to improve the permeation of this anti-cancer drug into the skin.

Imiquimod acts as an immune response modifier, stimulating the innate and adaptive immune response [142]. Imiquimod 5% cream was initially approved for the treatment of genital and perianal warts and later for the treatment of superficial basal cell carcinomas and actinic keratoses of patients who would not be candidates for surgery. Treatment with imiquimod reveals similar disadvantages to treatment with 5-fluorouracil, exhibiting, in some cases, local inflammation [143].

Photodynamic therapy is a relatively recent therapeutic method [144], also approved for the treatment of non-melanoma carcinoma and results in the administration of a drug or pro-drug, which will contribute to the formation of a photosensitive compound, which will accumulate in tumour tissues, followed by irradiation with visible light, which causes a set of photochemical reactions that cause the elimination of target cells [130, 145]. Photosensitization obtained for photodynamic therapy of superficial carcinomas is usually obtained by topical application of 5-aminolevulinic acid or its methyl ester, which will increase the formation of protoporphyrin IX in the skin, since 5-aminolevulinic acid is the precursor of protoporphyrin IX [146]. Subsequently, the tumour will be irradiated with light with a wavelength corresponding to the maximum absorption of protoporphyrin IX, initiating a complex of chemical, biological and physiological reactions, in which very reactive oxygen singlets are produced, which cause necrosis and/or apoptosis of cells [147]. Thus, for the treatment to be specific for the death of tumour cells, the photosensitizer must accumulate in high concentrations in the target cells, that is, 5-aminolevulinic acid must selectively accumulate in the tumour tissue so that consequently there is an increase in the concentration of protoporphyrin in that location [148]. This fact appears as a limitation for this technique, in the treatment of carcinomas in deeper and non-superficial skin strata, as there is a greater difficulty for 5-aminolevulinic acid to penetrate the skin and reach these deeper strata [149]. Several methods have been developed to overcome this barrier, such as the development of lipid vectors, which will be addressed later. Photodynamic therapy is a non-invasive, effective method with very satisfactory cosmetic results, the formation of scars being an exception and not a consequence of treatment, as in the case of surgery. The fact that it is a very selective treatment, as it only acts on the area in the tumour cells, means that the risk of loss of function is very low. Photodynamic therapy may also appear as a supplement to surgery, with a reduction in the size of the tumour to simplify its surgical removal [150].

These recent topical treatments are fundamentally approved for the treatment of superficial non-melanoma carcinomas and are only used in the treatment of more invasive carcinomas when the patient cannot undergo surgery, as chemotherapeutic drugs may not reach invasive carcinoma

throughout its depth [141]. It is essential to emphasize once again the need to develop new methods that increase the penetration of these drugs into the skin for the treatment of different types of non-melanoma carcinoma [53, 151]. Several studies have been reported to overcome the limitations of existing treatments, such as the use of lipid delivery systems [152], for the delivery of chemotherapeutic drugs aiming at reducing their adverse side effects [153, 154].

Stimuli responsive lipid vectors for the treatment of non-melanoma carcinoma

A remarkable characteristic of cancerous cells is their low cytosol pH when compared to other cells. Increased hyperthermia sensitivity is also another almost exclusive feature of cancer cells [155]. Specific systems can be engineered to deliver their content only when exposed to proper environmental stimulus like light, pH gradients, sound, magnetic fields, or epitopes in the organism, leading to a controlled release both in time and space of drugs which can be very useful to target cytotoxic treatments [156, 157].

Low intracellular pH values enable the delivery of pH-sensitive nanoparticles through rupture of acidic-sensitive bonds with the consequent dismantling of the lattice covering the drug content, promoting drug release [158, 159]. Some examples in pH-sensitive systems are those possessing hydrazone bonds (sensitive to acidic environments) as in gemcitabine-loaded micelles with a stearic acid skeleton, GemC18 [160]. When GemC18 and micelles with the same drug but pH-insensitive are compared, GemC18 demonstrated higher cytotoxicity than the prior ones. The low-pH hydrolysis reaction is also a fundamental example of such phenomena, as in doxorubicin-loaded methacrylamide micelles (DOX-MA) [160, 161]. When applied to the *in vivo* cancer mouse model B16-F10, DOX-MA resulted in preeminent cytotoxic and pro-death effects than doxorubicin molecules alone [162].

The energy available as heat can be generated using the transformation of electromagnetic energy through electromagnetic coils (generating an electromagnetic field) or using radio shortwaves. Two mechanisms are usually considered when disserting about killing cancer cells - death by the direct incidence of heat or by targeting these cells with scaffolds made of heat-sensitive polymers allowing specific delivery of the drugs. An example of a system applied to clinical purposes is an inhibitor of heat-shock protein 90 (Hsp 90) – an anti-apoptotic protein which decreases the sensitivity of cancer cells to hyperthermia and reduces the expression of Akt kinase protein - geldanamycin (GA), which combined with ferromagnetic thermosensitive nanoparticles (FTN) and generates a GA-FTN formulation sensitive to magnetic fields [163, 164]. Compared to the prior formulations with GA molecules alone is distinguishable a prominent cytotoxic effect of the formulation.

To synthesize light-sensitive delivery systems some materials with unique properties (light responsiveness) shall be used during the process of formulation. They bring several advantages as the capacity to trigger a reaction only when exposed to specific wavelengths, during a minimum period, and with a minimum required intensity. The light used to trigger the therapeutic action of these systems may range the ultraviolet, visible, and infrared spectra [165]. A study using quantum dots composed of cadmium telluride wrapped in silica allowed, after laser incidence, to prevent the growth of melanoma with significant differences when compared to the tissues unexposed to the laser beam [165, 166].

Photodynamic therapy (PDT) uses three critical elements: oxygen, light with a specific wavelength, and a photosensitizer (PS) [167, 168]. This last element is an innocuous molecule but, when exposed to light in a certain wavelength (specific for each PS) the molecule becomes “active”, generating a flow of electrons that are transposed to molecular oxygen generating both reactive oxygen species (ROS) *via* type I reaction, or singlet oxygen (a very reactive form of molecular oxygen) *via* type II reaction [169]. The presence of

these products leads to cell impairment and death. The PS is also preferably taken by cancer cells than by normal ones. This therapeutic option carries with it the advantages of being small invasive and presenting no adverse effects in the long-term which makes it one of the most capable weapons to deal with cancer [170]. Despite such achievements, PDT is restricted on what concerns PS dependent on visible light as it cannot penetrate deeply into the skin. For this purpose, other PS molecules may be used such as those sensitive to infrared (IR) radiation to treat wider and deeper tumours [171]. Several studies point to the efficacy of this remarkable therapy such as chitosan-derived nanoparticles constituted by aminolevulinic acid to penetrate the skin [172]. Another study demonstrated the efficacy of nanoparticles of mesoporous silica entrapping two PS molecules that are sensitive to IR radiation and yielded significant stoppage of cancer development [168].

Ultrasounds are applied to deliver a sort of products including drugs, genes, and antigens. A brief example of this technology being employed is the liposomes, filled with perfluoropropane gas and specific melanoma cell antigens, that are placed in contact with dendritic cells. When the ultrasound stimulus is applied these liposomes are internalized and posteriorly activated generating crosstalk between dendritic cells and T-lymphocytes which lead to melanoma cell death [173].

In the last decades, several nanometric systems have been proposed for the diagnosis and treatment of different types of cancers [174, 175]. The development of therapeutic products at the nanoscale appears with the main objective of obtaining a controlled release of drugs to increase their effectiveness by the specific targeting to the site of action (tumour cells), consequently reducing the side effects, since healthy cells are not affected.

In the treatment of non-melanoma carcinoma, the stratum corneum of the epidermis appears as the greatest barrier for the penetration of drugs. The transport of drugs occurs mainly in the lipid region of the stratum corneum, which consists of ceramides, cholesterol, free fatty acids, and devoid of phospholipids [151]. Thus, in topical administration of drugs intended to reach deeper layers of the skin is essential to overcome this barrier so that sufficient amounts of drug reach the target cells. Lipid delivery systems have structural characteristics that allow the encapsulation of substances with different solubilities and increase the ability of chemotherapeutic drugs to reach tumour cells, making them more stable and reducing skin irritation, since they prevent direct contact of drug with the skin surface [176, 177].

Liposomes

Liposomes are the most studied lipid delivery systems for the treatment of cancer and are accepted in several strategies for systemic administration of drugs [178]. These lipid vectors consist of spherical vesicles with biocompatible and biodegradable phospholipid bilayers, with amphiphilic characteristics that allow the encapsulation of hydrophilic and lipophilic compounds, in the polar zone or within the lipid bilayer, respectively [173]. The main lipid material used in the production of liposomes is phosphatidyl choline [179]. The selection of the phospholipid bilayer composition is instrumental to determine the rigidity of the liposomal vesicles. Unsaturated phosphatidyl choline obtained from natural sources (e.g. soybean, egg) offers higher permeability but less stable bilayers, whereas saturated phospholipids with long acyl chains (e.g. dipalmitoylphosphatidylcholine) increase the rigidity and impermeability of liposomes [180]. The higher the rigidity of the vesicles, the higher the controlled release of the loaded drugs.

The lipid bilayers have a structural affinity with the stratum corneum of the epidermis, allowing an optimized release of the drug in the different strata of the skin. Many of the studies involving liposomes in the treatment of non-melanoma carcinoma are related to photodynamic therapy [177]. The 5-aminolevulinic acid used in this technique is a hydrophilic molecule and has zwitterionic properties at physiological pH, which results in the main limitations of this compound in the ability to cross the stratum corneum of the skin. Thus, the encapsulation of 5-aminolevulinic acid in liposomes

Table 2

Examples of lipid delivery systems recommended for the treatment of non-melanoma skin cancers, their lipid composition, loaded anti-cancer drug, associated treatment, and in vitro/in vivo results.

Lipid Delivery System	Lipid composition	Anti-cancer Drug	Associated Treatment	In vitro and/or in vivo results	Reference
Liposomes	Hydrogenated soy phosphatidylcholine	Curcumin	Photodynamic therapy	Decreased cytotoxicity of phototoxic agents loaded in liposomes toward normal skin cells	[206]
AS1411-aptamer conjugated liposomes	Egg Yolk Phosphatidylcholine and cholesterol	5-Fluorouracil (5-FU)	-	Semi-solid hydrogel based on sodium alginate and hyaluronic acid containing 5-FU-loaded AS1411-aptamer conjugated liposomes increased drug permeability in comparison to free liposomes, with higher anti-tumor efficiency and lower irritation potential on the skin	[207]
PEGylated solid lipid nanoparticles	Tefose 1500	Curcumin	Photodynamic therapy	Skin accumulation of drug in vivo was twice when delivered by SLN in comparison to free suspension; cytotoxicity in A431 cells increased with the loading and with irradiation	[208]
Lipid nanoparticles dispersed in sodium carboxy methylcellulose hydrogel	Stearic acid and lecithin	5-Fluorouracil (5-FU)	-	Mice-bearing Ehrlich's ascites carcinoma treated with 5-FU-loaded SLN exhibited reduced inflammatory reactions, reduced keratosis, and reduced symptoms of angiogenesis when compared to mice with non-loaded 5-FU.	[209]
Lipid nanoparticles dispersed in a cream	Glycerol monostearate or cetyl alcohol, and lecithin	Sesamol	-	In vitro antiproliferative and DNA fragmentation assays pm HL 60 cell lines confirmed sesamol-induced apoptosis. Significant retention of sesamol in the skin with minimal flux across skin when administered in cream-based SLN both in vitro and in vivo. In vivo anticancer studies on TPA [†] -induced and benzopyrene-initiated tumour production (ROS mediated) in mouse epidermis showed the histological normalization of skin cancers post their induction.	[210]
Cationic lipid nanoparticles	Stearic acid and monoolein	Doxorubicin (DOX)	Iontophoresis	Loading DOX increased drug in the lipid matrix of the stratum corneum. The association with iontophoresis created DOX reservoirs in the follicles of the skin. Nude BALB/c mice-bearing squamous cell carcinoma treated with DOX-SLN and iontophoresis was effective in inhibiting tumor cell survival and tumor growth, with increased keratinization and cell death.	[211]
Nanostructured lipid carriers	Sorbitan monooleate; cupuaçu butter	Imiquimod and copaiba oil	-	Imiquimod-loaded NLC did not show any changes in healthy skin cells (keratinocytes, HaCaT); in vitro skin permeation/penetration using pig skin resulted in increased drug retention in the skin layers.	[201]

[†] TPA, 12-O-tetradecanoylphorbol-13-acetate.

has been investigated to overcome the limitations of photodynamic therapy [181]. Pierre *et al.* reported on a controlled release system of 5-aminolevulinic acid-based on liposomes made up of lipids similar to those of the stratum corneum of the epidermis [182]. These studies revealed that the liposomes with incorporated 5-aminolevulinic acid present adequate retention of the compound in the epidermis without stratum corneum and in the dermis, and low retention in the stratum corneum [181]. This behaviour indicates that the developed liposomes allow the controlled release of 5-aminolevulinic acid in tumour cells in deeper layers of the skin, for treatment by topical photodynamic therapy [150]. Studies carried out on the influence of different vectors on the formation of protoporphyrin IX by topical application of 5-aminolevulinic acid show the accumulation of the latter in tumour tissues when encapsulated in liposomes, as well as their elimination from the blood circulation after 24 hours of administration, maintaining them if, after this time, only in the tumour cells [150, 181, 183]. The development of ultra-deformable liposomes with different charges on the surface has recently been

reported, with greater efficiency in cationic liposomes, which revealed greater stability and permeability, and a release of 5-aminolevulinic acid in deeper layers of the skin by topical application, contributing to the optimization of photodynamic therapy [150, 184]. The encapsulation of polyphenols present in green tea in liposomes has also been studied, to increase their antioxidant efficacy [185] and anti-cancer activity in the treatment of basal cell carcinoma [23]. As in previous studies, these lipid vectors promoted the accumulation of polyphenols in the tumour and induced cell death from basal cell carcinoma more effectively than the polyphenol hydroalcoholic solution [186]. These results are because liposomes can keep polyphenols stable, and it is possible to conclude that these lipid vectors are quite effective for the controlled release of drug, ensuring their accumulation in the target cells as well as their anticancer activity [187].

Fang *et al.* [188] carried out a comparative study between liposomes and ethosomes to verify the efficacy of the ethosomes with encapsulated 5-aminolevulinic acid to promote the production of a greater amount of

protoporphyrin IX in the target cells, due to a greater accumulation of 5-aminolevulinic. The ethosomes correspond to a "new generation" of liposomes being a modified form of them and consist of the mixture of phosphatidylcholine with ethanol showing greater efficiency in the release of drugs by topical administration in terms of quantity and depth concerning the liposomes. The study carried out by Fang et al. [188] allowed us to confirm this fact, having obtained an average size of the ethosomes smaller than the liposomes and a greater capacity of penetration in the strata of the skin of the former about the latter. Ethanol emerges as the main responsible for the ethosomes having a smaller size than the liposomes, producing compact and deformable vesicles, since ethanol has a steric stabilization due to the modification of the total ethosomes charge, which is fundamental for the reduction of the size of the vesicles [189]. The greater capacity of penetration into the skin strata of ethosomes with liposomes is also related to ethanol, but also the surfactant used. Ethanol interacts with the skin and with the lipids of the stratum corneum, making them more fluid and creating channels that allow the increased targeting and delivery of drugs [189].

Pandey et al. proposed to encapsulate the anti-cancer paclitaxel, in ethosomes to promote a controlled release of the drug in the target cells for the treatment of squamous cell carcinoma. Paclitaxel is an extremely hydrophobic molecule, which easily accumulates in the stratum corneum, not penetrating deeper layers of the skin. In this way, the ethosomes allowed to increase the proliferative activity of paclitaxel, since they improved the permeation of drugs in the stratum corneum of the epidermis [190]. The percutaneous permeation profile of paclitaxel encapsulated in ethosomes was approximately 23.2 times higher than that observed for paclitaxel in a hydroalcoholic suspension, suggesting a much greater capacity of the encapsulated drug to reach deeper strata and exercise its function for the elimination of squamous cell carcinoma [190–192].

Other liposomes-based vesicles have also been developed to improve cutaneous permeation of 5-fluorouracil. This anti-cancer is hydrophilic and shows low skin permeation capacity, which consequently reduces its activity when topically administered. The encapsulation of 5-fluorouracil in niosomes allows the penetration of drug through the stratum corneum, allowing to increase its cytotoxic effect in the intended tissues. Niosomes, like ethosomes, are vesicles similar to liposomes, however, they are nonionic. The ability to increase the skin permeability of niosomes is related to the flexibility and deformability that these vesicles present and the fact that they allow them to pass through the skin layers [178].

Lipid nanoparticles

Lipid nanoparticles also play an important role in improving the efficacy and safety of chemotherapy in non-melanoma skin cancers [193, 194]. Solid lipid nanoparticles (SLN) consist of a solid lipid matrix (solid at room temperature) that allows the release of poorly soluble anti-cancers into target cells.

Nanostructured lipid carriers (NLC) are made up of a mixture of solid lipid and liquid lipid (in a combination that is also solid at room temperature) and have also proven the ability to deliver drugs to deeper layers of the skin, maintaining the stability of drugs and ensuring their accumulation in the skin, tumor cells and their anti-cancer function [178, 195]. The solid lipids commonly used in the production SLN and NLC include fatty acids (e.g., stearic acid, palmitic acid, myristic acid), triglycerides (e.g., tribehenate, tristearate, tripalmitate, trimyristate), cholesterol, waxes (e.g., bee wax, cetyl palmitate), and less pure mixtures (e.g., Imwitor®, Softisan®, Witepsol®). The liquid lipids that are in the composition of NLC are usually natural oils that can have anti-cancer properties (e.g., essential oils, monoterpenes [176, 196–198]) or medium chain triglycerides [199].

Yu et al. [200] reported a higher concentration of paclitaxel in cancer cells, demonstrating an increase in the capacity of penetration, a controlled release,

and an increase in the anti-cancer activity of drug in the target cells when delivered by SLN.

Venturini et al. [201] proposed co-encapsulation of imiquimod and copaiba oil into lipid nanoparticles to show a synergistic effect against basal cell carcinoma. The chemical imiquimod approved for the treatment of this type of cancer and copaiba oil is known for its anti-proliferative properties. From the *in vitro* biocompatibility testing in healthy keratinocytes cell cells (HaCaT), no morphological changes were observed, whereas the skin permeation testing in pig skin the authors reported an increased drug retention in the skin layers when using the lipid nanoparticles for the delivery of chemotherapeutic drug.

Ali-von Laue et al. [202] produced SLN to load a guanosine-analogue phosphonate (OxBu) for the treatment of actinic keratosis, a precursor of cutaneous squamous cell carcinoma. The tumor response to the formulation was confirmed by increases in caspase-cleaved fragment of keratin-18, caspase-7 activation and reduced of matrix metalloproteinase-2 and Ki-67 expression. The drug efficacy was also found superior to the equimolar 5-fluorouracil solution.

Doxorubicin-loaded cationic lipid nanoparticles were successfully combined with iontophoresis to improve the bioavailability of the drug to skin tumour [203]. The loading of doxorubicin significantly changed partition coefficient through the diffusion cells and increased permeation of stratum corneum to the drug. The association with anodic iontophoresis in squamous cell carcinoma induced in nude BALB/c mice increased 50-fold the doxorubicin penetration *in vivo*. This combined approach effectively inhibited tumor cell survival and tumor growth followed by increased keratinization and cell death.

Topotecan loaded solid lipid nanoparticles were proposed for the treatment of cervical cancer [204]. The cytotoxicity of loaded particles was assessed against cervical squamous cell carcinoma cell line (HeLa) and human squamous cell carcinoma cell line (SiHa), confirming the biocompatibility of the developed systems.

Teaima et al. [205] described the development of a transdermal emulgel containing pomegranate extract-loaded SLN for the treatment of Ehrlich ascites carcinoma. The *ex vivo* permeation assay showed a non-Fickian diffusion transport through mouse skin. On a mouse model of skin bearing a solid form of Ehrlich ascites carcinoma, the authors confirmed statistically significant anticancer effects of the SLN-containing emulgel. Figure 3 illustrates a variety of lipid carriers that can be used in non-melanoma skin cancer, and Table 2 summarizes examples of anticancer-drugs formulated into lipid carriers, their lipid composition, associated treatment, and *in vitro/in vivo* results.

Conclusions

The treatment of non-melanoma carcinoma has been intensively studied and several currently available techniques allow dermatologists to choose the best solution for individualized and more effective treatment. However, existing topical therapies have some limitations and lipid delivery systems appear as very promising approach to reduce serious adverse side effects of local chemotherapy. The studies carried out show the advantage of encapsulating anti-cancer drugs in liposomes, ethosomes and in lipid nanoparticles, to increase the drug stability, penetration into the deeper skin strata, the accumulation in the target cells by controlled release thereof, and consequently increased cytotoxicity of drug in carcinogenic cells. The ultimate aim is to increase anticancer bioavailability in the site of action, sparing healthy cells from the contact with the drug thereby reducing the serious cytotoxic effects of chemotherapy.

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