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AN OVERVIEW OF CURRENT AND NOVEL TREATMENT APPROACHES FOR ACTINIC KERATOSIS

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ABSTRACT
In recent years global incidences of non-melanoma skin cancer and actinic keratosis (AK) have shown a marked increase of 16% per year compared to the previous year statistics. Nonmelanoma skin cancer tumours and actinic keratosis are treated with the help of chemotherapy, radiotherapy, surgery, and topical therapies. This overview attempts to elaborate on actinic keratosis, non-melanoma skin cancer, relationship between actinic keratosis (AK) and skin cancer, drugs used in dermal preparations for their management and novel approaches for targeting drugs to skin.

KEYWORDS: Actinic Keratosis, Non Melanoma, Microneedles, Dendrimers, Microsponges, Emulsions, Transfersosomes.

1. INTRODUCTION

Development of Skin cancer is most commonly seen in Caucasian population and damage of DNA due to ultraviolet radiations is the leading cause of such type of cancer. Actinic keratosis (AK) is also called as Solar keratosis or Senail keratosis.[1]

AK represent as a marker for an increase in non-melanoma skin cancer (NMSC), even in the absence of specific lesion progression. The risk for progression of AK to invasive squamous cell carcinoma (SCC) with the potential for metastasis provides the rationale for its treatment. Early diagnosis should be done for treatment of patients with skin cancer. Anticancer drugs administered orally or by the intravenous route are associated with serious side effects. Topical dosage forms can deliver most of the drug locally with fewer side effects when compared with other routes of administration.[2]

Limited numbers of synthetic molecules have been administered topically to treat skin cancer lesions or AK. This article provides an overview of skin physiology describes location and classes of skin cancers and reported treatment options.

2. SKIN STRUCTURE AND PHYSIOLOGY

One of the largest organs of the body is skin, which provides an interface between the internal organs and environment. Structurally, skin is a multi-lamellar organ and is involved in several physiological functions. There are three layers of the skin namely epidermis, dermis and subcutaneous tissue.

2.1 Epidermis

Epidermis has a number of layers. The outermost of the epidermis, the stratum corneum (SC) represents the major barrier that prevents water loss and is major route for percutaneous absorption of exogenous materials.[3]

It is a multi-layered structure whose thickness varies from 0.8 mm (on the palms and soles) to 0.06 mm (on the eyelids). The epidermis is further sub-divided into four different layers of cells.

The cells (keratinocytes) present at the dermal epidermal junction form the stratum basale (or stratum germinativum). The nuclei of these cells, are columnar in shape and anchored to the dermis via collagen fibres.[4] This layer also contains other cells like Melanocytes that are triangular in shape and consist of a central cell body with a number of branches or dendrites.

Melanocytes synthesise two melanin pigments: Eumelanin, a dark brown-black insoluble polymer, and phaeomelanin, a light red-yellow sulphur containing soluble polymer.[5] Tyrosine helps in production of melanin by an enzyme called tyrosinase through a series of oxidative steps which is stored in melanosomes ,present in melanocytes.[6] Melanin in the skin protects from UV induced DNA damage by absorbing UV photons and free radicals produced from interaction of UV photons with cellular lipids.[7]

There are 2 to 6 rows of cell layers above the stratum basale forming stratum spinosum (prickle cell layer or squamous cell layer). The stratum granulosum lies over the spinosum cell layer and consists of 1 to 3 cell layers.It contains basophil granules of material called keratohylain. A separate layer of the stratum lucidum is present in the palm and sole of the foot ie only found in thik skin. The cells of this layer are flat and compact and progress to become the anucleate and cornified dead cells of the SC.[8]

The SC is composed mainly of keratin (70 – 80%) and lipids that consists of flattened, keratinised dead cells (corneocytes). The lipid content of the SC is present between the corneocytes.[9]Corneocytes are linked together by desmosomes, forming a filamentous network of keratin in the cells. Many biochemical activities are carried by proteolytic and lipolytic enzymes which include lipid processing and desmosome breakdown. The unique composition and structure of the SC provides for its excellent barrier properties.[10]

2.2 Dermis

The dermis or corium is 20 to 30 times thicker (3 to 5 mm) than the epidermis and consists of collagen fibrils along with elastic connective tissues.[11] It has presence of mechanoreceptors that provide sense of touch and thermoreceptors that provide sense of heat. The penetration of drug through this layer is different from the SC, reduced permeation of lipophilic drugs may be seen in this layer because of the rich blood supply.[8]

2.3 Subcutaneous tissue (Hypodermis)

It is a layer of specialised fat cells interconnected with collagen and elastin fibres. Large quantity of fat is produced and stored in it. It shows effects like heat insulator and protects the body from mechanical shock and thereby stores large quantities of calories.[12]

3. SKIN CANCERS AND AK

Depending on the origin skin cancer is classified into two types: non-melanoma skin cancer (NMSC) and melanoma. Risk factors for skin cancer include:

(i) Skin phototype (i.e., skin's responsiveness to ultraviolet [UV] radiation, also known as Fitzpatrick skin type),
(ii) Excess of exposure to UV radiation, and
(iii) Immunosuppression.[13]

AK exists in a continuum with non-melanoma skin cancer (NMSC), 10% of AK lesions become cancerous if untreated.[14]

3.1 Non-melanoma skin cancer (NMSC)

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are classified as NMSCs. They develop in the basal and squamous (spinosum) layers of the epidermis, respectively. [12] BCC mainly occurs on the face and the back of the hands whereas most SCCs occur on the head and the neck. BCC progresses slowly with little or no metastasis, but SCC progress to invasive SCC and there is a 2-6% risk of metastasis.[15]

UV radiations primarily cause of NMSC. The UV spectrum include: UV-A (320-400 nm), UV-B (280-320 nm) and UV-C (100-280 nm).However, UV-C is most absorbed by atmospheric gases. UV-B is carcinogenic radiation. Long term exposure to UV-B results in photoaging and cancer. UV-A is less harmful to human skin compared with UV-B.[16] Cellular DNA absorbs UV-B photons and generates a number of photoproducts. If this DNA damage is not repaired, it causes specific DNA mutations which arise by substitution of a single cytosine (C) for a thymine (T) base and to a lesser extent, by substitution of a double base CC for TT at pyrimidine sites. Protection against DNA damage or mutation from UV radiation requires DNA repair mechanisms and production of melanin. In human cells, DNA photoproducts are mainly eliminated by a nucleotide excision repair (NER) mechanism, but with increasing age, the DNA repair mechanism is decreased and the incidence of NMSC is higher in older patients. However, melanin cannot prevent DNA damage in the superficial layers as it is shed from the SC along with keratinocytes.[17]

SCC is present in many distinct subtypes and presentations. The patterns of the various SCCs and BCCs are described in greater detail by Goldenberg and colleagues.[18]

3.2 Melanoma

Melanoma is a tumour which arises from the melanocytes.[12] It is most lethal type of skin cancer and unlike NMSC is more common in younger and middle aged patients.[15][19] Melanoma can develop in eyes and the mucous membranes of the vagina, anus, sinus and oropharynx as well, but occurrence in these sites consists of only 5% of total melanomas.[20] It is not possible to always classify malignant melanomas (MMs) because of their varying presentations.[21]

3.3 Actinic keratosis (AK)

AK is described as earlier stage of SCC in situ.[22]It is an important marker for invasive SCC; both AK and SCC share genetic tumour markers and the same p53 gene (tumour suppressor gene) mutations.[23] Development of AK in SCC involves several steps as shown in Figure 1.

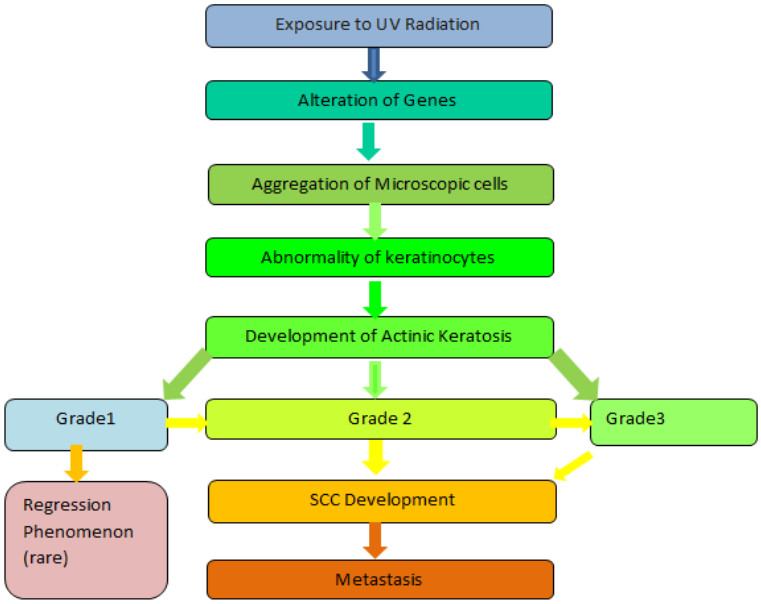

Fig 1: Stages of development of SCC from AK and invasive SCC.[23]

DNA damage and mutations induced by UV radiation initiate AK. The SCC development starts with development of a hot spot or aggregation of small, microscopic transformed cells. Features like atypia and pleomorphism are due to aggregates that form keratinocytes. The patient's immune response, decides whether the lesions may remain unchanged or grow and extend into the dermis. The presence of tumour cells in the dermis, is termed SCC and subsequently tumour cells may become metastatic.[23]AK lesions may represent as dry, scaly patches appearing as pink, red or brown in colour of various size. Yellowing and thickening of the dermis (solar elastosis) is commonly present, leading to infiltration of lymphocytes and plasma cells.[24] Hypertrophic keratosis are a subtype of AK that are present as thick and scaly plaques also present with conical growths or "horns".

AK is classified into three grades depending on the extent of atypical keratinocytes in the epidermis.[24]

Grade 1: In these, atypical keratinocytes are found above and in the stratum basale layer of the skin, occupying lower one third of the epidermis and show irregularities in nuclei.

Grade 2: In here keratinocytes are present in the lower two-third layer of the epidermis showing presence of buds of keratinocytes in the upper dermis.

Grade 3: Shows presence of Atypical keratinocytes in more than two third part of the epidermis and keratinocyte buds show presence particularly in the dermis.

4. TREATMENT APPROACHES FOR ACTINIC KERATOSIS

NMSC skin cancer is treated taking into consideration the type, size, location of the lesion and the patient's age. Radiotherapy and surgery could be the main treatment strategies. Dissection of lymph node is also considered for SCCs but this method is more aggressive with higher tendency to develop into metastasis.[22] Retinoids and cisplatin are agents used in oral chemotherapy. Photodynamic therapy, topical chemotherapy with retinoids,5-Flurouracil (5FU), Diclofenac sodium, Imiquimod, Ingenol mebutate are seen and laser surgery are the other treatment options.[25][20]

There are two types of treatment strategies for AK: lesion-directed and field-directed. Lesion-directed treats single lesions found in Grade 3 AK and in field-directed the entire field is treated irrespective of the number lesions present (≥10). Lesion-directed treatment includes cryosurgery, laser and curettage. Field-directed treatment includes photodynamic therapy, and topical chemo and immunotherapy. 5FU, Diclofenac sodium, Imiquimod and Ingenol mebutate show good efficacy in lesion directed treatment. Electrodessication and curettage is commonly used in the USA for treatment of AK.[26] [27]

4.1. Topical Treatment

Topical treatment is considered as an option when the tumours are present in the upper layer of the skin and for palliative treatment.

In the topical treatment of skin diseases the active pharmaceutical ingredient makes direct contact with the target site before it enters the systemic circulation. Thus the, systemic side effects are much reduced as compared to parenteral or oral drug administration, which is an important aspect for drugs with limited tolerability especially anticancer agents .For most topical actives, clearance of AK lesions leads to tissue inflammation, necrosis, skin discomfort, ulceration and crusting. Following is a review of reported literature of topical therapies that are currently available to enhance skin delivery of the molecules that are mentioned in (table 1).[28]

Table 1: Marketed products currently used in topical therapy of AK.[28]

Sr no.	Brand Name	Formulation w/w	Drug action	Dosing duration/Indication
1.	Efudex	5% FU cream 5%,2% 5-FU solution.	Antimetabolite	BID for 2-4 weeks. AK, Superfical basal carcinoma, Bowen's disease.
2.	Fluoroplex	1% Fluorouracil	Antimetabolite	BID for 2-4 weeks. AK
3.	Carac	0.5% 5-FU& 0.03% microsponge.	Antimetabolite	QD for 2-4 weeks. Actinic keratosis.
4	Actikerall	0.5% FU & 10% salicylic acid cutaneous solution.	Antimetabolite	Applied once daily. Actinic keratosis (grade 1/2)in adults.
5	Solaraze	3% Diclofenac sodium in hyaluronic acid.	Inhibit COX-2 And prostaglaidin E2	BID for 8-12 weeks. Actinic keratosis.
6	Aldara	5% Imiquimod	Immune response modifier.	BIW for 16 weeks. AK, superficial basal cell carcinoma.
7	Panretin	0.1% Alitretinoin	Activates RARS and RXRS resulting in gene modulation	Twice daily. AIDS related kaposis sarcoma, AK.
8	Zyclara	2.5% or 3.75% Imiquimod.	Immune response modifier.	BID for 2 weeks. AK, non hypertropic,non hyperkeratotic, visible or palpable lesions on head and face.
9	Picato	150 or 500 µg/g Ingenol mebutate	Lesion necrosis and neutrophil mediated cellular cytotoxicity.	Apply one tube daily for 3 days. AK, non-hypertropic, non-hyperkeratotic lesions.

4.1.1. Diclofenac sodium

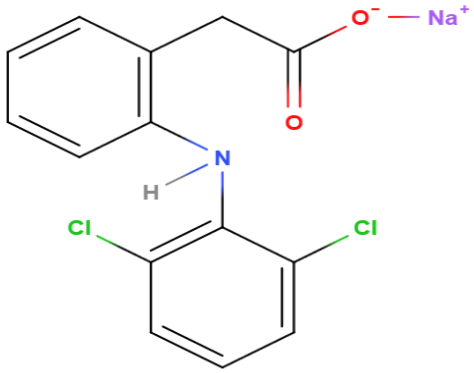

Fig. 2 Diclofenac sodium Chemical Structure.

Diclofenac has been used (as the sodium salt) for topical treatment of AK since the 1990s.[29] Non-steroidal anti-inflammatory drug is used due to over expression of the cycloxygenase-2 enzyme in AK and SCC compared with normal cells.[30] Compared with other topical actives for AK, the side-effects for topical Diclofenac are less severe. It was reported that there was no skin disposition and systemic absorption of Diclofenac on application of Solaraze™ to AK lesions.[31] Goh and Lane have studied the skin penetration characteristics of Diclofenac and its salts, using different formulation approaches for topical delivery. Various methods that promote enhanced permeation of diclofenac include: prodrugs, novel salt forms, supersaturation, use of penetration enhancers, microemulsions, lipid vesicles (including liposomes, Transferosomes™, lipid bicells), solid lipid nanoparticles, liquid crystalline mesophases, cyclodextrins, nano suspensions, films, patches, iontophoresis, laser microporation, ultrasound. Microneedle (MN) mediated delivery of NSAIDs has recently been reported this approach shows greater drug loading for treatment of lesions and may also increase the number of candidate NSAIDs for topical AK treatment.[32]

4.1.2. 5- Fluorouracil (5FU)

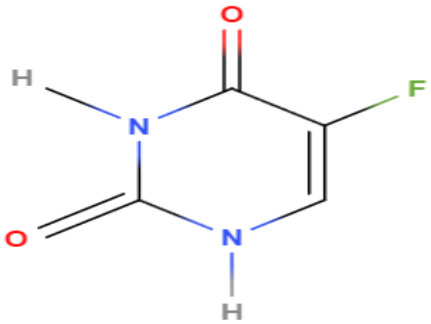

Fig: 3 5- Fluorouracil (5FU) Chemical Structure.

5-Fluorouracil (5-FU) is the approved molecule for the topical treatment of AK, superficial BCC and also for Bowen's disease. FU showed potential results in the management of AK in 1960, where the lesions disappeared in patients receiving systemic FU for different forms of cancer. FU inhibits enzyme responsible for synthesis of thymidine, a pyrimidine

nucleoside of DNA is its unique mechanism. FU shows sparing solubility in water.[33] Creams and solutions are currently available in a range of strengths (Table 1) with all formulations containing skin penetration enhancers. The permeation studies were carried out using procaine skin and human skin with 5% formulation.[34][35][36][37]

Dillaha et al.carried investigation of the systemic absorption of FU which was efficacious in treating the SCCs.[38] Levy et al. (2001b) reported that AK patients who were treated with either a 0.5% Microsponge FU formulation daily or 5% FU formulation twice daily for 28 days treated SCCs and FU was detected in the plasma of patients for both groups but in a higher proportion of the subjects who used the 5% FU formulation.[39]

4.1.3. Imiquimod

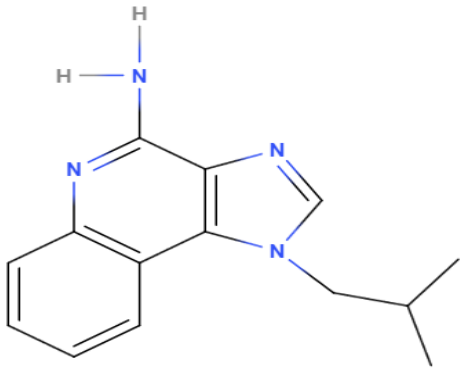

Fig.4 Imiquimod Chemical Structure

Topical Imiquimod cream (Aldara®) is FDA approved product for the treatment of superficial BCC and AK. This cream also shows effective results against skin diseases such as Bowen‟s disease, lentigo melanoma, SCC and cutaneous melanoma metastasis.[40] Imiquimod acts as an immunomodulator triggering cellular immune response through a toll-like receptor 7 (TLR7) resulting in up-regulation of a number of cytokines and apoptosis of neoplastic cells.[41] Zyclara® a lower strength preparation (3.75%) is available for AK lesions on specific body sites. This low strength preparation may be used daily, unlike Aldara® (5%) that has high concentration and may be applied over large skin area (table 1).

Imiquimod drug delivery was tested using a bioadhesive patch formulation and evaluated by Donnelly and co-workers.[42] De Paula et al. reported that in vitro permeation studies of imiquimod that was dermatomed by porcine skin using Franz cell showed good efficacy. Iontophoresis as a delivery for Imiquimod has been published in US Patent Application (US 2010/0331812 A1), although only data for rat models was disclosed.[43]

4.1.4. Ingenol mebutate

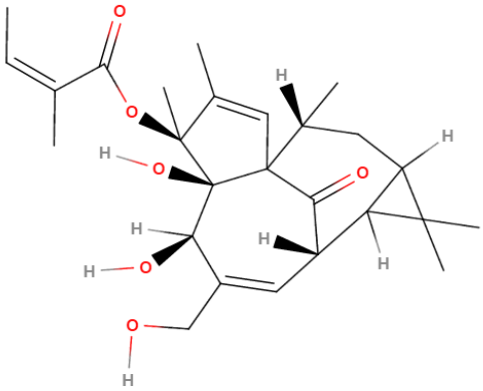

Fig: 5 Ingenol mebutate Chemical Structure.

Ingenol mebutate (IM) a natural macrocyclic diterpene ester was isolated from an indigenous Australian plant, *Euphorbia peplus*.[44][45] The precise mechanism of action of IM is not known, however it overcomes rapid lesion necrosis and neutrophil-mediated cellular cytotoxicity.[46] It modifies the protein kinase C isoforms in tumour cells in vitro.[47] Currently this is available as a gel formulation and in two strengths for the treatment of AK, the lower for face and the higher for the extremities refer (Table 1). Treatment regime is for three consecutive days which is shorter when compared with other topical AK therapies.

Erlendsson and co-authors (2015) recently reported effects of laser treatment on IM disposition in porcine skin. The studies indicate that 57% of the applied dose remain in or on the skin at the end of the experiment; for laser treated skin shows maximum values in layer of skin like epidermis and dermis respectively, that were 62% and 18% of the applied dose.[48]

4.1.5. Topical retinoids

Demonstration of Vitamin A analogues (retinoids) on hyperkeratinisation, inflammation and immunomodulation in topical or oral dosage have been reported a long time back.[49]Response of retinods was seen by interaction with retinoic acid receptors (RARs) or retinoic X receptors (RXRs) thereby activating genes containing retinoic acid response elements (RAREs) or retinoic X response elements (RXREs). First generation retinoids used for topical treatment of AK include tretinoin (all trans-retinoic acid) and isotretinoin (13-cis-retinoic acid); the third generation retinoid, adapalene, has also been investigated.[50] Tretinoin and adapalene were used to treat AK or NMSC in synergism along with laser therapy.[51][52]Topical tretinoin reduce the risk of both BCC and SCC. The efficacy of topical retinoids in the management of AK is much low, thus they remain unapproved for treatment of this condition. Alitretinoin (9-cis-retinoic acid) is a first generation retinoid activating both RARs and RXRs and shows effect on genes responsible for cell proliferation and differentiation. It is used for the management of skin

lesions in patients with AIDS-related Kaposi's sarcoma as well excluding the systemic Kaposi's sarcoma. Only formulation of alitretinoin is currently available and is licensed both in Europe and the United States is given in (Table 1).[53]

4.2. Cryosurgery

Cryosurgery (cryotherapy) denotes use of extreme cold conditions in surgery to destroy abnormal or diseased tissues, employed when the number of lesions are very few.CO_2 and nitrogen are the most commonly used agents in this procedure. Mechanism involved in cryotherapy is that the heat transferred from the keratosis growth to the liquid freezing nitrogen such that growth begins to dry up and falls off. Intra cellular contents of frozen skin growth may leak out after the liquid nitrogen has dried and during the leaching out of cellular contents of keratosis growth an individual will feel inflammation, redness of skin and pain occurs in treated tissues because of intracellular ice formation. The degree of damage depends on the rate of cooling and the minimum temperature achieved.[54]

4.3. Photodynamic therapy (PDT)

Photosensiting drugs are activated by visible light like red light (Metvixia®) and blue light (Levulan®)there by generating cytotoxic oxygen species and free radicals, which selectively destroy rapidly proliferating cells. 5-aminolevulinic acid (5-ALA) is a form of topical photosensitizer that absorbs to a great extent by rapidly proliferating cells than by normal cells, getting converted to protoporphyrin IX (PpIX), a very potent photosensitizer inside the cell. Activation of PpIX in visible light produced singlet oxygen species and free radicals, leading to cell destruction.[55] Using an artificial form of white light for photodynamic therapy gave effective results and was tolerated in same way like the daylight photodynamic therapy in men with actinic keratosis.[56]

4.4. Curettage and Electrodessication

Electrodessication is a surgical method that combines cutting and electrocautery. Thick actinic keratosis, unable to be treated with liquid nitrogen or topical creams is treated with a procedure called electrodessication and curettage. Small amount of lidocaine is used to anesthesize AK. Sharp instrument called a curette, helps to scrape away the very thick keratosis portion. Abnormal kerationocyte cell remain at the base after the curette is used, these cells are then treated with electrodessication using a device called hyfrecator. This delivers a controlled amount of heat to the lesion destroying remaining abnormal cells. The process is painless. It may show complications like infection, scarring, and hypo- or hyperpigmentation.[57]

4.5. Combination Therapy

New approaches for treatment of AK bring together combination of lesion-directed therapies with field-directed therapies there by resulting in optimization of photo damaged skin. Examples of combined treatment that have been evaluated in trials are as follows.

1. Use of cryotherapy before or after topical 5-FU.[58]
2. Use of cryotherapy after topical Imiquimod.[59]
3. Use of PDT before or after Topical Imiquimod.[60]

4.6. Chemical Peeling

Use of chemical peeling is reported to treat unaesthetic cutaneous alterations such as photoageing, actinic keratosis, senile lentigo, and post-acneic scars and those of non-strictly aesthetic nature such as seborrhoeic keratosis and flat warts. Use of chemical agents depends on the depth of peeling to be obtained. The commonly used agents include alpha-hydroxy-acids, Resorcinol, Jessner's solution (containing resorcinol 14 g, salicylic acid 14 g, lactic acid 14 mL in ethanol to make 100 mL) , and Trichloroacetic acid(TCA). This technique can cause temporary discoloration and even irritation.[61]

4.7. Laser Therapy

Laser treatment is one of the options wherein either ablative lasers (CO_2 and Erbium Yttrium Aluminium Garnet) or non-ablative fractional laser systems can be used. Superficial layer of skin is ablated, including epidermal and superficial dermal active damage. The important risk of this treatment is scarring and dyspigmentation, which is overcome by using fractional lasers. These produce small coloumns of ablation or coagulation in the skin leaving surrounding skin intact.[62]

5. NOVEL APPROACHES FOR PRESENT TOPICAL TREATMENT

5.1. Microneedles

Superficial basal cell carcinoma and actinic keratosis are treated with topical 5-Fluoro uracil. 5-FU shows poor skin permeation. Microneedles that are prepared improve the skin permeability of these small and large molecules, and even nanoparticles, this is done by creating micron-sized pores in the stratum corneum layer of the skin. The flux of 5-FU through the skin increased up to 4.5-fold when the skin was pretreated with microneedles.[63]

5.2. Dendrimers

Dendrimers are tree like structures that originate form the core of the molecule. They are also called as 'Arborols' that means a monocascade spheres.[64] Use of Janus type of dendrimer showed increase in the permeability of Dicolfenac sodium with G-1 and G-2 oligidendirmers.[65] Dendrimers that were synthesized using arginine and other terminal amino acids showed a remarkable increase in the penetration through the epidermis and enhanced the deposition of drug.[66]

5.3. Vesicular Systems

Ethosomes, contain good amount of ethanol to increase the fluidity of stratum cornium same is the case for transferosomes where surfectants are used. The high content of alcohol in ehtosomes increases intre and intracellular permeability.[67] Z.Zang.,et.al by his studies

concluded that 5-Fluououracil was effective and safe as transdermal delivery system as ethosomes.[68] Saeed G., et.al by his research concluded that diclofenac sodium showed increased permeability through skin as transferosomes and ethosomes working as permeation enhancer.[69]

5.4. Microsponges

Diclofenac sodium microsponges reveled good spreadibility, efficacy and time based drug release which was better than conventional gel or cream.[70] Levden JJ.,et.al in his study with tretinoin 0.1% microsponge gel did not show better efficacy than 0.1% tazarotene gel for acne vulgaris.[71] Studies on 5-fluouo uracil 0.5% cream microsponge showed better efficacy and tolerability in treatment of actinic keratosis.[72]

5.5. Emulgels and Emulsions

Nanoemulsions are new delivery systems that are formulated for increase in penetration of drugs with low solubility. They are more effective than polymeric nanoparticles and liposomes. Nanoemulgel are nanoemulsion formulated as hydrogel base show better permeation, due to decreased surface and interfacial tension.[73] Microemulsions are colloidal carrier systems thermodynamically stable, diclofenac sodium microemulsions show increased penetration as compared to conventional gel formulation.[74] 5-Fluoro uracil based ionic liquid-in-oil (IL/o) microemulsions show better penetration, solubility and efficacy against skin cancer.[75]

6. CONCLUSION

Reported literature suggests that incidences of non-melanoma skin cancer and actinic keratosis (AK) are continuously increasing per year which draws the attention of researchers towards seeking new treatment options and making the existing ones more efficient. Conventional topical therapies are less efficient in providing sustained release of the active agent since it is freely suspended in the vehicle. Also, the presence of free drug has severe side effects when it directly comes in contact with the skin. Novel approaches may provide solutions to overcome this problem by encapsulating the drug into vehicles which will can provide sustained effect and decrease the side effects.

REFERENCES

1. Bradford PT. Skin cancer in skin of color. Dermatology nursing/Dermatology Nurses' Association, 2009; 21(4): 170.
2. Ibrahim SF, Brown MD. Actinic keratoses. J Clin Aesthetic Dermatol, 2009; 2(7): 43-8.
3. Baroni A, Buommino E, De Gregorio V, Ruocco E, Ruocco V, Wolf R. Structure and function of the epidermis related to barrier properties. Clinics in dermatology, 2012; 30(3): 257-62.
4. Wertz PW, Downing DT. Stratum corneum: biological and biochemical considerations. Transdermal drug delivery, 1989; 35: 1-7.
5. Ito S, Wakamatsu K. Quantitative analysis of eumelanin and pheomelanin in humans, mice, and other animals: a comparative review. Pigment cell research, 2003; 16(5): 523-31.
6. Raposo G, Marks MS. The dark side of lysosome-related organelles: Specialization of the endocytic pathway for melanosome biogenesis. Traffic, 2002; 3(4): 237-48.
7. Park HY, Kosmadaki M, Yaar M, Gilchrest BA. Cellular mechanisms regulating human melanogenesis. Cellular and Molecular Life Sciences, May 1, 2009; 66(9): 1493-506.
8. Benson HA, Watkinson AC, editors. Topical and Transdermal Drug Delivery: Principles and Practice. John Wiley & Sons, 2012.
9. Elias PM, Cooper ER, Korc A, Brown BE. Percutaneous transport in relation to stratum corneum structure and lipid composition. Journal of Investigative Dermatology, 1981; 76(4): 297-301.
10. Potts RO, Guy RH. Predicting skin permeability. Pharmaceutical research, 1992; 9(5): 663-9.
11. Katz M, Poulsen BJ. Absorption of drugs through the skin. InConcepts in Biochemical Pharmacology, 1971; (103-174).
12. Vella F. The human skin: By EJ Wood and PT Bladon. Pp 68. Edward Arnold, London. 1985.£ 2.95 ISBN 0-7131-2900-X. Biochemical Education, 1986; 14(3): 149.
13. Murphy, Gillian M. "From precursor to cancer: field cancerization and the opportunities for therapy." Non-Surgical Treatment of Keratinocyte Skin Cancer. Springer Berlin Heidelberg, 2010; 1-7.
14. Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. Dermatologic Surgery, 2007; 33(9): 1099-101.
15. Jerant AF, Johnson JT, Sheridan C, Caffrey TJ. Early detection and treatment of skin cancer. American family physician, 2000; 62(2): 357-86.
16. Maddodi N, Setaluri V. Role of UV in cutaneous melanoma. Photochemistry and photobiology, 2008; 84(2): 528-36.
17. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. International Journal of Cancer, 2007; 121(9): 2105-8.
18. Goldenberg, G., L. E. Golitz and J. Fitzpatrick. Histopathology of skin cancer.Managing Skin Cancer. Springer Berlin Heidelberg, 2010; 17-35.
19. Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, Vernon SW, Cronin K, Edwards BK. The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer, 2000; 88(10): 2398-424.
20. Skeel, Roland T.,and Samir N. Khleif, eds. *Handbook of cancer chemotherapy*. Lippincott Williams & Wilkins, 2011.

21. Markovic SN, Erickson LA, Rao RD, McWilliams RR, Kottschade LA, Creagan ET, Weenig RH, Hand JL, Pittelkow MR, Pockaj BA, Bardia A. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. InMayo Clinic Proceedings. Elsevier, 2007; 82(3): 364-380.
22. McGuire JF, Norman NG, Dyson S. Nonmelanoma skin cancer of the head and neck I: histopathology and clinical behavior. American journal of otolaryngology, 2009; 30(2): 121-33.
23. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). Journal of the American Academy of Dermatology, 2000; 42(1): S11-7.
24. Röwert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, Sterry W, Stockfleth E. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. British Journal of Dermatology, 2007; 156(s3): 8-12.
25. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. British Journal of Dermatology, 2008; 159(1): 35-48.
26. De Berker D, McGregor JM, Hughes BR. Guidelines for the management of actinic keratoses. British Journal of Dermatology, 2007; 156(2): 222-30.
27. Zalaudek I, Piana S, Moscarella E, Longo C, Zendri E, Castagnetti F, Pellacani G, Lallas A, Argenziano G. Morphologic grading and treatment of facial actinic keratosis. Clinics in dermatology, 2014; 32(1): 80-7.
28. McGillis ST, Fein H. Topical treatment strategies for non-melanoma skin cancer and precursor lesions. InSeminars in cutaneous medicine and surgery, 2004; 23(3): 174-183.
29. Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. Archives of dermatology, 1997; 133(10): 1239-42.
30. Buckman SY, Gresham A, Hale P, Hruza G, Anast J, Masferrer J, Pentland AP. COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. Carcinogenesis, 1998; 19(5): 723-9.
31. Goh CF, Lane ME. Formulation of diclofenac for dermal delivery. International journal of pharmaceutics, 2014; 473(1): 607-16.
32. McCrudden MT, Alkilani AZ, McCrudden CM, McAlister E, McCarthy HO, Woolfson AD, Donnelly RF. Design and physicochemical characterisation of novel dissolving polymeric microneedle arrays for transdermal delivery of high dose, low molecular weight drugs. Journal of Controlled Release, 2014; 180: 71-80.
33. Moffat AC, Osselton MD, Widdop B, Watts J. Clarke's analysis of drugs and poisons. Pharmaceutical Press, 2011.
34. Møllgaard B, Hoelgaard A, Bundgaard H. Pro-drugs as drug delivery systems XXIII. Improved dermal delivery of 5-fluorouracil through human skin via N-acyloxymethyl pro-drug derivatives. International Journal of Pharmaceutics, 1982; 12(2-3): 153-62.
35. Bond JR, Barry BW. Damaging effect of acetone on the permeability barrier of hairless mouse skin compared with that of human skin. International journal of pharmaceutics, 1988; 41(1): 91-3.
36. Levy S, Furst K, Chern W. A comparison of the skin permeation of three topical 0.5% fluorouracil formulations with that of a 5% formulation. Clinical therapeutics, 2001; 23(6): 901-7.
37. Mutalik S, Shetty PK, Kumar A, Kalra R, Parekh HS. Enhancement in deposition and permeation of 5-fluorouracil through human epidermis assisted by peptide dendrimers. Drug delivery, 2014; 21(1): 44-54.
38. Dillaha Cj, Jansen Gt, Honeycutt Wm, Holt Ga. Further studies with topical 5-fluorouracil. Archives of dermatology, 1965; 92(4): 410-7.
39. Levy S, Furst K, Chern W. A pharmacokinetic evaluation of 0.5% and 5% fluorouracil topical cream in patients with actinic keratosis. Clinical therapeutics, 2001; 23(6): 908-20.
40. Taveira SF, Lopez RF. Topical administration of anticancer drugs for skin cancer treatment. INTECH Open Access Publisher, 2011; 247-272.
41. Sligh Jr JE. New therapeutic options for actinic keratosis and basal cell carcinoma. Semin Cutan Med Surg, Jun 1, 2014; 33(4): S76-80.
42. Donnelly RF, McCarron PA, Zawislak AA, Woolfson AD. Design and physicochemical characterisation of a bioadhesive patch for dose-controlled topical delivery of imiquimod. International journal of pharmaceutics, 2006; 307(2): 318-25.
43. Paula DD, Martins CA, Bentley MV. Development and validation of HPLC method for imiquimod determination in skin penetration studies. Biomedical Chromatography, 2008; 22(12): 1416-23.
44. Siller G, Gebauer K, Welburn P, Katsamas J, Ogbourne SM. PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: Results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. Australasian Journal of Dermatology, Feb 1, 2009; 50(1): 16-22.
45. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. New England Journal of Medicine, 2012; 366(11): 1010-9.
46. Rosen RH, Gupta AK, Tyring SK. Dual mechanism of action of ingenol mebutate gel for topical treatment of actinic keratoses: rapid lesion necrosis followed by lesion-specific immune response. Journal of the American Academy of Dermatology, 2012; 66(3): 486-93.

47. Kedei N, Lundberg DJ, Toth A, Welburn P, Garfield SH, Blumberg PM. Characterization of the interaction of ingenol 3-angelate with protein kinase C. Cancer research, 2004; 64(9): 3243-55.
48. Erlendsson AM, Taudorf EH, Eriksson AH, Haak CS, Zibert JR, Paasch U, Anderson RR, Haedersdal M. Ablative fractional laser alters biodistribution of ingenol mebutate in the skin. Archives of dermatological research, 2015; 307(6): 515-22.
49. Elias PM, Williams ML. Retinoids, cancer, and the skin. Archives of dermatology, 1981; 117(3): 160-80.
50. Kang S, Goldfarb MT, Weiss JS, Metz RD, Hamilton TA, Voorhees JJ, Griffiths CE. Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. Journal of the American Academy of Dermatology, 2003; 49(1): 83-90.
51. Prens SP, Vries KD, Neumann HM, Prens EP. Non-ablative fractional resurfacing in combination with topical tretinoin cream as a field treatment modality for multiple actinic keratosis: a pilot study and a review of other field treatment modalities. Journal of Dermatological Treatment, 2013; 24(3): 227-31.
52. Pearce DJ, Williford PM. Another approach to actinic keratosis management using nonablative fractional laser. Journal of Dermatological Treatment, 2014; 25(4): 298-.
53. Prens SP, de Vries K, Neumann HA, Prens EP. Non-ablative fractional resurfacing in combination with topical tretinoin cream as a field treatment modality for multiple actinic keratosis: a pilot study and a review of other field treatment modalities. J Dermatolog Treat, 2013; 24: 227.
54. Thai K, Fergin P, Freeman M, et al. A prospective study of the use of cryosurgery for the treatment of actinic keratoses. Int J Dermatol, 2004; 43: 687–692.
55. Dover JS. Cosmeceuticals: A practical approach. Skin Therapy Lett Pharmacist Edition, 2008; 3(1): 1-3.
56. O'Gorman SM, Clowry J, Manley M, McCavana J, Gray L, Kavanagh A, Lally A, Collins P. Artificial White Light vs Daylight Photodynamic Therapy for Actinic Keratoses: A Randomized Clinical Trial. JAMA dermatology, 2016; 152(6): 638-44..
57. Mcintyre WJ, Downs MR, Bedwell SA. Treatment options for actinic keratoses. Am Fam Physician, 2007; 76(5): 667-71.
58. Hoover 3rd WD, Jorizzo JL, Clark AR, Feldman SR, Holbrook J, Huang KE. Efficacy of cryosurgery and 5-fluorouracil cream 0.5% combination therapy for the treatment of actinic keratosis. Cutis, 2014; 94(5): 255-9.
59. Tolosa, Nancy Rivas, et al. "Imiquimod enhances the effect of cryotherapy in the management of cutaneous melanoma metastases: A retrospective study of 20 patients." Journal Of The American Academy Of Dermatology. Vol. 72. No. 5. 360 Park Avenue South, New York, NY10010-1710 USA: Mosby-Elsevier, 2015.
60. Held L, Eigentler TK, Leiter U, Garbe C, Berneburg MJ. Effective combination of photodynamic therapy and imiquimod 5% cream in the treatment of actinic keratoses: three cases. BioMed research international, 2012 Dec 27; 2013.
61. Lawrence N, Cox SE, Cockerell CJ, Freeman RG, Cruz PD Jr. A comparison of the efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Arch Dermatol*, 1995; 131: 176–81.
62. Ostertag JU, Quaedvlieg PJ, van der Geer S, et al. A clinical comparison and long-term follow-up of topical 5-fluorouracil versus laser resurfacing in the treatment of widespread actinic keratoses. Lasers Surg Med., 2006; 38: 731.
63. Naguib YW, Kumar A, Cui Z. The effect of microneedles on the skin permeability and antitumor activity of topical 5-fluorouracil. Acta Pharmaceutica Sinica B., 2014; 4(1): 94-9.
64. Donnelly, Ryan F., and Thakur Raghu Raj Singh. *Novel delivery systems for transdermal and intradermal drug delivery*. John Wiley & Sons, 2015.
65. Kalhapure RS, Akamanchi KG. Oleodendrimers: A novel class of multicephalous heterolipids as chemical penetration enhancers for transdermal drug delivery. International journal of pharmaceutics, 2013; 454(1): 158-66.
66. Mutalik S, Shetty PK, Kumar A, Kalra R, Parekh HS. Enhancement in deposition and permeation of 5-fluorouracil through human epidermis assisted by peptide dendrimers. Drug delivery, 2014; 21(1): 44-54.
67. Godin B, Touitou E. Ethosomes: new prospects in transdermal delivery. Critical Reviews™ in Therapeutic Drug Carrier Systems, 2003; 20(1).
68. Zhang Z, Wang X, Chen X, Wo Y, Zhang Y, Biskup E. 5-Fluorouracil-Loaded Transfersome as Theranostics in Dermal Tumor of Hypertrophic Scar Tissue. Journal of Nanomaterials, Dec 16, 2015.
69. Ghanbarzadeh S, Arami S. Enhanced transdermal delivery of diclofenac sodium via conventional liposomes, ethosomes, and transfersomes. BioMed research international, 2013; 2013.
70. Hussain H, Dhyani A, Juyal D, Bahuguna A. Formulation and evaluation of gel-loaded microsponges of diclofenac sodium for topical delivery. Pharm Innovation J., 2014; 3: 58-63.
71. Leyden JJ, Tanghetti EA, Miller B, Ung M, Berson D, Lee J. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1% microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis, 2002; 69(2): 12-9.
72. Menter A, Vamvakias G, Jorizzo J. One-week treatment with once-daily fluorouracil cream 0.5% in participants with actinic keratoses. Cutis., 2008; 81(6): 509-16.
73. Chellapa P, Mohamed AT, Keleb EI, Elmahgoubi A, Eid AM, Issa YS, Elmarzugi NA. Nanoemulsion and

Nanoemulgel as a Topical Formulation. Journal Of Pharmacy, 2015; 10(5): 43-47.
74. Dima S, Popescu M. Topical delivery of diclofenac using microemulsion systems. Roum Biotechnol Lett., 2001; 13: 6.
75. Goindi S, Arora P, Kumar N, Puri A. Development of novel ionic liquid-based microemulsion formulation for dermal delivery of 5-fluorouracil. AAPS Pharm Sci Tech, 2014; 15(4): 810-21.