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Review Article

An insight on atopic dermatitis therapy: from conventional to lipid-based nanocarriers

Layla H. Hashem, Heba A. Gad*, Omaima A. Sammour

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt

ABSTRACT

Atopic dermatitis (AD) is a common itching disorder that begins in infancy and may occur in persons with a family history of atopic disease. The disease is characterized by several changes in the epidermal layer with elevated serum immunoglobulin E (IgE) antibodies and histamine. Until now, there is no evident treatment for AD disease; however, topical therapy including topical corticosteroids has been used in both children and adults. Although the preferable route is the topical route, the low penetration across the stratum corneum (SC) layer is a great challenge for researchers and scientists. Nowadays the available drugs have severe side effects and low skin availability. Nanocarriers including liposomes, nanoparticles, nano-mixtures, nanogels, nano-emulsions, and others, offer a good solution to these problems. Nanocarriers enable the treatment of different forms of dermatitis, enhance drug bioavailability at the site of inflammation, reduce the side effects, and increase the safety profiles. Nanoparticulate systems can enhance topical medication delivery because of their ability to upgrade the drug loading, dissolution, and protect the unstable drug from degradation. This review offers an overview of AD types, different management modalities, systemic versus topical treatment, in addition to different types of lipid-based nanocarriers that have been investigated for the management of AD.

Keywords: *Atopic dermatitis; conventional therapy; corticosteroids; topical delivery; lipid nanocarriers.*

***Correspondence** | Heba A. Gad; Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt. Email: h.gad@pharma.asu.edu.eg

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1. INTRODUCTION

To understand the action of the topically applied medicaments, an in-depth comprehensive study of the skin structure as the target organ should be undergone.

1.1. Skin Structure

Skin is formed of three layers, which are the epidermis, dermis, and hypodermis. Histologically, the epidermis is considered as an epithelial layer with stratified squamous cell type in which the abundant cells (keratinocytes) are composed of five unique strata. These strata are particularly called: 1- stratum basal (which is in high contact with dermis), 2-stratum spinosum, 3-stratum granulosum, 4-stratum lucidum, and 5-stratum corneum (which are in contact with the environment).

The epidermis is essential for protective purposes, while the dermis has capillary anastomoses, which helps in bringing oxygen and supplement to the epidermis layer and clarify the dermis from the metabolic products of cells and foreign agents **[1]**. Continuous renewal and

regeneration maintain the epidermis in healthy condition and offer great defense properties toward the environmental conditions. Epidermis might be essentially recognized in the viable epidermis (thickness 50-100 nm) and the stratum corneum (thickness 10-20 nm) and its shape can be designed by brick and mortar **[2]**.

The most important layers for drug penetration into the systemic circulation are the epidermis and the dermis. Stratum corneum (Sc) is the rate-limiting step for drug penetration **[3]**, as it represents the main barrier for drug permeation owing to its unique structure. Sc barrier properties are related to the high density of the cells, low hydration, composition of keratin and lipids, and presence of intercellular regions of desmosomes. In consequence, lipophilic drugs can easily penetrate the Sc due to its hydrophobicity **[4]**.

The third layer of the skin is the hypodermis layer, which is a layer of fatty or adipose tissue. It serves as a caution for the dermis and epidermis, and a thermal barrier to the body from low external temperatures by synthesizing and storing high-energy chemicals, and it also acts as a buffer against trauma **[5]**.

1.2. Factors affecting skin absorption

The lipid matrix of the skin is responsible for maintaining skin homeostasis **[6]**. Generally, factors affecting skin permeation may be recognized in three various classes:

1. Skin conditions and location at the site of application (skin integrity, orifice dimension, appendages density).

2. Physico-chemical properties of the substance that can penetrate the skin (pka and partition coefficient of the substance, which determines its solubility in the skin, the molecular weight of the agent must be < 600 Da).

3. Physico-chemical properties of solvent dissolving/dispersing the penetrating substance e.g. pH of the vehicle.

2. There are four types of Dermatitis

2.1. Atopic dermatitis (AD)

Atopic dermatitis is an unending incendiary skin disease related to cutaneous hyper-reactivity to natural triggers and is regularly the initial phase that outcomes in unfavorably susceptible rhinitis and asthma. The clinical manifestations that describe atopic dermatitis are the result of connections between environmental, genetic, and immunologic reactions and defects in the skin barrier role **[7]**. This pathological case requires high skincare and pharmacological treatment because it has serious effects on patient life. The analysis of AD depends on the accompanying grouping of clinical discoveries: facial and extensor skin inflammation in babies and kids, pruritus, flexural skin inflammation in grown-ups, and chronicity of dermatitis. AD normally exacerbates in the earliest stages of childhood and adolescence, yet it can hold on into or begin in adulthood **[8]**. The lifetime pervasiveness of AD is 10– 20% in kids and 1– 3% in grown-ups.

Two types of AD have been portrayed: an "extrinsic" shape related with Immunoglobulin E (IgE)-mediated sharpening including 70– 80% of the AD patients, and an "intrinsic" shape without IgE-intervened including 20– 30% of the patients **[9]**. The two types of AD have related eosinophilia. In AD, memory T-cells communicating the skin-homing receptor and cutaneous lymphocyte-related antigen (CLA) create expanded levels of Th2-type cytokines. These incorporate interleukins (IL-4 and IL-13), which are known to actuate isotype changing to Immunoglobulin E (IgE) combination, and IL-5, which assumes a critical role in eosinophil improvement and survival. These CLA+T-cells deliver anomalous low levels of interferon (IFN-γ), a Th1-type cytokine known to restrain Th2

cell work. Extrinsic AD is characterized by more IL-4 and IL-13 creation than intrinsic type **[7]**.

Most researchers revealed that the increment in the commonness of atopic infection has occurred during the last decade, the explanation behind this increase is not known. Exposure to air contamination, chemicals, a decrease in breastfeeding, and the use of additives in food may influence people's health in general and induce atopic dermatitis **[10]**. In addition, they believed that asthma might induce atopic eczema.

2.2. Irritant contact dermatitis (CD)

Irritant contact dermatitis has been characterized as a non-immunological non-particular response of the skin to an aggravation. It may be triggered by a blend of exogenous and endogenous factors, which may introduce a pathophysiological effect to the skin barrier, causing cell harm to the keratinocyte film and resulting in the release of the inflammatory mediator.

Two fundamental sorts of CD might be perceived to be specific, the first one is the aggravation contact dermatitis and the other is a topic susceptible contact dermatitis. Other extra types of CD are photo contact (phototoxic and photoallergic) dermatitis.

Another type is the protein CD **[11]**. Upon skin contact with low molecular weight chemicals named haptens, it will penetrate through the skin and attach covalently to the amino acid on the proteins. The Langerhans cells and dermal dendritic cells will internalize haptens and then migrate to specific lymph nodes. Hapten bounds peptide complex to T-cell. The sensitization phase leads to the proliferation of class I and class II of T-cell. Repeated exposure of the individual to this hapten evokes the ejector phase of contact dermatitis, which clinically brings skin inflammation and causes eczema **[12]**.

2.3. Dyshidrotic type of dermatitis

Dyshidrotic type of dermatitis influences patients near 20-40 years old. During the dyshidrotic type of dermatitis, the arrangement of spongy vesicles occurs because of different firey boosts. Symptoms include psychological discomfort and pruritus. Pathogenesis-causing factors include contact hypersensitivities, atopy, aggravation, and smoking. Avoidance of this pathogenesis does not lead to complete healing **[13]**.

2.4. Seborrheic dermatitis

Seborrheic dermatitis is a skin oily inflammation, happening regularly on the scalp, face, and chest. It is related to Juvenile seborrheic dermatitis and diaper rash. Seborrheic dermatitis is especially found in patients with HIV/AIDS and Parkinson′s disease. The reason for seborrheic dermatitis is obscure. These incorporate exogenous variables (more typical in winter) and different exogenous factors.

Despite the absence of an unmistakable relationship between sebum levels and the improvement of seborrheic dermatitis, there is still some association between sebum level and seborrheic dermatitis. Except for childhood seborrheic dermatitis, the ailment is rare before pubescence and is most normal in puberty and young adulthood, when sebaceous organs are at the higher activity. The scalp, face, chest, and back are the most normally influenced zones. Moreover, the skin surface lipid structure in men with seborrheic dermatitis has been shown to vary from that of unaffected controls **[14]**.

3. Management of atopic dermatitis

AD is not a curable disease, but the treatment aims to diminish the disease exacerbation, there are wide varieties of medications used in the treatment of dermatitis, however, the drug choice depends on many factors such as patient age, disease severity, and complication. Fortunately,

most AD patients can control the disease state by skin care and topical therapy. However, severe AD patients with eczematous lesions may not respond to topical drug application or moisturizers, so patient compliance is our real issue **[15]**. The treatment line may be classified as follows:

1- Non-pharmacological approaches.

2- Natural remedies (Emollients).
3- Topical therapy (corticosteroids, doxepin, and calcineurin inhibitors).
4- Other medications including phototherapy, vitamin D, antihistamines, anti-viral agents, antibiotics, and sometimes the use of biologics if needed.
5- Systemic therapy (oral corticosteroids, azathioprine, cyclosporine A, methotrexate).

3.1. Non-pharmacological approaches

Non-pharmacological approaches include avoidance of some food types; this approach may be helpful in children rather than adults with severe AD symptoms**.** Some studies supported the exclusion of eggs and milk in some cases **[16].** Other studies supported egg-free diets in AD infants who produce IgE-Ab to egg protein. However, highly restricted diets are not recommended because of malnutrition **[17]**.

3.2. Natural remedies (emollients)

Aromatherapy is a type of therapy that depends on the use of aromatic compounds present in natural plants, including essential oils and other compounds in the management of diseases. Aromatherapy is characterized by both topical and systemic application of oils, which are prepared by the distillation of water vapor of the flowers, fruits, and leaves of the plants **[18]**. Among the essential oils used in the treatment of dermatitis are almond oil, horse oil, coconut oil, olive oil, tea tree oil**.** These oils can act as emollients, which increase skin hydration of the epidermis, by reducing water evaporation, forming an occlusive layer on the skin surface **[19]**.

In addition, these oils were reported to increase the drug penetration by simple modification in the stratum corneum lipid layer, and therefore they are considered as good transdermal penetration enhancers **[20]**. These remedies were utilized to treat an assortment of skin conditions (e.g., dermatitis, eczema, sensitivities, and rash). Emollients may improve the xerosis (dry skin) and appearance of atopic skin**.** Some studies reported that emollients may reduce the topical corticosteroids need by 50% **[21]**. Another study has shown that the use of emollients may enhance the effect and the response to topical corticosteroids **[22].** Finally, these emollients can be used alone or in combinations with topical corticosteroids as first-line therapy in the treatment of atopic dermatitis disease **[13]**.

3.3. Topical treatments

3.3.1. Corticosteroids

Corticosteroids **(**CS**)** are a class of steroid hormone produced and released in the adrenal cortex, which can be divided into two classes, mineralocorticoids, and glucocorticoids. Corticosteroids are involved in many physiological processes such as immune and stress response, protein catabolism, carbohydrate metabolism, regulation of inflammation, and behavior**.** Synthetic corticosteroid drugs are used in the management of various conditions ranging from tumors to skin disease **[23]**.

Corticosteroids are considered the first line of treatment of atopic dermatitis. Corticosteroids, such as triamcinolone, clobetasol, betamethasone, and fluocinolone are proposed to modify the inflammatory reaction, which gives a helpful advantage to provide therapeutic benefit (anti-inflammatory effect*)* **[24]**. The mechanism of action of corticosteroid includes binding of the medication with steroid receptors inside the

cytoplasm or outside the nuclear membrane; this complex will bind to DNA and change the mRNA transcription, which synthesizes the proteins, which are responsible for particular impact **[25]**.

3.3.2. Immunosuppressive drugs (Topical Calcineurin Inhibitors)

Immunosuppressive drugs like tacrolimus and pimecrolimus act by binding to T-cell receptor immunophilin, this complex inhibits the formation of calcineurin, a protein phosphatase needed for T-cell activation. This prevents the transcription step and the release of pro-inflammatory cytokines and decreases the production of mast cell (e.g., TNF-alpha) and IgE induced pro-inflammatory mediators. Consequently, the effect is reducing the inflammatory response **[26]**.

Both tacrolimus and pimecrolimus are approved as second-line treatment. In the United State in 2005, the Center for Drug Evaluation and Research made an alert to study the link between these drugs and skin cancer and lymphoma based on the animal study. Health care professionals emphasized the use of these drugs only when first-line therapy has failed **[27]**.

3.3.3. Topical Doxepin

The use of topical doxepin resulted in relief from the itching effect within 2 days of use, but the drowsiness side effect was a problem **[28]**.

3.4. Other medications

In uncontrolled atopic dermatitis, many complications may occur to the patients such as fungal, bacterial, or viral infections, which require further therapy.

3.4.1. Antiviral therapy

AD patients have an excessive risk of virus-related infections due to the insufficient manufacture of the antimicrobial peptides. Herpes simplex infection may occur in patients with severe untreated skin lesions or with systemic symptoms and elevated serum IgE levels. Other symptoms like fever, lymphadenopathy, malaise, erupted pustules and blisters should be treated immediately in eczematous herpeticum patients using systemic antivirals such as acyclovir **[29]**.

Secondary infections with bacteria are common in AD patients. They may be more prone to infection with S. aureus, so a short course of antibiotics may be recommended such as cephalexin, floxacillin, and amoxicillin-clavulanate**.** Although the combinations of antibiotics and CS are used for AD, there is no study suggesting the additional benefits compared to the use of topical CS alone **[28]**.

3.4.3. Oral Antihistamines

Oral antihistamines may be used in atopic dermatitis therapy due to their sedative effects. However, the non-sedative type was found to be ineffective in reducing itching in AD patients. A previous study failed to show the benefit of the long-term use of the antihistamine drug (cetirizine) in the treatment of atopic dermatitis in children **[30]**.

3.4.4. Ultraviolet light

Phototherapy may be considered as a second- or third-line treatment, however, itching and burning may be side effects and carcinogenicity resulted from long-duration therapy may be a concern**.** One study has shown that high-intensity ultraviolet A and narrowband ultraviolet B are beneficial in short term AD treatment **[28]**.

3.4.5. Vitamin D

It has been reported that the deficiency of vitamin D elevated the risk of AD disease Due to its effect on the adaptive and innate immune system; vitamin D may inhibit both B-cell and T-cell proliferation and increase the function of the

regulatory T-cell**.** Therefore, there is a great relation between vitamin D deficiency and AD as vitamin D deficiency affects the skin barrier and makes it more prone to inflammation **[31]**. A supplement of vitamin D of 4000 IU / day for 21 consecutive days should be given to a lesioned AD skin Patients with atopic dermatitis disease and low serum 25-OH D3 level should have supplementation of vitamin D for approximately 3 months to decrease the subjective and objective severity of the disease **[32]**.

3.4.6. Biologics

Biologics have been used in several types of dermatological diseases, particularly for autoimmune disease and psoriasis, despite these biologics were not approved for AD treatment, it had been reported that they can target the mediators and cytokine which play a significant role in the pathogenesis process of AD disease **[33].**

3.4.6.1. Anti-CD20

Upon B-cells depletion, anti-CD20 or B-lymphocyte antigen CD20 acts as antigen-presenting cells and promotes the activation of T-cells increases the production of IgE and the pro-inflammatory cytokines. As a result, the reduction in skin inflammation in most AD patients with anti-CD antibodies in 5 months of treatment can be achieved **[19]**.

3.4.6.2. Anti-IL-5

Eosinophil infiltration occurs as a result of AD skin inflammation, So treatment with interleukin inhibitors (Anti-IL-5) (e,g, 750 mg of mepolizumab twice daily) in the short-term will cause a good improvement in AD disease clinical symptoms**[34]**.

3.4.6.3. Anti-IgE

Most AD patients (about 80%) have an elevated serum IgE level, so therapy with anti-IgE antibody (such as omalizumab in a dose of 150 mg) will decrease the severity of the disease levels by 50% in 2 of 11 patients and by 25% in 4 from 11 patients **[35]**. A good result has been detected in concomitant AD patients with bronchial asthma taking omalizumab therapy. Meanwhile, combination therapy of rituximab and omalizumab had a good clinical improvement with long-duration effect **[36]**.

3.4.6.4. Anti-TNF-a

The treatment with anti-TNF-alpha was found to reduce the signs and symptoms of AD-like pruritus, which lasted only for a short duration rather than a long one. However, anti-TNF-alpha therapy had inadequate efficiency on AD patients, so it was not recommended **[37].**

4. Corticosteroids as the first-line therapy in dermatitis

Corticosteroids (CS) are often used to treat atopic dermatitis. However, these corticosteroid drugs have significant side effects that may restrict their wide use. The administration route, which may be oral, topical, intramuscular, intravenous, and intralesional determines the side effects, therefore the beneficial effects of CS must be weighed against its adverse effects before the decision to begin the treatment **[38]**.

4.1. Systemic Side effects of corticosteroids

Systemic corticosteroids for the treatment of dermatitis should be restricted only to short courses to avoid the severe side effects associated with their use that include:

4.1.1. Cutaneous

Cushing's syndrome (also called hypercortisolism) is an endocrine disorder that resulted from chronic administration of corticosteroids. Cutaneous signs of Cushing's syndrome incorporate truncal corpulence, Nigerians (a smooth hyper-pigmented plaque that happens on the neck or in the axillary area), ecchymosis after a minor injury, hirsutism,

hyperpigmentation especially in patients on maintenance treatment **[39].**

4.1.2. Hypokalemia & Myopathy

Hypokalemia is related to the mineralocorticoid effect of prednisone, prednisolone, and hydrocortisone; however, hypokalemia rarely occurs with topical corticosteroids **[40]**.

There are two forms of myopathy: acute and chronic, hypokalemia may be the major cause of acute myopathy. Myopathy is characterized by both distal and proximal muscle weakness and an increase in creatine phosphokinase enzyme, which is related to muscle necrosis

In the chronic form, weakness occurs in proximal muscle groups, while the creatinine phosphokinase is slightly elevated or within the normal level. Muscle biopsy is essential for patients with long-term corticosteroid treatment **[41]**.

4.1.3. Glucose intolerance

Hyperglycemia may occur in some individuals mainly due to the immunosuppressive effect of corticosteroids, where the major cause is insulin resistance or inhibition of glucose metabolism **[42]**.

4.1.4. Hypertension

Corticosteroids affect human blood pressure mainly by elevating systolic blood pressure, they also cause an increase in sodium retention, and therefore, volume expansion appears in the pathogenesis. Consequently, corticosteroids cause an increase in renin substrate level, and this increases both pressor response to norepinephrine and angiotensin II and renin-angiotensin system respectively **[43]**.

4.1.5. Cardiac effect

The routine use of steroids in a cardiac patient for more than one year raises the risk of heart failure, myocardial infarction, and atherosclerosis. There is also a great risk to atrioventricular conduction, which may cause arrhythmia and finally cardiac arrest **[43]**.

4.1.6. Bone effect

Corticosteroids are known to inhibit calcium absorption by the GIT tract by opposing vitamin D action, in addition to renal tubule increase calcium excretion*;* so, this will decrease the calcium and protein uptake by the kidney, leading to a decrease in the activity of bone cells and osteocytes **[44]**.

4.1.7. Digestive system

Patients on steroid therapy may have a great incidence of ulcers, which is attributed to the increase in the secretion of gastric acid by the stimulation of the cholinergic nerve**.** Although producing pancreatitis after steroid therapy is rare, a fatal case has been reported. The mechanism is still unknown however, it has been reported that the increase in pancreatic secretion viscosity leading to the obstruction may be a cause, in addition to the change in lipid and calcium metabolism **[45].**

5. Topical corticosteroids for dermatitis

Topical delivery means targeting the drug to the skin with a minimum systemic absorption, so drug localization is an important issue. The delivery of topical formulations to the skin is a complex phenomenon that depends on the formulation type, the disease state, and the physicochemical properties of the active ingredient. The excipients present in the formulation may alter both the diffusion and the partition properties of the drug into the skin **[46]**. Topical preparations decrease systemic side effects associated with oral preparations like gastro-intestinal irritation. Also, the topical route avoids the metabolism of drugs in the liver and hence increases their bioavailability **[47].** The introduction of topical CS in 1952 by Sulzberger

was considered to be the most effective way in the treatment of dermatological disease. This historical event was then followed by the introduction of a various number of topical corticosteroid drugs of different potency rendering the inflammatory cutaneous disease therapy less time consuming and more effective **[48]**. Side effects of topical corticosteroids include thinning of the skin, telangiectases, and stretch marks; however proper use of corticosteroids may limit the risk of these side effects. Topical corticosteroid potency depends on its vasoconstriction ability. Besides, the use of topical CS on different body parts depends on its potency. In general, for the genital area and face, the use of weak to moderate strength corticosteroids is recommended. While a potent strength type may be used on other parts of the body **[28]**.

Low potency CS may be efficient for all body areas in younger children in 3-7 days to achieve a good effect. There is a small variance in the therapy outcome between the use of short-term use of potent corticosteroid and long-term use of weak one in mild to moderate atopic children **[49]**.

Reduced efficacy of topical corticosteroids may be related to the disease severity rather than to glucocorticoid resistance. There is little evidence that the application of topical corticosteroids twice a day is more effective than once-daily applications, in addition, more frequent use may cause more local side effects. The severity of the disease may affect topical CS efficacy. However, it does not cause resistance to CS **[50]**.

There is an increasing need to develop suitable drug carriers to localize, control, and improve drug delivery. Many drug carriers have been studied including lipid and polymeric based carriers. Nano-particulate systems can enhance topical medication delivery because of their ability to upgrade the drug loading, dissolution, and protect the unstable drug from degradation. A great deal of interest is currently being focused on lipid-based carrier systems, with a better understanding of the multiple roles lipids may play in enhancing bioavailability. Moreover, the emergence of novel excipients with acceptable regulatory and safety profiles coupled with advances in formulation technologies have greatly improved the potential for successful lipid-based formulations **[51]**.

6. Lipid-based carrier systems

Lipid carriers systems are composed of non-toxic physiological lipids, which may permit lipid exchange with the surface of the skin and can carry drugs in a controlled manner to the target site. These promising systems include nanoemulsions, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) **[52]**. Here, lipid-based systems are classified into hard and soft types **[53]** with some examples used in the treatment of atopic dermatitis.

6.1. Hard lipid nanoparticles include

6.1.1 Liposomes

Liposomes are small vesicles sphere-shaped that are formed from natural phospholipids with or without cholesterol. As a drug delivery system, liposome properties vary according to their lipid content, size, and the charge on the surface, which broaden their pharmaceutical applications including both systemic and non-systemic administration. They enhance the therapeutic index and efficacy of drugs by increasing their stability through the encapsulation process and have the ability to combine with specific ligands to achieve targeting thus decreasing tissue exposure to toxic drugs. There are, however, several drawbacks for liposomes as a high production cost, low stability, short half-life, less solubility, and leakage of the entrapped drug

[54].

Various types of liposomes include:

1. Multilamellar vesicles: in a size range from (500-5000 nm).
2. Small unilamellar vesicles: in size around 100 nm.
3. Large unilamellar vesicles: in a size range from (200-800 nm).
4. long-circulating liposomes: liposomes treated with specific polymers that can retain in blood for a longer time than non-modified types.
5. Immunoliposomes: liposomes with a specific antibody attached to their surfaces and accumulate in a specific area where the antibody binds its specific antigen **[55]**.

As a topical delivery system, liposomes act as penetration enhancers with a depot action on the localized skin. The limitation for the topical use of liposomes is that they are limited to the upper layers of the stratum corneum because of their huge size and non-flexible behavior, which upsets the penetration of these vesicles to the deep layers of the skin **[56]**.

Several studies utilized liposomes as a drug delivery system for the treatment of AD as shown in **Table 1**. It has been demonstrated that elastic liposomal systems of orgeonin revealed more superiority and flux value than its conventional cream for atopic dermatitis treatment **[57]**. In a previous study conducted by Korting *et al*., betamethasone dipropionate was successfully encapsulated into liposomes in an effectual means to treat atopic eczema by reducing scaling and erythema score with greater efficacy than propylene glycol- commercial gel **[58].** Another study developed liposomal hydrogel of adenosylcobalamin, a derivative of vitamin B12, which has a good effect on atopic dermatitis. Liposomal hydrogel exhibited an enhanced skin permeability with 17-fold than conventional adenosylcobalamin-gel **[59].**

Augustin *et al.* developed a liposomal hydrogel of polyvinyl pyrrolidine-iodine (3%) as an anti-inflammatory agent and tested its effectiveness on 20 patients for the one-month duration. They found that the liposomal gel was able to improve both life quality and disease severity in atopic dermatitis patients **[60]**. In another study, IL-13 antisense oligonucleotide complexed with liposome was found to suppress the production and release of IL-13, IL-4, and IL-5 **[61]**.

6.1. 2. Niosomes

Niosomes are microscopic vesicular structures formed from the hydration of cholesterol and non-ionic surfactant**s.** Non- ionic surfactants are non-toxic, biodegradable, and biocompatible surfactants with no charge; they include Tween, Brij, Span, polyglycerol alkyl ethers, and crown ethers **[62]**. Niosomes have many advantages including high drug encapsulation efficiency despite their small size**,** high chemical stability**,** high patient satisfaction issue, and more effectiveness than marketed oily preparations. Noisome physicochemical properties can be easily controlled by altering their composition and preparation method. Niosomes have been used in the atopic dermatitis field as shown in **Table 1** as a propitious carrier in topical delivery due to their merits like increasing drug penetration, a satisfactory drug release pattern, good drug stability, and carrying both lipophilic and hydrophilic drugs **[63]**. A previous study demonstrated the possibility of the self-penetration property of levocetirizine loaded liposomal vesicles. The prepared vesicles showed satisfactory EE%, good skin retaining capacity, and topical sustainability with extreme peripheral action of the drug and reduced scratching frequency and erythema score **[64]**. Another study revealed the potential application of liposomal vesicles of ammonium glycyrrhizinate (AG) extract (suitable for the treatment of various

skin diseases including eczema and dermatitis) with similar effects to that of corticosteroids and good skin tolerability **[65]**.

Table 1. A survey on lipid based nanocarriers used for the treatment of atopic dermatitis

System	Drug	System targets or merits	Reference
Nanoemulsions	Prednicarbate	Good formulation for the treatment of AD patients	**[90]**
	Pioglitazone	Decreasing the level of inflammatory cytokines, such as IL-1β, IL-6 and TNF-α	**[91]**
	Rice bran oil	Having a good pH value and improving the skin moisture	**[92]**
Liposomes	Betamethasone—dipropionate	Reducing erythema, scaling and inflammation with greater efficacy than commercial gel	**[58]**
	Adenosylcobalamine	Enhancing in skin permeability by 17-fold in a murine model and improving the immune response.	**[59]**
	Orgeonin	4-fold deformability index greater than conventional liposomal formulation	**[57]**
	Cetirizine/ levocetrizine Dihydrochloride	Ameliorating the penetration and permeation in a murine model, reduce erythema and itching scores as compared to conventional cream and ointment	**[93]**
Niosomes	Levocetrizines	Reducing the erythema score and scratching effect	**[64]**
	Ammonium glycyrrhizinate extract	Similar effectiveness to that of corticosteroids	**[65]**
Ethosomes	Cyclosporine A	Aiming to increase the topical delivery of cyclosporine A, Attainment to deeper skin layers	**[94]**
	Tacrolimus	Better pharmacological effects than conventional ointment	**[84]**
	Cetrizine	Higher permeation and skin retention value compared to marketed formulations	**[85]**
Transfersomes	Tacrolimus	Higher drug skin retention value compared to marketed ointment	**[80]**
	Glycyrrhizic acid	Effective in atopic dermatitis therapy	**[81]**
	cetrizine	giving 2-fold amount of drug permeated and reducing in itching score as compared to the marketed cream	
SLNs	Prednicarbate	Improving the penetration of prednicarbate by 30% compared to conventional cream	**[69]**
	Cyclosporine A	2- fold more skin penetration, reducing the release and production of IL-3 and IL-4 in murine models	**[72]**
	Tacrolimus	Exhibiting good drug-controlled release compared to marketed ointment (protopic®).	**[70]**
		Decreasing immune response by 3.5 times and fewer side effect than conventional ointment.	
	Tacrolimus	Reaching to deeper skin layers than 0.1% Protopic® with good drug delivery, Satisfactory permeation and Efficacy and decreasing the unwanted side effect related to tacrolimus high dose	**[95]**
NLCs	Fluticasone propionate	Decreasing unwanted side effect of systemic corticosteroid therapy	**[74]**
	Tacrolimus	Greater cutaneous permeation rate than marketed products	**[96]**
	Diflucortolone valerate	Targeting the drug in the stratum corneum layer and forming a reservoir to provide a continuous release of difluocortolone to the damaged tissues	**[75]**
	Betamethasone dipropionate	Good skin retention value and less irritation effect than commercial ointment	**[76]**
	Dexamethasone acetate	Enhancing both skin deposition and permeation value	**[77]**
	Clobetasol propionate	High anti-inflammatory and rapid onset of action	**[78]**

6.1.3. Solid lipid nanoparticles (SLNs)

SLNs are derived from (o/w) nano-emulsions by substituting solid lipid instead of liquid lipid. Solid lipids include beeswax, carnauba wax, triglyceridescetyl alcohol, and cholesterol butyrate, which solidify at room temperature upon dispersion with water. In the preparation of SLNs, solid lipids are used in concentrations ranging from 0.1% to 30% (w/w). Surfactants like Tweens, Brij, and Poloxamers in concentrations of 0.5-5% are added to increase the stability of the nanodispersions. The suitable choice for both lipid and surfactant has a significant effect on particle stability, size, drug loading, and drug release behavior **[66]**. In comparison to other types of nanoparticles, SLNs have many advantages, which include lower toxicity, easier scale up production as compared to liposomes and polymeric nanoparticles.

Generally, SLNs increase drug bioavailability, prevent drug degradation, and offer controlled drug release**.** The high contact with the surface of the skin by the nano-range particles increases drug penetration into the skin. Because SLNs are composed of normal and non-toxic lipid content, they are suitable for use on damaged and inflamed skin **[67]**.

The major drawback related to SLNs is the low encapsulation efficiency for some drugs, which depends on two factors. First is the drug solubility in the solid lipid. Second is the high expulsion of the drug out of the lipid matrix both during cooling and due to the moderately high percentage of water content (70-90%) or during storage because of the recrystallization of the lipid to the more stable ß-adjustment **[68]**.

In the dermatitis field, the penetration of prednicarbate from SLNs increased by 30% as compared to conventional cream **[69]**. Tacrolimus was also successfully loaded into SLNs for potential atopic dermatitis treatment (with 93.2% EE). Tacrolimus loaded SLNs exhibited high skin penetration and increased drug skin accumulation **[70]**. SLNs of betamethasone valerate were formulated using solvent infusion technique, where monostearate-based SLNs exhibited less permeation rate and higher drug concentration in the epidermis, while beeswax-based SLNs were unable to increase the drug content in the upper skin layers **[71]**. Another study demonstrated that topical administration of cyclosporine A loaded into SLNs relieved some signs and symptoms of atopic dermatitis and improved cyclosporine skin penetration **[72].**

6.1.4. Nanostructured lipid carriers (NLCs)

NLCs systems were developed to overcome the drawbacks of SLNs like particle growth and gelation tendency, low drug incorporation, and burst drug release. NLCs are manufactured from blending liquid and solid lipids, which is seen macroscopically solid at normal body temperature. There are three forms of NLCs: imperfect, formless, and multiple type, the first type is imperfect in which both liquid and solid fats are mixed in various lipid structure, this increase the ability of the drug to enter the matrix. The second is formless, non-crystal, or amorphous structure, which inhibits the drug expulsion. The third is the multiple types which are similar to (w/o/w) emulsions, in this type the solubility of the drug in liquid lipid is more than in solid lipid, and thus prevents the decomposition of the drug by solid lipid **[73]**.

Regarding dermatitis treatment, several drugs loaded NLCs have been investigated as shown in **Table 1**. In a previous study, NLCs loaded with fluticasone propionate were successfully prepared to aim to decrease the unwanted side effect of systemic corticosteroid therapy NLCs encapsulating tacrolimus simply prepared by sonication method revealed a greater cutaneous permeation rate than protopic® (a commercially

manufactured dermal ointment of tacrolimus) **[74]**.

Difluocortolone valerate was successfully incorporated into NLCs systems, aiming to target the drug in the stratum corneum layer forming a reservoir to provide a continuous release of difluocortolone to the damaged tissues **[75]**. Betamethasone dipropionate loaded NLCs ointment had a good skin retention value and less irritation effect than traditional ointment **[76]**. Also, NLCs loaded with dexamethasone acetate hydrogel in an amorphous core-shell structure enhanced both the skin depositions by 3.8% and permeation value by 7.3% as compared to dexamethasone acetate solutions in the hydrogel **[77]**. An optimized topical NLCs system incorporated with clobetasol propionate-based gel displayed a higher anti-inflammatory activity and rapid onset with a prolonged duration of action via paw edema compared to the traditional gel **[78]**.

6.2. Soft lipid nanoparticles

6.2.1 Transfersomes

Transfersomes are deformable and ultra-flexible vesicles consisting of an inner aqueous core bounded by lipidic bilayers with an edge activator such as Span 60, Span 80, Tween 60, and Tween 80. This highly flexible nature of transfersomes could effortlessly enhance the skin penetration, by enfolding themselves in a self-adapting method. Also, they possess a unique ability to get accommodated with a wide range of solubility and act as an effective carrier for both low and high molecular weight drugs, e.g. corticosteroids, hormones, insulin, anticancer drugs, with high entrapment efficiency and protection of the encapsulated drug from metabolic degradation **[79]**. In the dermatitis field, transpersonal tacrolimus was successfully prepared using Tween 80 that was able to achieve high drug skin retention **[80]**. A Glycyrrhizic acid loaded deformable vesicle also has a great effect on atopic dermatitis therapy **[81]**. Besides, a novel vesicular transfersomal formulation of cetirizine was prepared and used in atopic therapy giving a 2-fold increase in drug permeation with a significant reduction in itching score as compared to the marketed cream **[82]**.

6.2.2. Ethosomes

Ethosomal transporters are vesicles composed mainly of a phospholipid, water, and alcohol (ethanol)**.** They are soft and flexible vesicles that professionally enter the skin and permit improved delivery of various composites. Ethosomes have been developed as promising carriers for hydrophilic and lipophilic molecules **[83]**. Li and coworkers, 2012 formulated an autosomal delivery system of tacrolimus and studied its ability to reduce the allergic reaction in mice, targeting to improve the pharmacological outcome of tacrolimus over the marketed formulation and giving appropriate suppression for the atopic dermatitis allergic reaction **[84]**. While Goindi, 2014 showed a maximum permeation flux and skin retaining value for cetirizine-loaded ethosomal vesicles as compared to marketed formulations. The in-vivo study exhibited a good reduction in both scratching and erythema scores, eosinophil count, and hyperplasia **[85]**.

6.2.3. Nanoemulsions

Nanoemulsions are thermodynamically unstable systems, submicron in size that are formed by mixing two immiscible liquids (oil and water) with appropriate surfactants to form a single phase. The particle size of nanoemulsions fall typically in a range from (20 to 200 nm) with a narrow distribution size, however, they may be considered good in the size range from (0.5 to 100 nm). They have wide application areas such as being a vehicle for lipophilic drugs, in cancer treatment, as a mucosal vaccine, and in self-nano

emulsifying drug delivery systems **[86].** Nanoemulsions have many advantages over liposomes and polymeric nanoparticles such as highly hydrophilic and lipophilic drug-carrying systems and low-cost production procedures. It can be considered advanced nanoparticle systems for controlled and targeted drug delivery by increasing drug penetration especially for poorly soluble drugs, which improves drug retention time and decreases the side effects in the target area **[87]**. Regarding the topical route, nanoemulsions of lecithin loaded Nile red dye was able to increase the skin penetration by 9.9-fold greater than Nile red loaded conventional emulsion **[88].** Also, Yilmaz and Borchert assessed the effectiveness of nanoemulsion formed from ceramide-3, ceramide-3B, palmitic acid, cholesterol using Carbopol-940 as a thickener agent in AD patients. Results of the clinical study on 14 patients revealed an increase in both the elasticity and hydration of the skin upon nanoemulsion application **[89]**. **Table 1** shows examples of drugs loaded within nanoemulsions for the treatment of AD.

Conclusion

Nanotechnology is a well-thought talented method in atopic dermatitis therapy, even in a resistant form that gives: a) good drug bioavailability and transdermal targeting at the inflammation site and exhibits better permeation and diffusion. b) Gives a satisfactory dose of controlling value and improves patients' clinical signs and symptoms which have a good impact on the quality of life.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

All literature is available

Competing interests

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