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Nanovesicular System for Management of Atopic Dermatitis

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ABSTRACT: Atopic dermatitis (AD) is a very common skin disease with chronic and relapsing immunological abnormalities in the skin characterized by recurrent eczematous lesions and intense itch. The primary etiology behind atopic dermatitis is still not known. Nowadays, scientific focus is being driven from conventional therapies to the advanced nanovesicular-based regimen for an efficient management of AD. These nanovesicular which include liposomes, ethosomes and glycerosomes provide efficient roles for the target specific delivery of the therapeutic. The success of these targeted therapies is due to their target-site specific delivery, better therapeutic outcome, no induce toxic effect, enhanced bioavailability, enhanced dissolution rate & permeability of poor water-soluble drugs. The objective of present review is to focus on prospecting the therapeutic superiority of advanced nanovesicular-mediated strategies over the conventional therapies used in the management of AD.

Keywords: Atopic dermatitis, Advanced nanovesicular-mediated, Liposomes, Ethosomes, Glycerosomes

I. INTRODUCTION

The largest organ in the human body is skin and it covers an area of 2 square meters, which is 15% of total human body weight & its thickness is <0.1 mm. The skin main function is to provide protection to the body from physical and chemical attacks & from microbial invasion. The skin is composed of three layers, the uppermost layer epidermis, dermis and hypodermis [1-2].

EPIDERMIS

The outermost layer of skin is epidermis. It is composed of different layers. The layers are stratum corneum, stratum lucidum, stratum granulosum & stratum spinosum, stratum germinativum [1-2]. Epidermis is made of different types of cells that are keratinocytes which are major cells, constituting 95% of the epidermis, merkel cells and melanocytes.

Langerhans cells are also present. It does not contain any blood vessels and is totally dependent on the dermis for nutrient delivery and water disposal. Epidermis provides protection against physical &biological barrier to the outside environment & it also prevents loss of water and maintains homeostasis [1-2].

DERMIS

Dermis is comprised of two layers are:

- The thinner layer consisting of loose connective tissue containing capillaries, elastic fibre & some collagen is the papillary dermis.
- The thicker layer which consists of dense connective tissue containing blood vessels, elastic fibres & the thicker bundles of collagen is the reticular dermis.

Within the dermis collagen, elastin and viscous gel are synthesized by fibroblast which is the major cell type of the dermis.

Dermis has complex network of blood which is responsible for thermoregulation. Dermis also consist hair follicle, sweat glands, connective tissues and sebaceous glands, apocrine glands [1-2].

HYPODERMIS

It is subcutaneous layer. It consist fat& connective tissue. The stored fat protects the internal organ of the body. The major role play by hypodermis is to provide structural support for the skin and as well as insulating the body from cold &shock [1-2].

VARIOUS SKIN DISEASES

Normal skin barrier is impaired, when the skin hydration is increased as result of skin diseases, excoriation, erosion, fissuring or prematurity percutaneous absorption. Various types of skin disorder are there which are vary from one another in term of symptoms and severity. Many skin diseases are acute, some are chronic, and they may

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be painless and others may be painful. They may be due to situational causes, while others may be genetic [3].

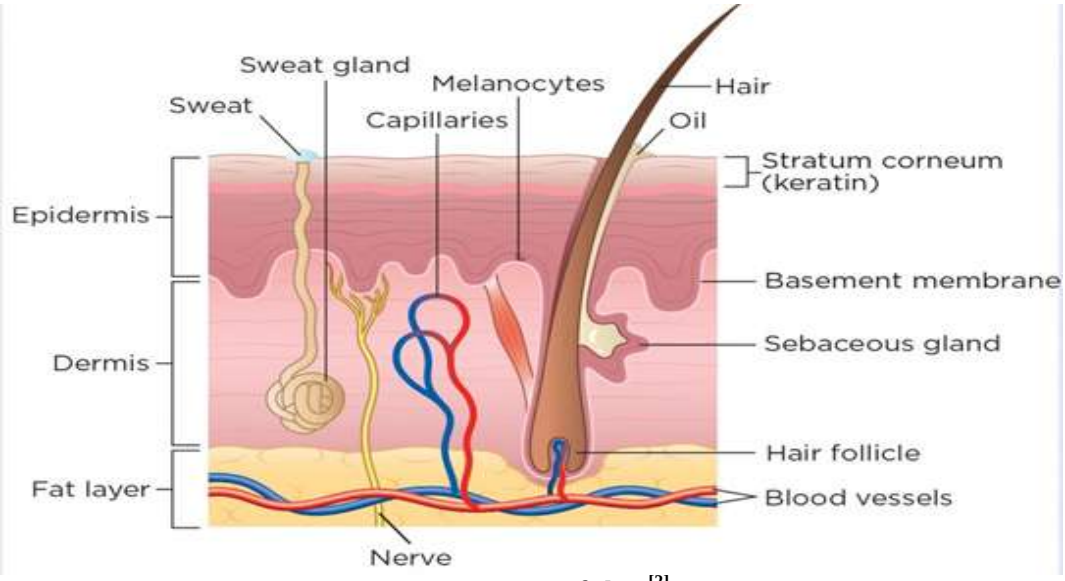

Fig1.Structure of skin [2]

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VARIOUS TYPES OF SKIN DISEASES ARE:

1. Acne: Acne occurs due to excess production of oil, hormonal change and dead skin cells.
2. Cold sore: Cold sore occurs due to herpes simplex virus. It can spread from one person to another person. It is in the form of red, fluid – filled blisters.
3. Hives: Hives occur due to allergic reaction to a medication or food.
4. Actinic keratosis: It occurs due to aging or due to long-term exposure to sunlight. In this skin become rough, scaly, spots appearing on hand arm or face.
5. Rosacea: It may be due to heredity and environmental factors. The main reason behind it not known. It is chronic disease there is no cure for this disease. Its symptoms are small, red, pus- filled bumps on the skin.
6. Carbuncle: Its symptoms are cluster of boils that appear on the skin due to bacterial infection. Boils have multiple pus heads. They can appear on face, neck, armpit, or any area you sweat.
7. Latex allergy: It is type of allergy that occurs due to latex, a natural rubber used in the gloves & IV tubing. Its symptoms are rashes, itching, red wheals at site of contact after exposure to latex.
8. Eczema: It is also called atopic dermatitis. The cause is not known yet, but it may due to abnormal response to proteins. Its symptoms are dry, itchy skin & rashes on the affected area.
9. Psoriasis: It is a chronic and autoimmune disease. It only cures for some time, no permanent treatment is there for this disease. Its symptoms are scaly patchy which is silvery or red in colour and can be itchy & painful.
10. Cellulitis: It is a common type of bacterial infection. Affected area become red and swollen that feels hot and painful when this occurs.
11. Vitiligo: It is rarely occurring disease due to autoimmune destruction of the cells. Its symptoms are loss of skin colour in only a few small areas that merge.
12. Wart: It occurs due to human papilloma virus. It is contagious disease. Its symptoms are a fleshy, painless growth on the skin & affected area of hand, feet & genitals.
13. Melasma: Melasma cause is not known yet. Its symptoms are brown or grey-brown patch that appears on the skin and affected area are cheeks, forehead, nose and chin.
14. Ringworm: It is type of fungal infection. Its symptoms are red, itchy or scaly patches that develop blister or pustules [3].

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II. DERMATITIS

It is a chronic relapsing pruritic inflammatory skin disorder. Numerous factors which may be responsible are seasonal allergies, low humidity, and exposure to harsh detergent, cold weather & specific allergens. In this type of skin disorder crusty scales, painful cracking and blisters oozing fluid are appeared on the skin. It is mostly found in children as compared to adult [4-5].

Types of dermatitis:

There are different types of dermatitis which include:

a) Allergic contact dermatitis
b) Atopic dermatitis
c) Irritant dermatitis
d) Neurodermatitis
e) Perioral dermatitis
f) Seborrheic dermatitis

2.1. Atopic dermatitis

Atopic dermatitis (AD) is also known as eczema. Numerous factors which are responsible atopic dermatitis are genetic, environmental & impaired immunity, epidermal barrier dysfunction. Epidermal barrier dysfunction causes increased transepidermal water loss & permeation of antigen, which leads to characteristic lesions. Genetic & immunological origin of atopic dermatitis is responsible for its recurring nature.It is not properly cure but only managed by various ways like avoidance of irritants &specific trigger and repair, maintenance of the skin barrier through proper skin care & hydration. It can be managed by using topical corticosteroids, calcineurin inhibitors, phototherapy and immunomodulators like cyclosporine, azathioprine, methotextrate& biologic drugs like monoclonal antibodies. The primary etiology behind atopic dermatitis is not known yet, but only assumption is there, it is maybe due to numerous factors like genetic, immunity impaired or environmental [6].

Figure 2: Structure of healthy skin and skin affected with atopic dermatitis [1]

Atopic dermatitis is due to IgE mediated hypersensitivity reaction and itching that leads to physical scratching thus injuring the skin . Exogenous allergens or microbial toxin are also responsible for itching. Skin injuries activate keratinocytes to produce pro –inflammation cytokines such as IL-β, IL-6 and TNF-α involved in the process of pathological pain and also promote inflammation. Major source of cytokine is T-lymphocytes is further divided into Th1 (helper cells) & Th2 (helper cells).Acute atopic dermatitis is caused Th2 lymphocytes and chronic is caused by Th1 lymphocytes .In chronic condition IgE level is high .High concentration of IgE is due to hypersensitivity reaction or allergen [7].

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III. CONVENTIONAL THERAPIES

3.1 Non pharmacological approaches

There are certain ways for management of atopic dermatitis which are non-pharmacological approaches. These includes

- Avoiding eating food items such as cow milk, eggs, and wheat and soy products [8, 9].
- Following skin care routine like using topical moisturizer, hydrate your skin by drinking enough water and also prevent transepidermal water loss [10-13].
- Avoiding direct contact with sensitizing allergens.
- Using wet wrap therapy (WWT) to reduce the severity of symptoms of atopic dermatitis Through this therapy the skin can be moisten which can provide relief to AD patients. It also increases percutaneous penetration of topically drugs around the affected area [1, 14, 15].

3.2 Pharmacological therapies

- Use of certain topical corticosteroids. It is use in the condition when other therapies have failed. Different type of corticosteroid which are available in different strength & formulation to treat mild to severe atopic dermatitis. In severe case, clinician prefer super potent topical corticosteroids followed by using least potent topical corticosteroids [1,16-19].
- Use of certain topical calcineurin inhibitors (TCIs). Calcineurin is an enzyme which is responsible for activation of T-cells. Calcineurin inhibitor inhibits the synthesis of pro-inflammatory cytokines. Tacrolimus &Pimecrolimus are the two TCIs available. In acute condition tacromilus is used &Pimecrolimus is used in chronic condition [1,20].
- Anti-infective therapy: When skin is injured, then the chances of infection are more. So, in AD skin lesions increased due to staphylococcus aureus. It also affects the physicochemical barrier of skin & make condition became more severe. The growth of staphylococcus aureus can be inhibited by taking bath containing sodium hypochloride [1, 21, 22].
- Phototherapy: In Phototherapy UV light is used to treat AD. It can be used alone or in combination with topical corticosteroids. In phototherapy there is a suppression of T-Lymphocytes cells [1, 23].
- Use of topical/systemic antihistamine: Anti-histamine inhibits the effect of histamine in blood& also reduces itching. It can also cause sedating effect [1, 24].
- Use of calcipotrial, a vitamin D_3 analogue: It is used to treat moderate to severe AD [1, 25].

IV. NOVEL DRUG DELIVERY SYSTEM

All the conventional therapies are not able to provide target specific delivery & do not give desired results. So, new drug delivery systems were developed which can deliver the drug at target site & without any toxic effect. This delivery system was named as novel drug delivery system. Various novel drug delivery system used in treatment of AD are liposomes, ethosomes, nanoemulsion& polymeric nanoparticles. All these novel drug delivery systems have many advantages over conventional therapies [1] which include

- Target-site specific delivery
- Better therapeutic outcome
- No toxic side effect
- Enhance bioavailability
- Enhanced dissolution rate & permeability of poor water-soluble drugs.

Delivery of drug across the subcutaneous can be possible only by using nano-carrier based delivery system. As there are various physicochemical barrier in the skin which give protection to the skin & permeation of drug through the skin is very difficult.

Vesicular system used in atopic dermatitis is liposomes, ethosomes, transferosomes and glycerosomes.

4.1Liposomal delivery system

Liposomes are composed of phospholipid and have an aqueous core which encapsulated both hydrophobic and hydrophilic drugs. The drugs encapsulated in liposomes are adequately protected from any enzymatic degradation and immune attack. Liposome has certain advantages over conventional delivery system. To improve drug delivery potential and overcome the drawbacks of conventional dosage form by vesicular carrier system. To reduce barrier properties of the stratum corneum, liposomes have been used in dermatology. These are formed of amphipathic phospholipids which assembled in singular or multiple bilayers. Liposomes can intact, take up the role of local reservoirs for drugs and thus can assure sustained release of the drug. Liposomes and other vesicular drug delivery system fuse with cellular membrane and allow cystolic delivery of the drug. They are more useful for local delivery of drugs than the systemic delivery.

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Korting et al. (1990) developed betamethasone dipropionate loaded liposome. The effect of a liposomal preparation of betamethasone dipropionate has been compared to that of a commercial propylene glycol-gel. The results indicated that liposome preparation reduced erythema and scaling more than the convention gel [30].

Kim et al. (2009) developed elastic liposomes for topical delivery of interleukin-13 antisense oligonucleotides and performed animal studies to examine therapeutic significance of the liposome-based delivery system in reducing the severity of AD. The result indicted a greater decrease in the levels of interleukin-4(IL-4) and interleukin-5(IL-5) in animals treated with interleukin-13 antisense oligonucleotides loaded elastic liposome. Interleukin -13 antisense oligonucleotides loaded elastic liposome- treated AD mice showed reduced infiltration of inflammatory cells into the various skin layers [31].

Jung et al.(2011)developed liposomal hydrogel for transcutaneous delivery of adenosylcobalamine, a vitamin B_{12} derivative. Topical administration of formulation showed remarkable reduction in dermatitis scores of AD-like skin lesions, dorsal skin thickness. The therapeutic effect of adenosylcobalamine in reducing the severity of AD was also observed [32].

Briuglia et al. (2015) had prepared the liposome having different ratio of phospholipid and cholesterol. The result indicated that phospholipid: cholesterol in 2:1ratio gives the best liposome formation [33].

Eroğlu and co-workers (2016) developed betamethasone valerate/ diflucortolone valerate-loaded chitosan –based liposomes which was found to be safe and effective in atopic dermatitis patients [34].

4.2 Ethosomal delivery system

Ethosomes are composed of phospholipid and has an aqueous core which encapsulated both hydrophobic and hydrophilic drugs. Ethosome penetrate through physicochemical barrier more efficiently compared to conventional liposomes. This was achieved due to modification of conventional liposomes by adding ethanol which played a crucial role in ethosomal drug delivery through skin. As they have higher flexibility they are also called as elastic vesicles.

Li et al.(2012) developed Tacrolimus-loaded ethosomes in reducing the severity of AD. They noticed that high amount of tacrolimus retained in epidermis and dermis after the topical application of ethosomal formulation thus indicating a greater potential of this delivery system to accomplish target-specific delivery of drugs [37].

Paolini et al. (2012) reported that ethosomes showed better skin permeability where they fuse with the lipids of the skin and release the drug[40].

Goindi and co-workers (2013) developed elastic vesicle containing phospholipon90G and edge activators to improve the topical skin delivery of a piperazine-derived second generation anti-histaminic drug cetirizine/levocetirizine dihydrochloride. The optimized formulation was found to be satisfactory with respect to stability, drug content, entrapment efficiency, viscosity, vesicle size and spreadability. The optimized formulation was assessed against oxazolone-induced atopic dermatitis in mice. The result indicated that the developed formulation was highly efficacious in reducing the itching score compared to conventional cream [36, 38, 39].

Zhang Y et al.(2019) developed hyaluronic acid (HA) modified ethosomes with propylene glycol as a novel drug carrier for curcumin. The gel network formed by HA on the surface of phospholipid vesicles effectively reduced drug leakage, improved the stability of the preparation, and allowed the slow release of the loaded curcumin to cure inflamed skin [35].

Paliwal et al. (2019) prepared flurbiprofen loaded vesicular ethosomes and characterized it. Ethosomal formulation provided consistent skin permeability and enhanced drug permeation from lipid vesicles having ethanol as one of key components. Thus, the overall study concluded that this ethosomal approach offers a new delivery system for sustained and targeted delivery for flurbiprofen [41].

Kumar P et al.(2021) prepared piperine loaded ethosomes cream and compared with conventional cream. They noticed that high amount of piperine was retained in epidermis and dermis after the topical application of ethosomal formulation, indicating a greater potential of this delivery system to accomplish target-specific delivery of drugs. Ethosomal cream of piperine

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showed good potential for the management of AD in comparison to conventional cream [42].

4.3 Transferosomes

Transferosomes are also known as ultradeformable liposomes. It has several advantages over liposomes as it possesses high vesicle deformability, elasticity and high penetration capability. Transferosomes can be suited for transdermal and dermal delivery. It has an ability to transfer 0.1mg lipid per hour per cm^2 area across undamaged skin [43]. Surfactant like sodium cholate, polysorbate, Tween 80 in transferosomes made vesicles more elastic, deformability and it also increased the penetrability through intercellular lipids of stratum corneum[44].

Cevc et al. (2003) formulated halogenated corticosteroid triamcinalone acetonide as transferosomes for dermal delivery. The vesicles formed had the ability to pass through minute pores and showed deposition in the skin for prolonged period of time as compared to creams and ointment [45].

Cevc et al. (2004) formulated transferosomes loaded two corticosteroids, dexamethasone and hydrocortisone. The results showed that there was prolonged and robust effect that translated into reducing the frequency of dosing and increased the benefit/risk ratio of the drug [47].

Lei et al. (2013) developed tacrolimus loaded transferosomes for the treatment of atopic dermatitis. The prepared transferosomes were compared with commercial ointment and liposome gel of tacrolimus. Transferosomes showed several advantages over ointment & liposomes gel like high permeability & elasticity. Surfactants used in preparation of transferosomes were disodium cholate (SDC), Tween 80 & Span 80. Maximum entrapment into transferosomes achieved was with Span80(83.88%).Mean particle sizes of transferosomes were 135.6, 123.1, and 260.6 nm with SDC, Tween 80 and Span 80 respectively. Transferosomes had1.4-2.1 times higher deformability than compared to liposomes and also showed higher retention levels. Transfersomes were considered as one of the useful carrier for dermal delivery to treat atopic dermatitis [48].

Barani et al. (2017) Formulated and optimized the piroxicam loaded transferosomes for the bioavailabilty enhancement. Transferosomes were prepared by rotary evaporation method and characterized for various parameters like determination of vesicle size, shape and size distribution, drug entrapment studies and in vitro skin permeation and histopathological studies. Entrapment efficiency and permeation studies through wistar rat skin were found to be 91.4 and 73.16. Histopathological examination and skin irritation studies were done and it showed 0.26 value for transferosomal gel, indicating that all the excipients used in the formulation development were safe[46].

Abdellatif et al. (2017) formulated several vesicular systems like liposomes, ethosomes, glycerosomes and transferosomes containing sertaconazole nitrate and compared all these vesicles. Then the formulations were converted into gel. The transferosomes gel displayed superior characterstics compared to other vesicles due to presence of surfactants [49].

4.4 Glycerosomes delivery system

Glycerosomes are sphere-shaped versatile vesicular system consisting one or more phospholipid bilayers, similar to liposomes but containing high concentration of glycerol which modify the liposome bilayer fluidity. It has ability to encapsulate both hydrophobic and hydrophilic drugs, make glycerosomes promising vehicle in the field of drug delivery [27-31].

They can prepared at room temperature and also suitable for incorporation of heat sensitive material. Glycerosomes increases the penetration enhancing action and encapsulation enhancing action.

Penetration enhancing action: Due to presence of glycerol in glycerosomes vesicles are soft and elastic which increases the penetration through the small pores. Glycerol acts as a co solvent which makes the skin surface more hydrous.

Encapsulation enhancing action: Due to presence of high concentration of glycerol which increases the size of the vesicles and also more drugs encapsulated into the vesicles.

Glycerosomes as carrier was first introduced in 2012 (Manca et al., 2012b) by using diapalmitophatidylcholine (DPPC) & high concentration of glycerol (10-20%) in the water phase. It was composed of hydrophilic head, hydrophobic tail and bond. It showed greater morphological stability than liposomes [27-29].

Manca et al. (2017) had prepared the vesicles using DMPC and compared the results with other reported

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glycerosomes formulated with different phospholipids. The results revealed that whatever the phospholipid used in each and every case glycerosomes enhance the penetration through the skin [54].

Salem et al. (2018) had prepared the glycerosomes formulation of cupferon and celecoxib for delivering them topically. The prepared glycerosomes were showed greater drug release, better permeability and had enhanced bioavailability [53].

Manconi et al. (2018) formulated citrus limon loaded glycerosomes. They had formulated different vesicles namely glycerosomes, liposomes and penetration enhancing vesicles and compared them. The result indicated that glycerosomes and penetration enhancing vesicles showed better characteristics than liposomes and also showed protective effect against oxidation stress [52].

Moolakkadath et al. (2020) had prepared and optimized Fiestin loaded glycerosomes for dermal delivery by Box-Behnken design. The results indicated that the optimized vesicles showed nano-sized vesicles, good entrapment efficiency and good penetrability [50].

Naguib et al. (2020) had formulated lacidipine loaded glycerosomes to improve its bioavailability. The results revealed that prepared glycerosomes were small in size and non-toxic and had enhanced penetration through nasal route [51].

V. CONCLUSION

Atopic dermatitis is one of the prevalent skin inflammatory disorders which compel a significant burden to the patient, healthcare providers and the healthcare system. Non-pharmacological approaches are well accepted for the management of mild to moderate atopic dermatitis. In case of chronic atopic dermatitis pharmacological therapies are needed. All the conventional therapies are not able to provide target specific delivery & do not give wanted results. So, new drug delivery was developed which can deliver the drug at target site & without any toxic effect. This delivery system was named as novel drug delivery system. Various novel drug delivery system used in treatment of AD are liposomes, ethosomes, transferosomes, nanoemulsion& polymeric nanoparticles. All vesicular system such as liposomes, ethosomes, transferosomes and glycerosomes has certain advantages over conventional delivery system. To improve drug delivery potential and overcome the drawbacks of conventional dosage form by vesicular carrier system. The vesicular delivery systems have similar bilayer structure like biological membrane. So, it can easily interact with biological membrane and thus can improve local drug concentration.

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