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Review Article

Nanotechnology: A novel approach for treatment of skin disorder

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Abstract

Skin, the integument system; pertaining to our body which consists of mainly three layers (i) Epidermis (ii) Dermis (iii) Subcutaneous Tissue. It acts as a protective barrier against many diseases and infections. Skin disorders vary greatly in symptoms and severity. Some may be attributed to situational causes while others may be genetic like atopic dermatitis, melanoma, acne vulgaris, wound healing and psoriasis. Conventional therapies are used to analyze various topical disorders suffers from many limitations i.e. less efficacy, poor patient compliance, and poor bioavailability. Therefore, novel approaches should be investigated for the development of better treatment of the disease. Novel carriers such as Liposome, Niosomes, Ethosomes, Silver nanoparticles, Solid lipid nanoparticles are utilized through almost all the routes of administration to treat dermatological disorders. These Nano systems are used to provide targeted drug delivery and a site-specific delivery of dosage form at a particular receptor site and thus enhance the uptake of poorly soluble drugs and overcome the issues related to poor bioavailability. The root cause for the development of such carriers lies on making the existing drugs more effective and safe for the patients.

Keywords: Skin, Skin disorders, NDDS, Novel Carriers, Nanotechnology

Introduction

Skin disorder was the fourth leading cause of disability worldwide in 2013. Skin disorders are one of the most common illness affect millions of people every day, occurs at all ages. It has been mainly caused due to many infectious pathogens or inflammatory conditions. Skin relating disorders enclose a vast variety of situations ranging in extremely from benign such as psoriasis to life threatening as in case of skin melanoma. Skin disorders vary considerably in symptoms and severity. Some may be attributed to situational causes while others may be genetic by dependent¹. These situations depend upon the types of pathogen involved, integrity of skin layers & Structure. Recent variations have been made in the field of dermatology that suggests effective treatment of skin disorders i.e. requires timely identification, management and estimation of causative agent, efficient treatment and as well as route of administration². There are various infectious disease related to skin and hair follicles that is due to bacterial, fungal or viral infection and results in an eruption of skin surface. Chronic inflammatory diseases of skin such as psoriasis, atopic dermatitis and allergic contact dermatitis are the results of infiltration of inflammatory T cells with increased production of cytokines in the lesions³. These diseases are the significant cause of morbidity & mortality. Skin ailments invent up to total of 1.79% to the global burden of disease measured in DALYs from 306 diseases & injuries in 2013. Individual skin disorders extends in size from 0.38% of total burden for dermatitis (atopic, contact, and seborrhea

dermatitis), 0.29% Vulgaris, 0.19% for psoriasis, 0.19% for urticaria, 0.16% for viral skin diseases where as for fungal skin infections i.e. 0.07% for scabies, 0.06% for malignant skin cancer, 0.05% & 0.04% for Pyoderma & cellulites, 0.03% for keratinocyte carcinoma, 0.03% for decubitus ulcer, and 0.01% for Alopecia. All other skin & subcutaneous diseases composed of total 0.012% DALYs.

Skin

Skin is the body's protective barrier against an entity of environmental invader against both of natural and anthropogenetic origins. Skin is also the primary surface for medical treatment and nursing care, ranging from transdermal drug delivery & attachment of devices to keep an eye on various physiological functions, etc. Major role of the skin is to prevent invasion of microorganisms by creating a physical barrier from the external environment⁴. The defensive mechanism of skin not only presents physical protection but also extend immunological, metabolic and UV protection.⁵

The skin consists of mainly three layers⁶

1. Epidermis
2. Dermis
3. Subcutaneous Tissue

Epidermis-

Epidermis is made up of Keratinocyte, but also accommodates the melanocyte & dendrite cells such as Langerhans cells⁷. Nerve fibers have been demonstrated to stimulate all nucleated layers of epidermis. The nucleated cells of epidermis has three layers, the stratum basale (where stem cells as well as post mitotic, transiently amplifying cells are located) the stratum spinosum (or prickly layer), and the stratum granulosum. The keratinocyte develop structural proteins such as the epidermal keratin, the natural moisturizing factor (NMF), and the barrier lipid. It proliferate to heal the wounds or replace the corneocytes that are disoriented by exfoliation, transport water, glycerol and urea through the aquaporin, receive melanin from the melanocyte & accommodate the antigen presenting Langerhans cells. The epidermis also secretes miscellaneous chemokine's, growth factors etc., for cellular transmission enclosed by the epidermis along with dermal cells (fibroblasts, mast cells)⁹.

Dermis-

Dermis consists of about 90% of the weight of skin. Dermis consists of connective tissue along with collagen fiber which provides support and flexibility. Below this, the layer is condensing¹⁰; having deeper reticulated layer which exhibits a dense connective tissue matrix with thick and regularly align bundles of fibrils. Hair follicles & sweat glands enclosed in the dermis control the management of temperature⁹.The group of cells in the dermis are fibroblasts, which produce the extracellular structural proteins, collagen, elastin & glycosaminoglycan the major water belonging components

of the dermis¹⁹. Simultaneously, these components¹⁰ are known as the extracellular matrix.

Subcutaneous Tissue -

The subcutaneous tissue is also titled as hypodermis and is not considered as the part of the skin, and lies below the dermis¹². Its purpose is to attach the skin to essential bone and muscle as well as supplying it with blood vessels and nerves¹³. It comprise of loose connective tissue & elastin. The main cell types are composed of fibroblasts, macrophages and adipocytes. The subcutaneous tissue contains 50% of body fat. Fat serves as lining and insulation for the body.

Disorders of the skin

As skin sheath the external surface of the body. Skin contributes in thermoregulation; serve as water repellent and synthesis of many useful compounds like vitamin D²⁵ and acts as a preventing barrier between external environment and internal tissue. There are different disorders of skin¹³ as mentioned in figure 1.

1. Inflammatory skin diseases
2. Bacterial skin diseases
3. Viral skin diseases
4. Fungal skin disease

Epithelial layers and follicles consist of several important components as tight junction proteins whose localization and expression have been shown to be altered in the diseases characterized by a compromised skin barrier, such as psoriasis.

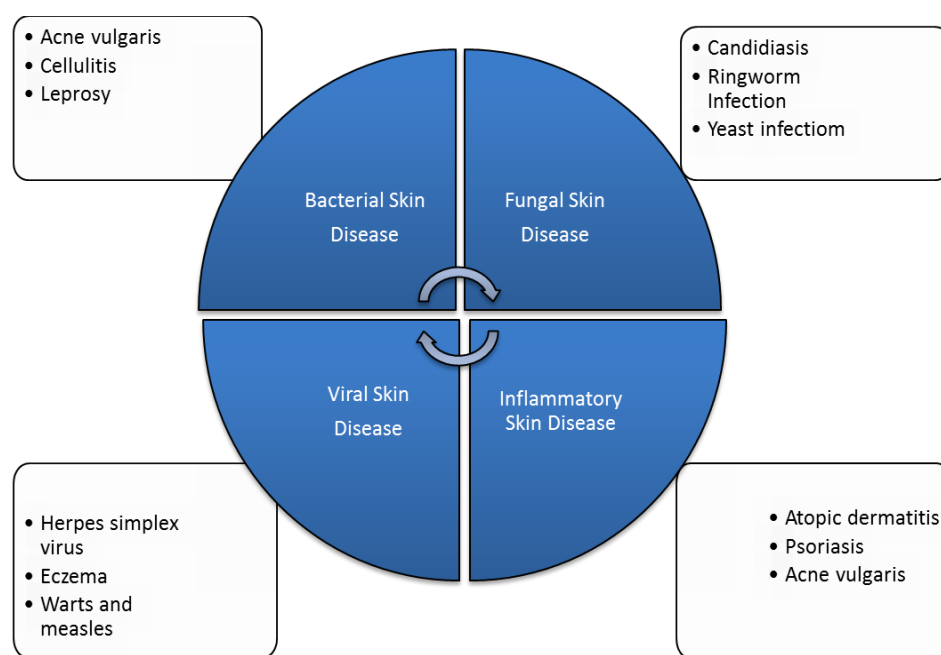


Figure1 Types of skin disorders

Psoriasis

Psoriasis is a T-cell mediated autoimmune inflammatory disorder i.e. acknowledged by skin surface inflammation, epidermal proliferation, which sometimes leads to hyperkeratosis, angiogenesis and anomalous keratinization also^{14, 23}. It appears in a variety of manifestations such as plaque psoriasis, inverse psoriasis, pustular and erythrodermic psoriasis¹⁵.Relapsing & spontaneous abeyance is a major problem associated with psoriasis.

Lymphocyte activation is the cause of psoriasis. Antigens attack the surface of antigen presenting cells in dermis and epidermis and forms MHC. Other cause is the risk factors in psoriasis which include abnormal alterations in eicosanoid metabolism, polyunsaturated fatty acids metabolic abnormalities and gene expression¹⁶.

Atopic dermatitis

Atopic dermatitis is also known as Atopic eczema .It is a type of inflammatory skin disorder characterized by severe

itching and repetitive eczematous lesions⁷. Pathogenesis of this disorder is not completely known. It appears to result from the complex interaction between the defects in skin barrier functions, environmental factors, infectious agents and immune abnormalities¹⁸. Reactive oxygen species plays a major role in atopic dermatitis. Clear fluid come from the affected areas which often thicken over time. The condition may occur at any age, it normally starts in childhood with changing severity over the years^{16, 19}.

Impaired Wound healing

Non-healing wounds are the results in inhibition of the normal sequence of cellular and biochemical events towards the fixing of the skin's integrity. Factors delaying wound healing include diabetes, immunosuppression etc²⁰. A excessive and prolonged proteolytic activity results in the degradation of growth factors, considering wound in the inflammatory stage for too long²¹. Wounds that do not heal within 3 months are called or considered as chronic wound. In acute wounds, production & degradation of molecule such as collagen is lost¹⁷ & as in chronic wounds balance is lost and degradation plays a large role in healing.

Acne Vulgaris

Acne Vulgaris exist as a chronic disorder of the pilosebaceous follicles of the skin. The lesions of acne consist of comedones, erythematous papules and pustules, nodules & cysts, and scarring²³. The root cause of acne Vulgaris is the comedo and is initiate by hyperkeratosis of the lining of the pilosebaceous follicles with recognition of keratin and sebum. A closed comedo is known¹⁰ as a "whitehead" and an open comedo is called a "blackhead", the black color being due to melanin. The comedo is a non-inflamed lesion and it usually relapse automatically with little or faded scarring²⁴. Certain diseases which block passage through the follicular pores for example hidadenitis, suppurativa & necrotizing cellulites of the scalp, perhaps related with acne.

Melanoma skin cancer

Skin cancers are of different types based on cells that become malignant⁷. Melanocyte exists as a melanin-producing cell located inside basal layer of the epidermis. When it functions normally, the melanocyte comes up with basic skin pigmentation and defends against UV radiation²⁵. Melanoma is more acceptable to occur and proliferate to other parts of the body. When skin cancer cells spread, they escape from the original growth and enter blood vessels or lymph vessels. Therefore the cancer cells may be found in nearby lymph nodes. These are primarily tumors that affect adult and elderly patients²⁶.

Stages of Melanoma

These are the stages of melanoma:

- **Stage 0:** In this stage, melanoma involves only the top layer of skin. It is called melanoma in situ.
- **Stage I:** In this stage, the tumor is no more than 1 millimeter thick. The surface may acts broken down. The tumor is between 1 and 2 millimeters thick and the surface is not seemed broken.
- **Stage II:** In this stage, tumor is in between 1 and 2 millimeters thick & the surface acts broken down. Or, the thickness of the tumor is more than 2 millimeters and the surface may seem broken.
- **Stage III:** In this stage, the melanoma cells run into at least one of the nearby lymph node or the melanoma cells that have spread from the original tumor to adjacent tissues.

• **Stage IV:** In this stage, Cancer cells have spread to the lung or other organs such as skin areas or lymph nodes that are far away from the original growth. It commonly spread to further parts of the skin, tissue under the skin, lymph nodes, and lungs. It can also broaden to the liver, brain, bones, and other organs.

Conventional Therapies

An ideal dosage regimen in the drug therapy of any disease is one which immediately measured the desired therapeutic concentration of drug in plasma¹⁵ by maintaining its concentration for the entire duration of treatment & is possible through the administration of conventional dosage forms in a particular dose & at particular time²⁴. But it has some limitations; Conventional topical therapies suffers from the limitations and are compromised (settled) with regard to patient compliance, safety and efficacy of the therapy. Traditional therapies are used to perform an action on the outer surface of the skin⁷. Conventional topical cures of the skin imply the use of ointments or creams. Drugs from preparations such as ointments, creams, lotions when applied on the skin produced a concentrated layer of active ingredient that is rapidly absorbed and results in poor patient compliance due to problems like stickiness and greasiness and may also sometimes cause irritation and allergic reactions. The delivery from these therapies is nonspecific and skin penetration is very low. Distinct drawbacks involve uncontrolled evaporation of active ingredient and unpleasant odor. Like in psoriasis normal moisturizing factors (NMFs) i.e. water is almost absent in the psoriatic skin²⁷. As a result of various factors i.e. targeting the psoriatic tissues using topical route possesses a big challenge. Other topical therapeutic agents like liposomes are available for the treatment of psoriasis. In spite of these, none of them can be regarded as an ideal drug molecule²⁸. This may either be due to their inherent side effects or their improper concentration in the conventional vehicles. In some skin disorders, use of penetration enhancers increase transport rate through the epidermal barrier but in addition, it also increases unwanted effects due to an enhanced drug level in the blood³¹. Unpleasant or even toxic side effects of penetration enhancers examine their use in topical drug administration^{21, 29}.

Novel Drug Delivery Systems for Skin Disorders [NDDS]

The NDDS with their unique aspects provide suitable skin interactions as desired in the diseased conditions⁵. Scrutinize the benefits; there have been several recent attempts are used in NDDS approach to improve the existing topical drug formulations in Skin disorders⁷⁴. Novel carriers such as Liposome, Niosomes, Ethosomes, Silver nanoparticles, Solid lipid nanoparticles have been utilize through almost all the routes of administration because of less painful effects as given by injections. However, the topical route has been used as one of the most appropriate substances to treat dermatological disorders more effectively²⁷. In spite of the conventional formulations based on creams & ointments, these novel dermatological systems are different in their composition & concentration²⁶. Several pharmaceutical and dermatological variables influence the choice of the system as per the need of the drug and disease. The applications of such novel Nano-vehicle systems are able to deliver potent drugs to the preferred site in a very accurate manner³¹. The composition of Nano medicines based on Nano systems; apparently control the release of a therapeutic moiety to the affected region at the skin site with localized effect by

creating skin reservoirs. Such a fact that skin acts even as negatively charged membrane; the existence of charge on the surfaces of Nano carriers influences their drug diffusion

through the skin. A positively charged delivery system would strongly interact with cells & has shown better permeability and prolonged pharmacological activity^{32,33}.

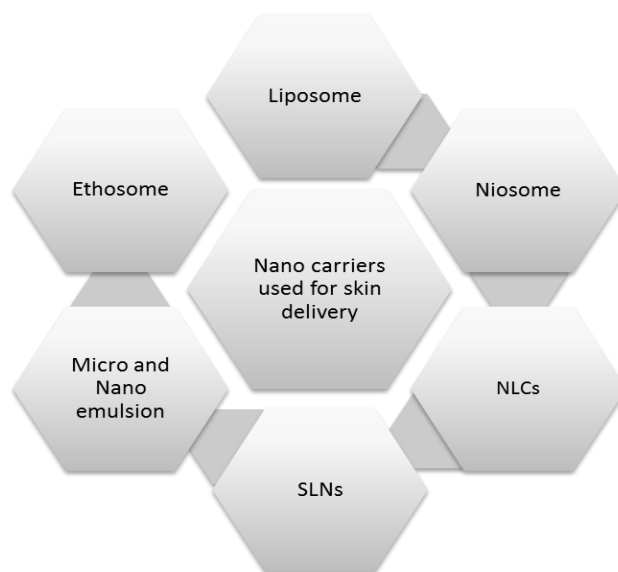


Figure 2 Novel approaches to treat various skin disorders

Novel Formulations-

Development of nanotechnology has been explored for treatment and diagnosis of various skin related diseases³³ as given in table 1.1.

Table 1 Novel formulation for different skin disorders

Types of dosage form	Drug	Disease	Study findings	Ref
Liposome	Methotrexate	Psoriasis	Improved therapeutic index	34
Ethosome	Methotrexate	Psoriasis	Favorable skin permeation characteristics ⁵	35
Niosome	Methotrexate	Psoriasis	Better efficacy and tolerance	36
Liposomes	Dithranol	Psoriasis	Higher solubility	37
Niosomes	Dithranol	Psoriasis	Better permeation	38
Liquid crystalline nanoparticles	Tacrolimus	Psoriasis	Higher solubility, Better anti-inflammatory	39
Microemulsion	Tacrolimus	Psoriasis	Higher drug skin penetration ⁴	40
Ethosomes	Resveratrol	Psoriasis	High permeation	41
Liposomes	Resveratrol	Psoriasis	Higher stability and loading efficiency ⁴	42
Transfersomes	Resveratrol	Psoriasis	High permeation	43
Nano lipid carrier	Tacrolimus	Atopic dermatitis	Enhance drug solubility	44
Nanostructured lipid carrier	Betamethasone dipropionate	Atopic dermatitis	Improved skin retention	45
Polymer nanoparticles	Hydrocortisone acetate	Atopic dermatitis	Increase in therapeutic efficacy	46
Nano emulsion	Clobetasol propionate	Atopic dermatitis	Increased anti-inflammatory activity	47
Nano emulsion	Prednicarbate	Atopic dermatitis	Increase retention time and bioavailability	48
Nano emulsion	Nadifloxacin	Acne vulgaris	Improved zone inhabitation	49
Nano emulsion	Dapsone	Acne vulgaris	Improved epidermal penetration	50
Nano emulsion	Isotretinoin	Acne vulgaris	Controlled release	51
Ethosomes	Econazole nitrate	Skin fungal infections	Controlled drug release, better anti-inflammatory activity ¹	52
Solid lipid nanoparticles	Eugenol	Fungal infections	Increase in membrane permeability	53
Microspheres	Insulin	Cutaneous wound	Promote tissue healing	54
Polymeric micelles	Clotrimazole	Superficial fungal infections	Improved drug bioavailability ¹	55
Microspheres	Benzoyl peroxide	Acne vulgaris	Favorable efficacy	56
Solid lipid nanoparticles	Triclosan	Acne vulgaris	Increase stability	57

Specific Nano formulations

Nanotechnology is at the leading stage of rapidly developing diseases for their treatment. Like in case of skin disorders for example Psoriasis, Atopic dermatitis, impaired Wound healing, Acne Vulgaris and so on¹. Nano carrier based drug delivery are efficiently used to develop the effectiveness of therapeutic agents & various Nano systems are utilized to treat skin disorders they are liposomes, inorganic nanoparticles, Niosomes, Ethosomes, solid lipid nanoparticles, Transferosomes. Nanoparticles are used to provide targeted drug delivery and a site specific delivery of dosage form at a particular receptor site and thus enhance uptake of poorly soluble drugs and bioavailability⁵⁸.

Liposomes -

Liposomes are the sort of novel drug delivery system consists of concentrated bilayer lipid particles used for treating many skin disorders such as acne, melanoma etc. It improves drug deposition at a specific site of skin, reduces systemic absorption, improve therapeutic effect of drug thereby providing localized effect². Formulations of these liposomes lead to better results in the treatment of acne as compared to conventional drug therapies by releasing the drug at a specific site and are more preferable for lipophilic drug⁵⁹. R.Kumar et al., Prepared the liposomal formulation of finasteride for topical treatment of Acne Vulgaris & objective is to increase skin permeation, deposition and stability of the drug which results in higher deposition of drug in the skin with increased permeability and stability was observed during evaluation⁶⁰.

Niosomes -

Niosomes are also being classified among novel drug delivery system which consists of unilamellar and multilamellar vesicles and are encapsulated by non-ionic surfactants that increase skin penetration. When applied topically, Niosomes increase the residence time of the drug in epidermis. They also increase the horny layer properties by reducing Tran's epidermal water loss & increase the smoothness via replenishing lost skin lipids. Niosomes possess higher chemical stability of the surfactants as that of phospholipids and can further be used in the preparation of liposomes⁶¹. Gupta et al., Studies the in vitro permeation and retention studies of topical niosomal gel containing a mixture of benzoyl peroxide and tretinoin were performed & compared to the permeation, retention of cream and alcoholic solution containing the same active substances as the niosomal gel³. Moreover anti-acne activity of the niosomal gel & cream containing the same combination was evaluated. The results have shown that the drug retention was higher in case of niosomal gel than the cream and alcoholic solution. In vivo studies of the niosomal gel and anti-acne cream of tretinoin and benzoyl peroxide showed that the niosomal gel had greater efficacy than the anti-acne cream with niosomal gels^{3, 62}.

Ethosomes -

It is a type of novel drug delivery system which involves noninvasive delivery carriers that enables the drug to reach deep skin layers². It mainly consists of phospholipids, water and high content of ethanol present in it. Due to the presence of ethanol in high concentration in Ethosomes it provides malleability to the vesicle membrane and enhances drug distribution in stratum corneum¹. Ethosomes increase efficacy, therapeutic index, permeation to the skin, make drug more stable and soluble. Being noninvasive, ethosomal drugs have better patient compliance⁶³. Verma P et al.,

Studies the preparation of nanosized ethanolic vesicles loaded with econazole nitrate for the treatment of fungal infections which results in controlled drug release¹, better anti-fungal activity¹ and good storage stability, ethosomal gel has tremendous potential to serve as topical drug delivery system⁶⁴.

Micro-emulsion and Nano-emulsion -

These emulsions are Transparent and optically isotropic but micro emulsions are thermodynamically stable composed of oil, water, surfactants & co surfactants whereas Nano emulsions are kinetically stable composed of oil, water, surfactants & co surfactants⁶⁵. Co-surfactants present in these emulsions act as penetration enhancer & improve skin penetration¹. Nano - emulsions are appropriate carrier for the transport of lipophilic compounds into the skin². They increase skin hydration and viscoelasticity⁶⁶. R.P.Bagwe et al., Prepared lecithinised micro-emulsion as promising colloidal carriers allowing higher skin permeation³ and retention power of tretinoin compared to a solution, gel and marketed preparations containing this active substance⁶⁷.

Solid lipid nanoparticles-

Solid lipid nanoparticles are colloidal systems consists of triglycerides and waxes dissolved in surfactant solution to achieve physical stability¹. These are also known as nanostructured lipid carriers⁶⁸. Lipids present in these formulation increase bioavailability and reduce plasma profile variability. They have the ability to reflect and scatter UV radiation and acts as physical sunscreens on their own³. Lin et al., Prepared the lipid Nano carriers loaded with tretinoin and tetracycline into negatively charged lipid carrier resulted in a significant anti- bacterial activity⁶⁹.

Microspheres-

Microspheres are spherical shaped particles made up of biodegradable polymer². They are prepared by the Encapsulation technique which provide fine, inert, synthetic polymer materials deposited around solid and liquid micronized particles⁷⁰. Microspheres absorb sebum from the skin surface, reduce oil from the skin and provide good efficacy and tolerability. They increase the therapeutic effect for the long term². When microspheres are used as the drug carrier system they have numerous advantages in dermatology and cosmetology. D. Rasool et al. prepared the gelatin microsphere for the controlled release of all trans-retinoic acid for topical formulation of acne⁷¹.

Inorganic Nanoparticles-

Inorganic nanoparticles such as gold, silver, metallic nanoparticles exhibit a wide range of applications in treatment of skin disorders. Silver nanoparticles have antimicrobial and anti-cancer activity as well as anti-inflammatory activity³⁴. AgNPs reduce the production of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-alpha and inhibit the pathway of growth factor that increases the permeability of endothelial cells. They promote wound healing through reduction of the cytokine- modulated inflammation⁷². Garg.S et al. prepared the silver nanoparticles hydrogel using *Arnebia nobilis* root extract for wound healing activity. It shows good anti-bacterial property⁷³.

Conclusion

In the present scenario the nanotechnology has been extensively investigated for developing the treatment strategies for the disease related to skin. It has already

proven successful in disease other than skin related disorders and provides a very wide scope.

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