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''Nanotechnology therapeutic contribution into the Skin Autoimmune Diseases”

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''Nanotechnology therapeutic contribution into the Skin Autoimmune Diseases''

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ABSTRACT

Skin autoimmune diseases represent a significant category of skin disorders affecting many people worldwide. Efforts to understand their background have been pursued for several years to be treated or eliminated. Nowadays, nanotechnology has gained great recognition due to its advantages and wide range of its applications. Novel therapeutic methods based on nanomaterials have attracted intense research interest, especially in dermatology. In this master thesis, there is a focus on nanomedicine-based treatments of Autoimmune Skin Disorders and Acne. There is a summary of the most prominent autoimmune skin diseases such as Psoriasis, Atopic Dermatitis, Vitiligo, Lupus, Urticaria, Pemphigus Voulgaris, and Bullous Pemphigoid along with Acne – the most frequent skin disorder worldwide. Therapeutic approaches and results of in vitro, ex vivo, and in vivo testing are described briefly while there is a presentation of some important recent clinical trials and patented therapeutic and diagnostic tools.

Subject area: Nanomedicine

Key words: Skin, Nanocarriers, Autoimmunity, Acne, Therapy, Drug delivery, Nano-dermatology

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1. INTRODUCTION

The nanotechnology impact is enormous in the last decades. Its contribution in the medical field has led to ameliorate not only the preventive way but also the diagnostic and therapeutical ones of various of important illnesses. The therapy of both autoimmune diseases and acne represents an important example of nanotechnology contribution. More than this, skin-targeted topical delivery is an effective therapeutic way of several serious autoimmune dermatological diseases.

The hereby presented dissertation entitled ''Nanotechnology therapeutic contribution to Skin Autoimmune Diseases and Acne'' was submitted to the Department of Medicine, School of Health Sciences, National & Kapodistrian University of Athens for the fulfillment of the requirements of the Degree of “Master of Science in Nanomedicine”. The work includes an extended literature review for the advancements of the nanotechnology platforms regarding the therapy of psoriasis, atopic dermatitis, vitiligo, lupus, urticaria, pemphigus, bullous and acne. The research was conducted during the period of March 2021-August 2021.

The goal of this study is to review the scientific knowledge related to certain skin autoimmune diseases along with acne and their therapeutic nanotechnology-based vesicles. Firstly, the basic concepts that enclose the general context of the subject are studied in detail through bibliographic research. Also, a comparative literature review is realized regarding the diseases and the different nanomaterials used. In the end, there is an attempt to choose the “right” nano-vesicle candidate for each skin disorder.

2. Skin

The skin represents 16% of the total body weight, so it is far the largest organ of the body. It acts as a physical barrier against external environmental threats providing protection against physical, chemical, mechanical, and microbial influences. In general, several important functions are regulated by it like the protection from microbes, the temperature regulation, and the sensations. (Wang et al, 2019)

The skin is comprised of 3 main layers: a) the epidermis, b) the dermis and c) the hypodermis. The dermis is the outermost layer of skin (50-150 μm thick). It is made of keratinocytes (>90%), provides a waterproof barrier and is comprised of five layers (listed in order from the innermost layer to the outermost layer): stratum basal, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (SC). The SC (15-20 μm) corresponds to the outermost layer of the epidermis, it is considered a "brick wall" made up of protein and lipids. It is basically a physical barrier against infection, dehydration, chemicals, and mechanical stress. The dermis, beneath the epidermis (250 μm thick) contains most of the ECM, blood vessels, fibroblasts and other mesenchymal cells tough connective tissue, hair follicles, and sweat glands). Drug binding, metabolism, active transport, and surveillance occur in this region. The deeper subcutaneous tissue is the hypodermis made of fat and connective tissue providing cushioning. (Bouwstra et al, 2002) The skin structure is shown in Figure 1.

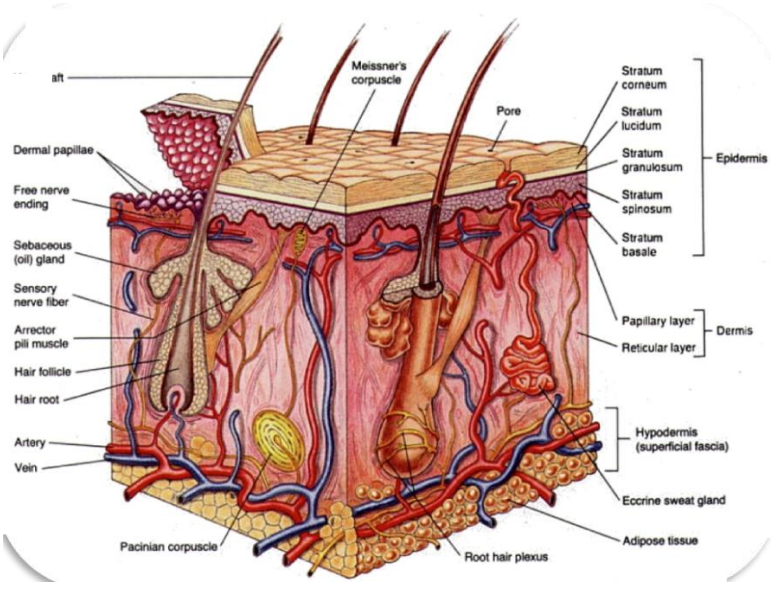


Figure 1: Skin structure (Skin Structure Detail, 2019)

The skin's large surface area (a total area of about 20 square feet) makes itself the most attractive and accessible route of drug administration. In general, small molecules (both lipophilic and hydrophilic) can penetrate the SC without assistance or traverse the epidermis through pathways created by sweat glands and hair shafts. In contrast, the delivery of larger molecules, such as peptides, proteins, siRNA, or DNA, through the skin continues to be a major research challenge. Physical enhancers (like sonophoresis, thermal ablation, electroporation, iontophoresis, microneedle arrays) and chemical enhancers (such as fatty acids, surfactants, esters, alcohols) are used to facilitate the penetration of a wide range of drugs. However, in the last decades, novel drug delivery systems have been widely investigated by providing opportunities to solve issues linked with conventional drug therapy such as instability, high toxicity, unfavorable pharmacokinetics, lower cellular uptake, and drug resistance representing an easy and non-invasive therapeutic approach of several diseases. (Bouwstra et al, 2002; Antonio et al, 2002)

The potential penetration pathways of drug molecules into the skin – across the stratum corneum, are intercellular, transcellular and/or trans appendageal routes. The intercellular route is considered as the principal penetration pathway of drug molecules, which is defined as the transport of drugs across intercellular lamellar lipid bilayers. The transcellular route signifies directly to the passage of drugs across keratinocytes and intercellular lamellar lipid bilayers to deeper skin layers. (Bouwstra et al, 2002; Antonio et al, 2002)

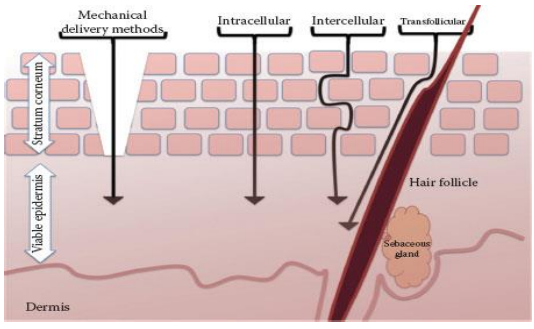


Figure 2: Skin penetration pathways (Antonio et al, 2012)

Bacteria trapped in skin pores and hair follicles, fungus, parasites, viruses, the weakened immune system, different allergens or irritants, genetic factors, or even illnesses affecting

the body systems are considered as possible causes of diseased skin. Generally, skin disorders symbolize a primary category of dermatologic illnesses representing the fourth leading non-fatal conditions after iron deficiency anemia, tuberculosis, and sense organ diseases. They vary greatly in symptoms and severity. They can be temporary or permanent, painless, or painful, minor, or even life-threatening. Generally, the most common treatment methods for skin conditions include antihistamines, medicated creams and ointments, antibiotics, vitamin or steroid injections, laser therapy, and targeted prescription medications. (Ramanunny et al, 2020)

3. Autoimmune diseases

Autoimmunity is defined as an immune response leading to a reaction with self-antigen (Theofilopoulos et al, 2017). The immune system is a complex network of cells, tissues, and organs that protects the organism from infections and other diseases. It is divided into two categories: i) the innate or nonspecific immunity, which consists of the activation and participation of preexistent mechanisms including the natural barriers (skin and mucosa) and secretions; and ii) the adaptive or specific immunity, which is targeted against a previously recognized specific microorganism or antigen. Innate immunity represents the host's first line of defense and is intended to prevent infection and attack the invading pathogens. Skin and mucosa provide an effective immune barrier between the internal and external environment. Skin acts as not only a physical barrier but also a chemical shield. That is why any malfunction of the skin is crucial and should be managed properly and efficiently. (Aristizábal & González, 2013; Ávalos-Díaz & Esparza, 2013)

Historically, the term "horror autotoxicus" by Paul Ehrlich over a hundred years ago, created the mistakenly belief that the immune system was unable to react against the body's own tissues. However, the research of Noel Rose, Donath and Landsteiner, Milgrom and Witebsky, Rose and Bona helped to the modern understanding. (Aristizábal & González, 2013)

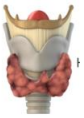
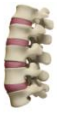
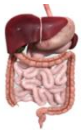
It should be noted that autoimmunity is a self-directed inflammation caused by aberrant dendritic cells and T and B cell behaviors that disrupt tolerance, resulting in an adaptive immune response that plays a central role in the phenotypical clinical expression of autoimmune diseases. In sharp contrast, autoinflammation leads to the activation of the innate immunity and may result in tissue damage through the alteration of cytokine cascades, which induce site-specific inflammation and is independent of the adaptive immune response. (Aristizábal & González, 2013; Ávalos-Díaz & Esparza, 2013)

Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunological tolerance to self-antigens. Most of them exhibit clinical heterogeneity, a polygenic nature and multifactorial contributions that often require both genetic factors and environmental factors. Inevitably, the rapid evolution of the understanding of genetics and the molecular mechanisms involved in the pathophysiology has challenged the old

autoimmunity paradigm of classification (localized and systemic autoimmune diseases) developing a classification system of: 1) monogenic autoimmune diseases, 2) polygenic diseases exhibiting a prominent autoimmune component, 3) monogenic autoinflammatory diseases, 4) polygenic disease exhibiting a prominent autoinflammatory component, and 5) mixed pattern diseases. Most autoimmune skin diseases belong to the second category, like pemphigus and pemphigoid, while one example of autoinflammatory skin disease is psoriasis. (Aristizábal & González, 2013)

Generally, autoimmune diseases have a high prevalence (7–9%) in the population, "preferentially" afflict women, strike at the prime of life and cause considerable morbidity and mortality There are more than 80 types of ADs. Celiac disease, diabetes mellitus type 1, Graves' disease, Sjogren's syndrome, inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus are some of the most known ADs as they are referred in Table 1 below. (Theofilopoulos et al, 2017) The diagnosis is generally based on the presence of adaptive immune system–mediated disease caused by self-reactive antibodies, T cells, or both. (Kono & Theofilopoulos, 2017). The treatment depends on the type and severity of the condition. Most of autoimmune diseases are chronic and there is no definitive cure, but symptoms can be alleviated and controlled with immunosuppressant drugs. The use of monoclonal antibodies, antigen-specific immunotherapy or regulatory T cell therapy may be other therapeutic options. (Theofilopoulos et al, 2017).

Table 1: Autoimmune Diseases

Autoimmune Diseases		
Brain		Multiple sclerosis, Autism, Guillain-Bone Syndrome
Thyroid		Thyroiditis, Grave's Disease
Bones/Muscles		Rheumatoid arthritis, Polymyalgia Rheumatica, Ankylosing Spondylitis
Skin		Psoriasis, Vitiligo, Eczema, Scleroderma
Lung		Fibromyalgia, Wegener's Granulomatosis
Nerves		Peripheral neuropathy, Diabetic neuropathy
Blood		Leukemia, Lupus Erythematosus, Hemolytic Dysglycemia
GI Tract		Diabetes Type I, Cellac's Disease, Crown's Disease

3.1 Skin autoimmune Diseases

Skin autoimmune diseases symbolize a significant category of dermatological illnesses affecting most of the world population. They consist of disorders like scleroderma, psoriasis, atopic dermatitis/eczema, vitiligo, bullous, pemphigus and lupus of the skin. Unfortunately, they are a psychological, social, and financial burden not only for the patients but also for the society. Despite the great progress in dermatological treatments, still there is a lack of knowledge in many basic skin autoimmune diseases and that is due to not enough consideration. It should also be noted that their conventional treatment suffers the limitations about patient compliance, safety, and efficacy of the therapy,

that's why different novel therapeutic approaches are being investigated (Preethi et al, 2021). The general background of the most frequent skin autoimmune diseases such as psoriasis, atopic dermatitis, vitiligo, lupus, urticaria and the rarest pemphigus and bullous of the skin along with the most common skin disorder in general – acne vulgaris is representing below.

Psoriasis

Psoriasis is a chronic inflammatory immune-mediated disease of the skin that affects around two percent of the population worldwide (Boehncke & Schon, 2015). It is characterized by increased dermal vascularity and keratinocyte hyperproliferation. Symptoms include the presence of erythematous red patches covered with scaly dry and whitish, pain, itchiness, and bleeding. Psoriatic lesions are distributed mainly on the scalp, elbows, knees, trunk, and gluteus creases. Psoriatic arthritis is an extra-cutaneous manifestation observed in 5-20% of patients. It is associated with a group of susceptibility genes: PSOR 1–7, the LCE3B/3C gene (related to epidermal differentiation), the IL-23 gene, and the gene encoding transcription factor NF-kB. Moreover, it is associated with a genetic background accompanied by autoinflammation. Beyond the traditional treatments, current therapeutic approaches focus on biological agents to ameliorate inflammation, including the use of chimeric or human anti-TNF monoclonal antibodies and recombinant anti-cytokine receptors. Lately, IL-12 and IL-23 blockage has been suggested as a new strategy to prevent the production of TNF, IFN-γ, and IL-2 cytokines and may represent an effective way to arrest the differentiation of the Th17 phenotype via IL-1 signaling, which drives the inflammation pathway in psoriasis. (Preethi et al, 2021; Ávalos-Díaz & Esparza, 2013). The skin structure of psoriatic patient is shown in Figure 3.

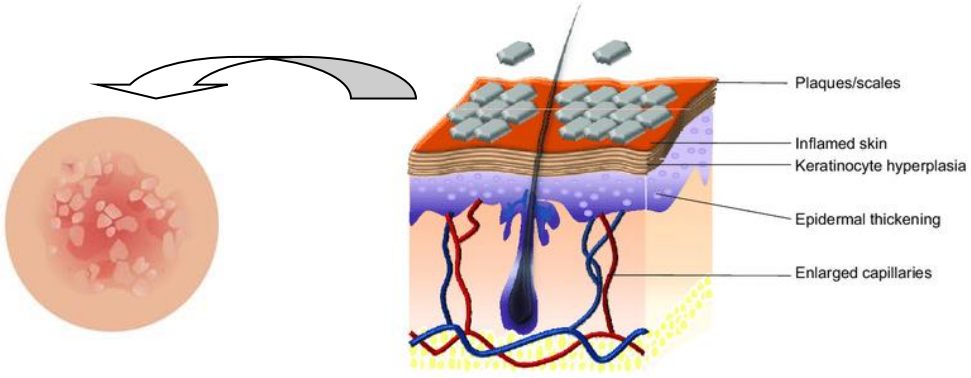


Figure 3: Psoriatic skin structure (Hung-Li et al, 2016)

Conventional therapeutics for Psoriasis

Topical treatments, systemic administration of anti-inflammatory medicaments, β-blockers, lithium, antimalarials and phototherapies are the main approaches used to control the disease. The list of drugs used to treat the skin affected by psoriasis includes methotrexate, cyclosporin, clobetasol propionate, calcipotriol, betamethasone, tazarotene, temoporfin, tretinoin. Natural agents such as curcumin, hypericin, hyperforin, indirubin, berberine and capsaicin has shown promising therapeutic results. Also, synthetic drugs like TNF-α inhibitors, Vitamin D_3 analogues and synthetic drug combinations have a therapeutic impact in the patients. Nevertheless, topical treatments are not particularly effective since they do not efficiently reach effector cells. Also, systemic treatments are used only in severe forms of psoriasis given their important side effects like burning sensation and erythema. (Prosperi et al, 2017; Ávalos-Díaz & Esparza, 2013). Table 4 shows briefly the current therapeutic approaches in Atopic Dermatitis.

Table 2: Overview of current therapeutic approaches in psoriasis

Treatments options for psoriasis	
Mild to moderate	
➢ Topical therapy	corticosteroids, retinoids, dithranol, vitamin D_3 analogues, calcineurin inhibitors, tar, keratolytic agents
Moderate to severe	
➢ Systemic therapy	oral agents, biologics
➢ Photo therapy	ultraviolet B therapy, psoralen plus ultraviolet A therapy (PUVA)

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic skin illness that affects thirty percent of both children and adults worldwide. AD is specified for the abnormally increased IgE level and cytokines (IL-4, IL-5, and IL-13) level while interferon-gamma (IFN-γ) levels are reduced. It is characterized by itchy, reddish, and scaly lesions along with a continuous inflammation combined mostly with allergic rhinitis or bronchial asthma, and food allergies. AD results from a multiplicity of factors such as susceptible genes, over-stimulatory immune system, and environmental factors. (Souto et al, 2019; Damiani et al, 2019; Ávalos-Díaz & Esparza, 2013). The skin structure of AD patients is shown in Figure 4.

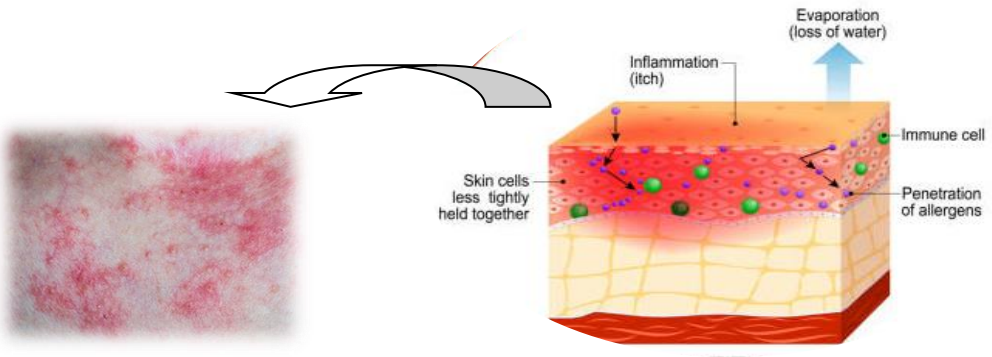


Figure 4: Dermatitis's skin structure (Tergum, 2021)

Conventional therapeutics for Atopic Dermatitis

Generally, AD treatments focus on improving patients' quality of life, reducing the severity of the pathology, preventing further infections, and controlling the illness in the long-term. AD prevention profile consists of the exclusion of food-allergens, the reduction of the contact with pollens, mite dust, traffic or tobacco smoke, volatile organic compounds, and animal fur and the application of daily skin emollients and lotions. The non-pharmacological approaches for conventional AD therapy include moisturizers and bath/wraps. The pharmacological approaches consist of the use of topical corticosteroids to reduce inflammation, antibiotics (namely antimicrobials) to eradicate infections induced by bacteria or other parasites, antihistamines to reduce pruritic symptoms, and calcineurin inhibitors to prevent eczema propagation and to reduce inflammation as well. Phototherapy and immunomodulation by systemic administration of immunosuppressant drugs have also a positive therapeutic impact on the patients. In fact, topical administration of drugs is still the main therapeutic approach for AD. However, there are several disadvantages like reduced patient compliance, low efficiency, and specificity of these systems in delivering therapeutic drugs. (Damiani et al, 2019; Shao et al, 2016). Table 3 shows briefly the current therapeutic approaches in Atopic Dermatitis.

Table 3: Overview of current therapeutic approaches in Atopic Dermatitis

Treatments options for Atopic Dermatitis	
➢ Topical therapy	antibiotics, corticosteroids, calcineurin inhibitors
➢ Systemic therapy	antibiotics, corticosteroids, immunosuppressant drugs
➢ Photo therapy	UVB, UVA
➢ Skin care	moisturizers, emollients, bathing
➢ Education	

Vitiligo

Vitiligo is a chronic depigmentation disease that affects melanocytes. The destruction of the melanocytes is the central pathological event that causes this depigmentation. This pathology can be presented clinically as a primary disease or can be a component of multiple autoimmune processes such as thyroid disease, pernicious anemia, rheumatoid arthritis, lupus, adult-onset autoimmune diabetes, chronic depigmentation disease that affects melanocytes and Addison's disease. Vitiligo is present in 0.5 percent of the population, distributed equally in males and females, starting during the second decade of life. In vitiligo, one locus of particular interest is on chromosome 17p13 linked in lupus patients who simultaneously develop vitiligo. This is in the NALP1 gene, which encodes NACHT leucine-rich-repeat protein 1, a regulator of the innate immune response, and contributes to the risk of GV susceptibility. Another gene involved in vitiligo is TYR (encodes tyrosinase), which is involved in melanin biosynthesis and is the major GV autoantigen. (Ávalos-Díaz & Esparza, 2013). The skin structure of a vitiligo patient is shown in Figure 5.

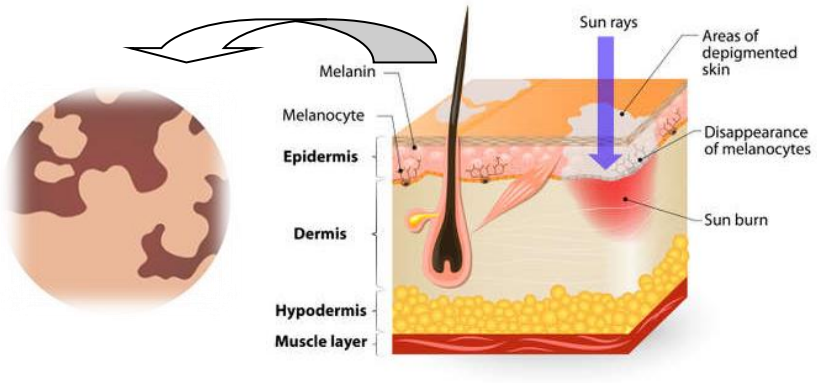


Figure 5: Vitiligo's skin structure (Vitiligo, 2021)

Conventional therapeutics for Vitiligo

Different therapeutic approaches are being used for vitiligo with variable results so that they can ultimately prevent the expansion of existing white spots on the skin, promote repigmentation and reduce psychological burden. Classical treatments include the corticosteroids like betamethasone and dipropionate, tacrolimus, pimecrolimus calcineurin inhibitors, and narrow-band UVB or UBA radiation combined with the administration of oral photosensitizing molecules such as psoralen. Recently, immunomodulatory therapies – like the neutralization of IFN-γ with antibodies – have been studied using an engineered mouse model of this condition. (Harris et al, 2012; Ávalos-Díaz & Esparza, 2013; Sun et al, 2020). Table 4 shows briefly the current therapeutic approaches for Vitiligo.

Table 4: Overview of current therapeutic approaches in Vitiligo

Treatments options for Vitiligo	
➢ Drug therapy	topical corticosteroids, immunomodulators, antioxidants
➢ Photo therapy	NB-UVB, PUVA
➢ Others	surgical therapies, depigmentation, cosmetic approaches, natural and holistic remedies

Lupus

Lupus, technically known as systemic lupus erythematosus (SLE) is a chronic, inflammatory, autoimmune-mediated multisystem disease. It is characterized by the presence of autoantibodies, deposition of immune complexes in various organs, recruitment of autoreactive and inflammatory T-cells, and excessive levels of plasma proinflammatory cytokines. Both genetic and environmental factors may cause this disorder. Symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, swollen lymph nodes, feeling tired, and a red rash. The disease was named "wolf" (lupus in Latin) in the thirteenth century as the rash was thought to appear like a wolf's bite. Its incidence is 20–70/100,000 people – predominantly affecting women (20–40 years), worldwide while seventy percent of the patients deal with skin symptoms. The three main categories of lesions are chronic cutaneous (discoid) lupus, subacute cutaneous lupus, and acute cutaneous lupus. (Ting et al, 2001; Understanding Lupus, 2021). Lupus's skin structure is shown in Figure 6.

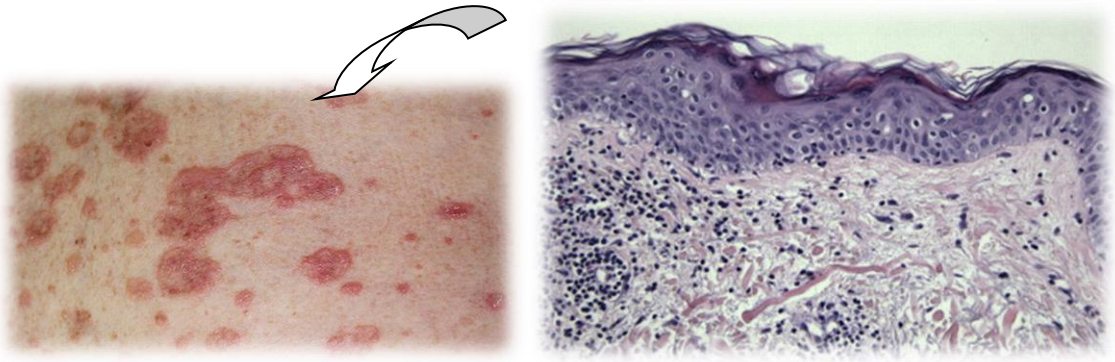


Figure 6: SLE's skin structure (Crowson & Magro,2009)

Conventional therapeutics for Lupus

Conventional management of the disease involves combination of local and systemic interventions. Local therapy consists of sun protection and topical pharmacologic agents, e.g., topical corticosteroids while systemic therapy uses several severe drugs. In fact, anticoagulants are used to help prevent blood clots, antimalarials to protect skin from rashes and UV light, biologics to help the immune system work correctly, *i*mmunosuppressives to help keep your immune system from attacking your body *and* *s*teroids to help with inflammation. Also, consistent sunscreen protection enhances

significantly better outcomes. (Momtazi-Borojeni et al, 2018; Ting et al, 2001). Table 5 shows briefly the current therapeutic approaches for Lupus.

Table 5: Overview of current therapeutic approaches in Lupus

Treatments options for Lupus	
➢ Topical therapy	Topical/occlusion/intralesional corticosteroids
➢ Systemic therapy	Systemic drugs like hydroxychloroquine/chloroquine/quinacrine
➢ UV protection	Sunscreen (physical & chemical), sun avoidance

Urticaria

Urticaria (also called hives, wheals, or nettle rash) is one of the most common skin disorders characterized by short-lived, superficial, itchy pale swellings with a surrounding red flare that become pink and flatten as they resolve over hours (wheals), and/or deep pale swellings of the subcutis and submucosa that may be painful rather than itchy and last longer (angio-oedema). It basically occurs when the body (mast cells) reacts to an allergen and releases histamine and other chemicals from under the surface of the skin. The histamine and chemicals cause inflammation and fluid to accumulate under the skin, causing wheals. That is why it is considered as autoimmune disease affecting around twenty percent of the population at some time in its life. It can be classified as acute (with or without angioedema) or chronic (with or without angioedema and spontaneous or inducible), depending on the duration of symptoms and the presence or absence of inducing stimuli. It can be diagnosed based on clinical history, physical examination, and diagnostic tests like skin prick tests (SPTs), serum specific IgE tests, basophil activation tests and food allergy tests. (Ávalos-Díaz & Esparza, 2013; Grattan et al, 2012) Urticaria's skin structure is shown in Figure 7.

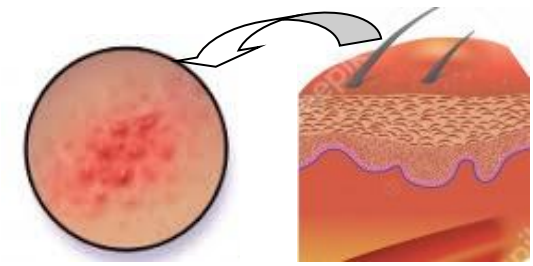


Figure 7: Urticaria's skin structure (Lee & Jorizzo, 2019)

Conventional therapeutics for Urticaria

The treatment is not very complicated as it targets in controlling and preventing its symptoms. Conventional management of the disease involves antihistamines such as cetirizine or fexofenadine which help by blocking the effects of histamines and reducing the rash and stopping the itching (Grattan et al, 2012; Radonjic-Hoesli et al, 2017). Corticosteroids and various immunomodulatory/immunosuppressive therapies contribute also to the mainstay of therapy for more severe cases. Antibiotics like dapsone can also be helpful by reducing redness and swelling. It should be noted that Omalizumab (a chimeric monoclonal anti-IgE biologic), or Xolair, plays a significant role in urticaria's therapy since its FDA approval in 2003. It represents an injectable drug that blocks immunoglobin E, a substance that plays a role in allergic responses. It can reduce symptoms of chronic idiopathic urticaria, a type of hives of unknown origin that can last for months or years. (Kolkhir et al, 2020; Metz et al, 2014; Kudryavtseva et al, 2018). Table 6 shows briefly the current therapeutic approaches for Urticaria disease.

Table 6: Overview of current therapeutic approaches in Urticaria

Treatments options for Urticaria	
➢ 1st line treatment	local heat, clothing pressure, emotional stress, non-steroidal anti-inflammatory drugs, dietary pseudo allergens, antihistamines (H_1, H_2)
➢ 2nd – 4th line treatment	oral corticosteroids or immunosuppressive drugs (e.g., ciclosporin, methotrexate or mycophenolate mofetil)

Pemphigus

Pemphigus (in Greek, pemphix means blister) is a group of blistering diseases with organ-specific autoimmune pathogenesis that affects the skin and mucous membranes. The disease is characterized by blisters and erosions caused by intraepidermal cell detachment in a process termed acantholysis. The lesions are induced by the presence of autoantibodies against proteins in the desmosomes, which are the attachment structures of keratinocytes. The incidence is 0.1 to 0.5/100,000 and occurs more often in women (1.5:1) between the fourth and fifth decade of life. Pemphigus can be divided into three major forms: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic

pemphigus (PNP). The disease is diagnosed according to the overall clinical picture, histopathology, and a positive direct immunofluorescence (DIF) microscopy while immunodiagnostic tests are particularly useful to differentiate the various diseases. Pemphigus autoantibodies are IgGs (IgG1 and IgG4 isotype) and target different proteins in the desmosome (protein that connects squamous cells together) complex even though its etiology, pathogenesis, and triggering factors are still not well known. (Ávalos-Díaz & Esparza, 2013; Singh, 2010). The skin structure of a patient suffering from pemphigus is shown in Figure 8.

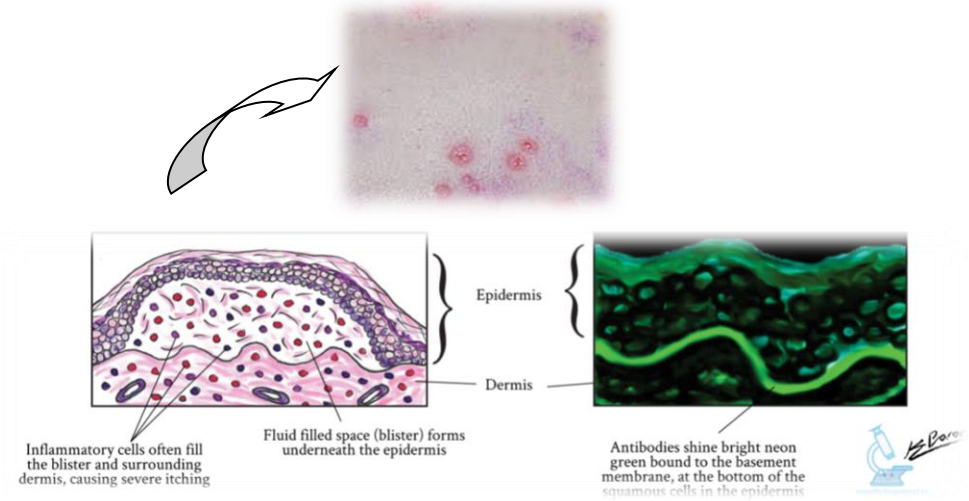


Figure 8: Pemphigus' skin structure under microscope (left) and via immunofluorescence (right) (Campbell & Osmond, 2021)

Conventional therapeutics for Pemphigus

The disease can be life-threatening if left untreated. Conventional treatment relies on the administration of corticosteroids and immunosuppressive agents to maintain complete remission, regarding the absence of new or established lesions. In the case of resistant pemphigus, using IVIG (intravenous immunoglobulin) and Rituximab is effective. Other experimental therapies have been proposed to neutralize the pemphigus IgG through of anti-idiotype antibodies or apoptosis inhibitors, and these have demonstrated experimental success in controlling blistering. Additionally, support therapy including the treatment of infections and fluid control is important for a positive outcome. So, immunosuppressive adjuvants, such as azathioprine and second-line adjuvants like cyclophosphamide, methotrexate, intravenous immunoglobulins, and immunoadsorption

could be the supplement therapeutic keys. (Ávalos-Díaz & Esparza, 2013; Tavakolpour, 2017). Table 7 shows briefly the current therapeutic approaches in Pemphigus.

Table 7: Overview of current therapeutic approaches in Pemphigus

Treatments options for Pemphigus	
➢ 1st line drugs	Corticosteroids, anti-CD20 monoclonal antibody (rituximab)
➢ 1st line adjuvants	Azathioprine
➢ Other adjuvants	intravenous immunoglobulins, immunoadsorption, cyclophosphamide

Bullous pemphigoid

Bullus pemphigoid is a rare blistering autoimmune disease described in 1953 by Walter Lever. BP is characterized by the separation of the dermal-epidermal junction (DEJ) accompanied by inflammatory cell infiltration in the upper dermis. The disease affects 1.2 to 2.1 cases per 100,000 people – mainly the elderly. It is clinically characterized by subepidermal blisters – developed on the arms, legs, torso, and in the mouth, that form tense bullae and erythematous urticarial plaques that cause pruritus and blistering on the chest and abdomen. In antigenic triggering, two major antigens have been described: the BP180 antigen described by Luis Diaz's group (5456), and the BP230 antigen described by John Stanley. (Ávalos-Díaz & Esparza, 2013; Lernia et al, 2020) Bullous skin structure is shown in the Figure below.

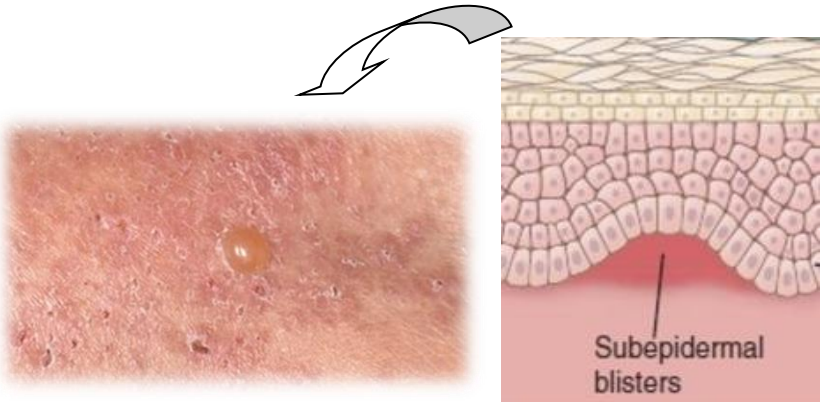


Figure 9: Bullous's pemphigoid skin structure (Saschenbrecker et al, 2019)

Conventional therapeutics for Bullous pemphigoid

Bullous pemphigoid's treatment helps heal blisters, ease itching, reduce skin inflammation, and suppress the immune system. (Lernia et al, 2020). It includes topical therapies with super potent topical corticosteroids, bacterial superinfection of erosions with local antiseptics, wound dressings for large wounds and sterile puncture of large blisters. Also, it should be noted that rituximab provides interesting clinical benefits although with less effectiveness while IgE targeted therapies, such as omalizumab, has been shown as promising in recent studies. Table 8 shows briefly the current therapeutic approaches for Bullous pemphigoid.

Table 8: Overview of current therapeutic approaches in BP

Treatments options for Bullous pemphigoid	
➢ 1st line drugs	Systemic corticosteroids
➢ Adjunctive therapy	Methotrexate, dapsone, rituximab, tetracyclines
➢ Localized forms	Topical corticosteroids, doxycycline

4. Acne vulgaris

Acne isn't an autoimmune skin disorder, but it is one of the most known skin disorder worldwide. It is considered as chronic inflammatory dermatological disorder involving the pilosebaceous unit. It is characterized by abnormal sebum secretion, follicular epithelial desquamation, bacterial growth, inflammation, papules, nodules (large papules), pustules, scars. It occurs when oils glands of the skin become clogged, forming spots and pimples. It is prevalent in teenagers and is related to the existence of bacterium P. acnes. Acne affects ten percent of the global population, making it the eighth most prevalent disease worldwide. It can be classified as mild, moderate, or severe. Genes, hormones, infections, diet, and stress are the main causing factors. At the same time, the sebum secretion is found to be the direct impact factor of acne, related to the severity of symptoms (Patel & Prabhu, 2020) The skin structure for acne's patients is representing in Figure 10.

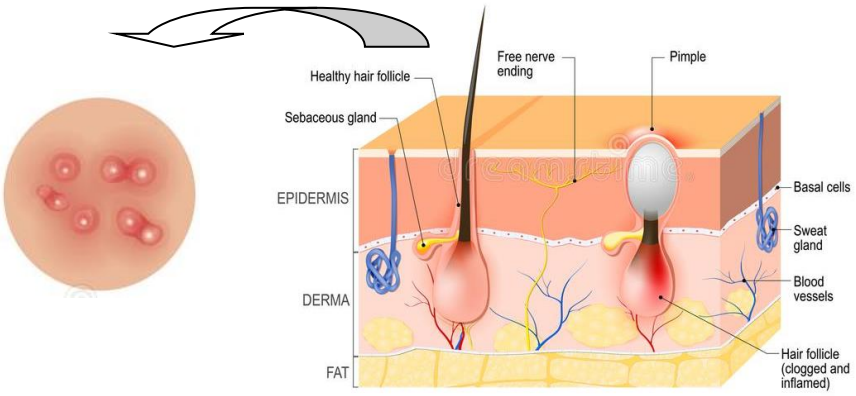


Figure 10: Acne Voulgaris's skin structure (Talianu et al, 2020)

Conventional therapeutics for Acne vulgaris

The therapeutic goal for acne corresponds to reducing inflammation, hormonal manipulation, killing C. acnes, and normalizing skin cell shedding and sebum production in the pore to prevent blockage. Topical treatment is first line therapy for mild to moderate episodes whereas moderate and severe acne necessitate systemic therapy. Herbs like aloe vera, juniper oil and red clover have shown positive therapeutic outcomes. Though, efficient conventional treatment includes the combination of antibiotics and retinoid applied topically while bacterial resistance can be avoided in some degree (Patel & Prabhu, 2020). Anti-acne agents like salicylic acid, lauric acid and dapsone have antibacterial activity while the ones such as isotretinoin, adapalene, tetracyclines and vitamin B_3 have other significant advantages. Table 9 shows briefly the current therapeutic approaches for Acne.

Table 9: Overview of current therapeutic approaches in Acne Voulgaris

Treatments options for Acne Voulgaris	
➢ Topical therapy	retinoids, antibiotics, azelaic acid, salicylic acid
➢ Oral therapy	antibiotics, anti-androgen agents, isotretinoin
➢ Other therapies	Light therapy, chemical peel, drainage, extraction, steroid injections

5. Nanotechnology

The idea of nanotechnology was first presented by physicist Richard Feynman in a lecture entitled “There is plenty of Room at the Bottom”, given on December 29th, 1959, Annual Meeting of the American Physical Society, California Institute of Technology. It represents the design, synthesis, characterization, and application of materials and devices to produce nano-sized materials, preferably 1–100 nm with brand-new physiochemical, electronic, optical, mechanical, catalytic, and thermal properties. These materials are called nanoparticles (NPs) and they include liposomes, micelles, nanoshells including quantum dots (QDs), carbon-based particles (including nanotubes and fullerenes), nanoemulsions, nanocrystals, and polymer-based ones (including dendrimers). Figure 11 shows a comparison of the dimensions of standard nanomaterials of biomolecules, cells, and objects.

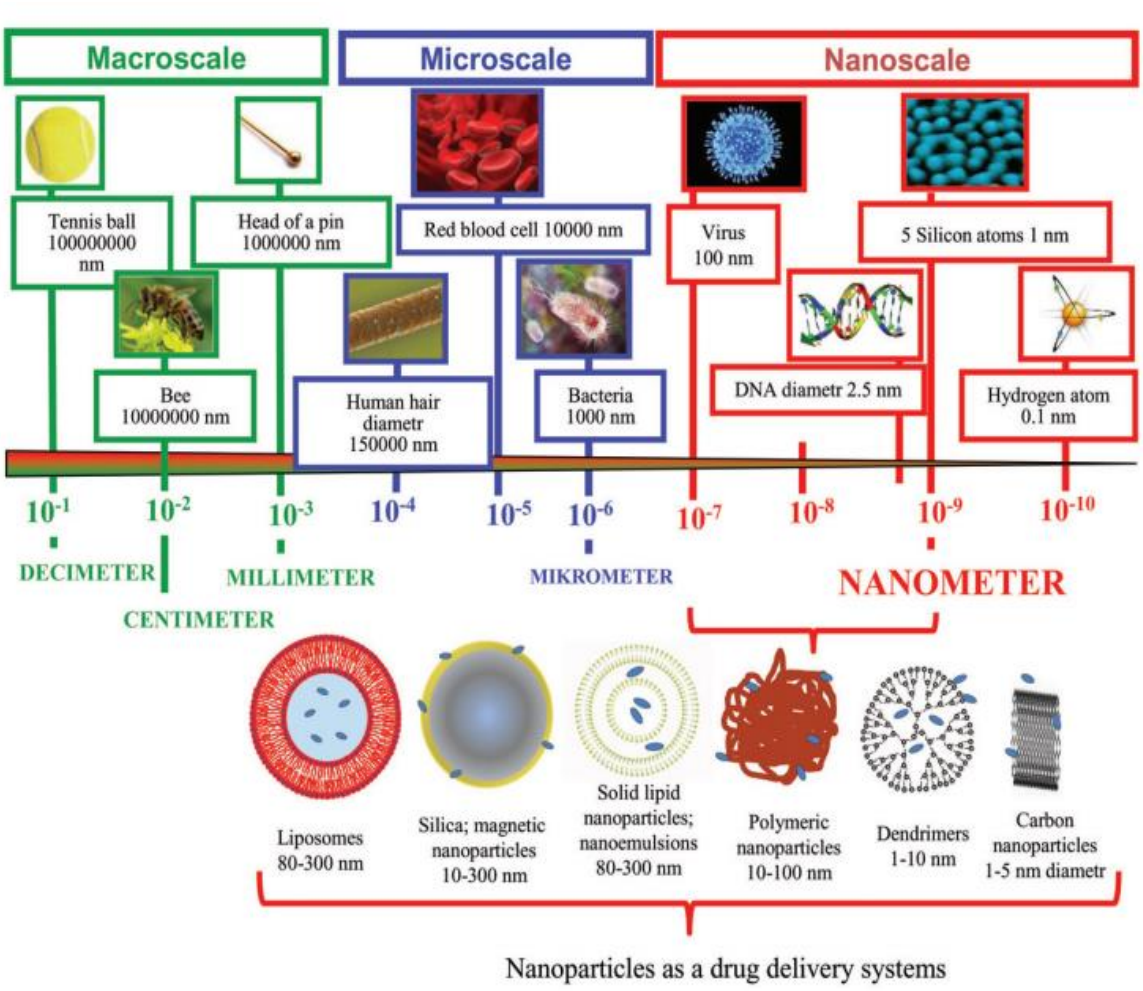


Figure 11: Comparison of the dimensions of different structures (Wilczewska et al, 2012)

According to the announcement of the European Commission Communities "Towards a European Strategy for Nanotechnology" (Brussels, 12.5.2004, COM (2004) 338 final, http://cordis.lu/nanotechnology) the effects of nanotechnology expand in the fields of biological defense, pharmaceuticals, IT, energy storage, materials science, economics, development of new techniques, automotive, clothing, and daily hygiene. Their unique advantages make them important research in the medical field. Nanobiotechnology-based applications in the prevention, diagnosis, and treatment of human diseases are referred to as Nanomedicine. One of the most attractive and fascinating applications of Nanomedicine is drug delivery and targeting. In the past few years, novel drug delivery systems have been widely investigated by providing opportunities to solve issues such as instability, high toxicity, unfavorable pharmacokinetics, lower cellular uptake, and drug resistance linked with conventional drug therapies. (Gupta et al., 2012; Demetzos, 2016; Wilczewska et al, 2012).

The advantages of NPs are vast and unique. In addition to their small size, the large surface/volume ratio and easy preparation, NPs can be used to encapsulate and protect drugs, genes, or proteins in which they are carrying from degradation, thus, enhancing their biodistribution and allowing sustained release. They also improve the bioavailability of hydrophobic molecules, and can be modulated for site-specific targeting, hence, decreasing the side effects of drugs. Moreover, their unique ability to pass intercellularly through corneocytes, intracellularly through corneocytes, and via other dermal appendages like hair follicles – due to their small size, is an important property in the treatment of different kinds of diseases. (Elsayed, & Norredin, 2020; Demetzos, 2016; Wang et al, 2019)

5.1 Nanocarriers and skin

Skin drug delivery is by far one of the most important applications of nanotechnology. As it is mentioned previously, the skin forms a barrier to the external environment, and it is mostly impermeable to the drugs due to epidermal cell cohesion and stratum corneum lipids. So, there is a requirement for efficient drug delivery systems to surpass this barrier (Gupta et al., 2012). Nanotechnology can be used to modify the drug permeation/penetration by controlling the release of active substances and increasing the period of permanence on the skin, besides ensuring direct contact with the stratum

corneum and skin appendages and protecting the drug against chemical or physical instability. Further, the delivery of therapeutic agents without the need for chemical enhancers is desirable to maintain the normal skin barrier function. (Vogt et al, 2016)

It is important to consider that the barrier nature of diseased skin is less efficient. Nanoparticles can penetrate the injured lesions more efficiently due to an altered stratum corneum, inflammation and increased keratinocyte turnover. So, nanocarriers may facilitate drug delivery by incorporating, encapsulating, or entrapping and/or conjugating pharmaceutical active ingredients. As stated, there are limited data available on skin penetration of nanoparticles through diseased skin. (Ramanunny et al, 2020; Vogt et al, 2016) However, the topical delivery by nanocarriers for local effects is generally to be used on diseased skin. The NPs penetration applied topically is done by at least one of three routes, i.e., intracellular route, intercellular route or through hair follicles and sweat glands having the parameters below regarding their diameter (d_p) (Souto et al, 2019):

- $d_p < 4nm$ NPs easily penetrate or permeate through the intact skin
- $4nm < d_p < 20nm$ NPs can be permeated via damaged or intact skin
- $d_p < 45nm$ NPs can be permeated or penetrate insalubrious skin
- $d_p > 45nm$ NPs are susceptible to be accumulated or translocated in, or through, skin appendices

Numerous novel nanocarrier systems have been investigated so far for the treatment of skin diseases. As it is mentioned in the previous section, nanostructured carriers are an optimal option for drug delivery due to their advantages over conventional formulations. The physicochemical characteristics of the nanocarriers, such as size, charge, chape, rigidity, hydrophobicity, and surface are crucial to the skin permeation mechanisms. So, the use of nanosized carriers in dermal drug delivery increases the specificity of drugs and thus reduces the side effects decreasing the dose of administered drugs. The most important engineered nanostructures used in topical drug delivery are described briefly below. (Ramanunny et al, 2020; Vogt et al 2016; Elsayed & Norredin, 2020; Saleem et al, 2020)

Lipid nanocarriers

The lipid nanocarriers comprise lipid-based nanoparticles including vesicular nanocarriers (liposomes, niosomes, tranfersomes, ethosomes) and Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLCs).

Liposomes

Liposomes are spherical vesicles made of phospholipids, cholesterol, bilayers, or other surfactants usually within the size range of 80–300 nm (Figure 12). They are biocompatible and biodegradable. They belong to the self-assembled colloidal nano dispersion systems and like biological membranes, they are capable to incorporate lipophilic (hydrophobic) bioactive molecules (drugs) or entrapping them into their aqueous core. They can interact with cells via adsorption, fusion, endocytosis, and lipid transfer. Generally, the liposomes act as a drug carrier system by entering the SC as intact vesicles, thereby localizing drugs in the SC and viable epidermis, reducing systemic absorption, and thus minimizing side effects. It is reported that they increase the solubility of drugs and improve their pharmacokinetic properties, such as the therapeutic index of chemotherapeutic agents, rapid metabolism, reduction of harmful side effects and increase of in vitro and in vivo anticancer activity. However, the penetration depth offered by them is limited as liposomes have a high tendency to adhere and fuse with the cell membrane, resulting in the early release of the encapsulated payload in the upper layers of SC before reaching deeper skin layers.

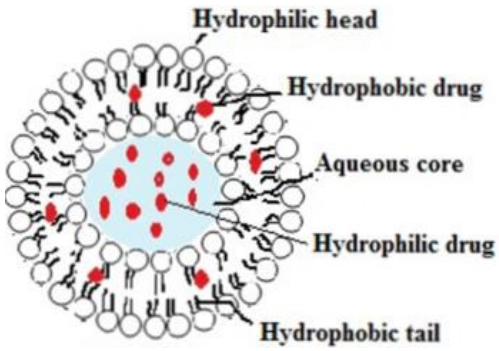


Figure 12: Liposome's structure (modified from Chamundeeswari et al, 2019)

Ethosomes/Transfersomes/Noisomes

Ethosomes are lipid vesicular systems mainly constituted of aqueous dispersions of phosphatidylcholine solubilized in ethanol. They constitute the third generation of liposomes, able to overcome some of the problems associated with liposomes' s use. They are considered transdermal vehicles, able to pass through SC and reach the lower skin strata up to derma. Moreover, they have higher loading capacity in the case of lipophilic drugs, longer physical stability as well as an easier and less expensive manufacture method compared to the liposomes. Transferosmes are highly deformable, elastic vesicular structures comprising of the aqueous core, phospholipids, and edge activators with a diameter of around 100nm. They can be used for the delivery of various active compounds, including proteins and peptides, insulin, corticosteroids, interferons, anesthetics, NSAIDs, anticancer drugs and herbal drugs by minimizing the undesirable side effects of the drugs and achieving a sustained drug release. Liposomes modified with non-ionic surfactants form unilamellar or multilamellar niosomes. They modify the structural arrangements of SC enhancing their permeability across the membrane with better chemical stability. Also, their biodegradability, biocompatibility, and non-immunogenic nature create superior characteristics over the conventional formulations. Figure 13 shows the different structures in the described lipid-based nanoparticles.

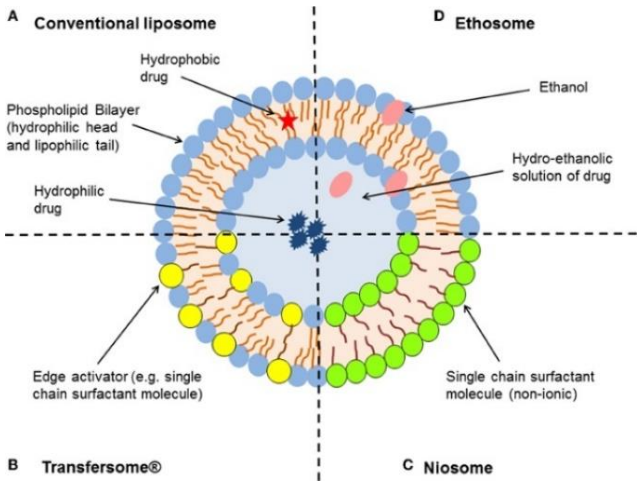


Figure 13: Different types of lipid-based vesicular delivery systems' structure (Hua, 2015)

Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLCs)

SLNs and NLCs are types of carrier systems based on solid lipid matrices (Figure 14). SLNs are particles made of solid lipids (purified triglycerides, complex glyceride mixtures, or waxes). Their advantages consist of good physical stability, protection of incorporated drugs from degradation, controlled drug release, less toxicity, good tolerability, and large scale-up capability. However, some disadvantages have been observed, such as low loading capacity, risk of gelation, drug expulsion after crystallization, and a relatively high-water content of the dispersion. In contrast, NLCs are modifications of lipid-based nanoparticles that have been developed to overcome the limitations of conventional SLNs. NLCs are produced by mixing solid lipids with liquid lipids, which leads to a special nanostructure with increased payload and prevented drug expulsion.

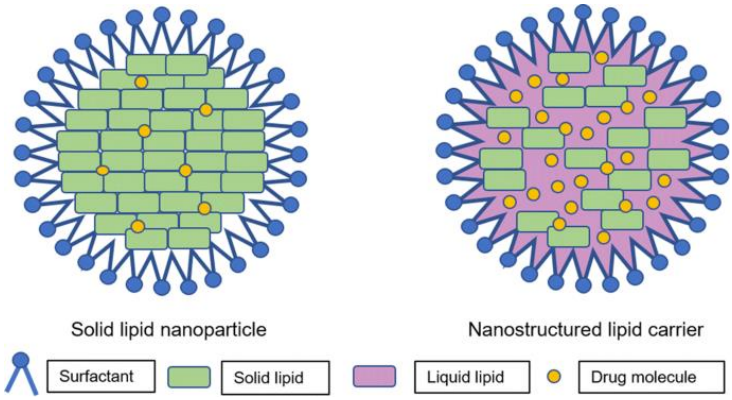


Figure 14: SLN's structure (modified from Subramaniam et al, 2020)

Polymeric carriers

The polymeric nanocarriers consist of nanoparticles (nanospheres, nanocapsules, and lipid-based nanocapsules), micelles, dendrimers, nanofibers, nanosponges, nanogels.

Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are substances of high molecular weight, consisted of repeated units called monomers that are connected onto a long chain (Figure 15). Their diameter ranges from 10 to 100 nm. They are obtained from synthetic polymers, such as poly- ε-caprolactone or natural polymers like chitosan or both. Based on in vivo behavior, PNPs may be classified as biodegradable and non-biodegradable. A bioactive molecule can be dissolved, entrapped, encapsulated, or connected to the polymer's surface and it

can be released by desorption, diffusion, or nanoparticle erosion in the target tissue. They can be designed as nanocapsules or nanospheres differing in their composition and structural organization. Nano capsules are systems where the drug is on the inside surrounded by a polymer membrane. Polymeric nanospheres consisted of a matrix where the drug is dispersed. They are of interest for skin administration because of the controlled release of encapsulated active ingredients, which need to diffuse through the polymeric matrix to permeate the skin. They are structurally stable due to their rigid matrix and can maintain their structure for long periods of time when topically applied.

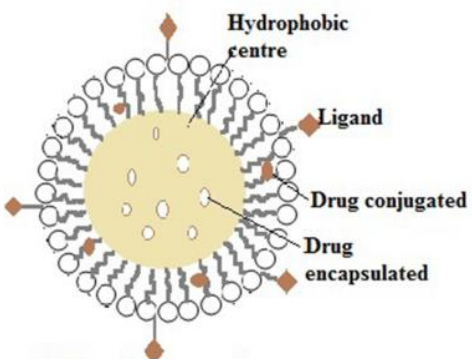


Figure 15: Polymer's structure (modified from Chamundeeswari et al, 2019))

Dendrimers

Dendrimers are unique polymers with well-defined size and structure (Figure 16). They are unimolecular, monodisperse, synthetic polymers, less than 15nm with highly branched 3D structures consisting of a core, dendrons, and surface-active groups. A biomolecule – both hydrophilic and lipophilic (drug) can be encapsulated in the internal structure of a dendrimer or it can be chemically attached or physically adsorbed on their surface. Although they might have cellular toxicity and high cost for their synthesis, etc., dendrimers are considered as potential carriers for targeted drug delivery due to multiple functional groups in their structure.

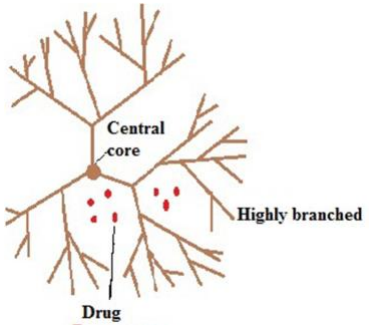


Figure 16: Dendrimer's structure (modified from Chamundeeswari et al, 2019))

Polymeric micelles

Polymeric micelles are nanosized molecules of core-shell structure that are formed by the self-association of amphiphilic block copolymers at/above specific polymer concentration called "critical micelle concentration" to decrease surface-free energy when they are added to an aqueous solvent (Figure 17). They have tunable chemical and physical properties. However, they have some limitations including dependence on critical micelle concentrations and low drug-loading capacity. However, this biocompatible, highly stable colloidal system with enhanced solubilization of drug and localized drug release to the targeted site makes the polymeric micelles more intact for dermatological conditions, mainly psoriasis, burns, and acne.

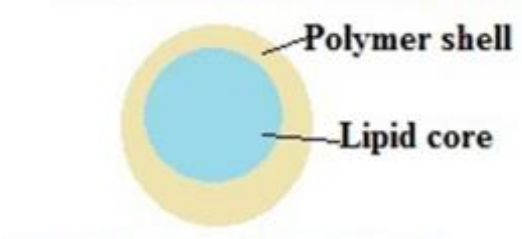


Figure 17: Micelle's structure (modified from Chamundeeswari et al, 2019))

Nanofibers/Nanosponges/Nanogels

Nano sponges are a class of materials made up of tiny sponge-like structures with narrow cavities with an average diameter below 1µm. They cross-link the segments of polyester to form a spherical shape that has many cavities where a hydrophilic or lipophilic drug can be stored. They are biocompatible, versatile, and capable to create different formulations such as oral, parenteral, and topical systems so they have wide pharmaceutical applications. (Ravi et al, 2019)

Inorganic nanoparticles

Metallic/metallic oxide NPs

Metallic NPs comprise a class of materials made with metals such as gold (Au) and silver (Ag) while metallic oxide ones like titanium oxide (TiO_2) and zinc oxide (ZnO) ranging from 1 to 100nm (Figure 18). They exhibit great optical and electronic properties as well as remarkable selectivity, biocompatibility, stability, and functionality creating a well-explored delivery system for drug delivery and diagnostic imaging. Moreover, metallic nanoparticles have the potential to carry large doses of drugs and increase their circulatory half-life. The drug can be encapsulated leading to easier penetration across the barrier to reach the target site.

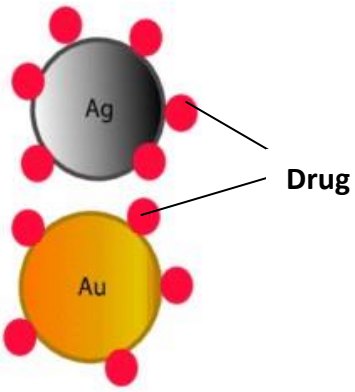


Figure 18: Ag/Au's structure (modified from Chamundeeswari et al, 2019)

Carbon nanotubes

Carbon nanotubes are hydrophobic cylindrical tubes formed of carbon allotropes with a similar structure to that of graphite (Figure 19). The size and geometrical configuration of carbon nanotubes vary showing the effectiveness in delivering therapeutic agents. This 3D structure of nanotubes favors the covalent or non-covalent binding of biomolecules on the inner side and the functional group on the outer surface of the nanotubes. The functionalization enhances solubility, biocompatibility, and tissue-selective targeting. In general, their high drug loading capacity in response to their large surface area enables them to be a versatile tool for skin therapeutics.

Figure 19: Carbon nanotube's structure (modified from Chamundeeswari et al, 2019))

Quantum dots (QDs)

QDs are nanosized three-component systems comprised of core, shell, and coated surfaces (Figure 20). The presence of semiconductors in the core is responsible for the quantum effect of absorption or emission of light. The fluorescence effects and photostability are the functions of the shell. The hydrophilicity and lipophilicity are determined by surface coating/ modification. The benefits of QD are biocompatibility, low toxicity, optical property, and luminescence.

Figure 20: Quantum dot's structure (modified from Chamundeeswari et al, 2019))

Figure 21 shows the different penetration ways of novel nanoparticles into the skin.

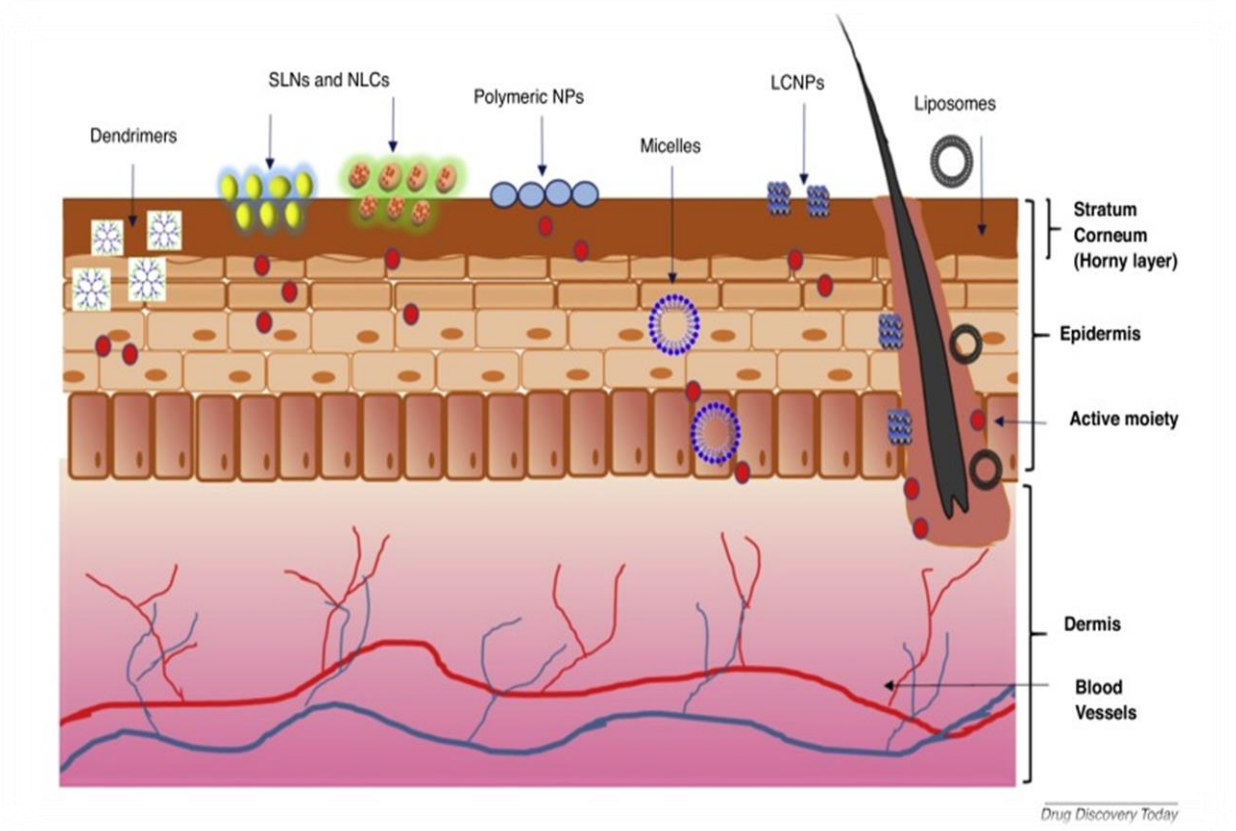


Figure 21: Nanoparticles' permeation upon topical application (Rappali et al, 2020)

Table 5 shows the basic pros and cons of the skin nanocarriers used for therapeutical reasons.

Table 10: Advantages and disadvantages of skin nanocarriers

Nanocarriers	Advantages	Disadvantages
Liposomes	Encapsulation both of hydrophilic and lipophilic drugs Protection of drug from environmental conditions Good biocompatibility and biodegradability Low toxicity	Poor stability Special storage Limited skin penetration
Niosomes/ Transfersomes/ Ethosomes	Incorporation of lipophilic/ hydrophilic drugs High encapsulation efficiency and stability Simple and inexpensive to manufacture Enhanced penetration and permeation Ability of intactly transport of across stratum corneum	Skin irritation
SLNs/NLCs	Large industrial scale production Protection of drug from environmental conditions Incorporation of lipophilic and hydrophilic drugs Low toxicity Low cost	Risk of gelation Storage drug expulsion Low drug loading
Polymeric nanoparticles	Drug release in controlled and sustained manner Incorporation of hydrophilic and hydrophobic drugs Tunable chemical and physical properties Higher stability than lipid-based ones Many preparation methods	Difficulty for their scale-up
Polymeric micelles	High solubility Tunable chemical and physical properties Protection of drug from environmental conditions Drug release in controlled manner	Only for lipophilic drugs Low drug-loading capacity
Dendrimers	High solubility Tunable chemical and physical properties Multiple functional groups for targeted drug delivery Acting like solubility enhancers	Cellular toxicity High synthesis cost

6. Psoriasis and nanotechnology

Nanotechnology contribution is showing great results in psoriasis's therapy up to now since nano-based studies for psoriasis's therapy are demonstrating enhanced efficacy and reduced toxicity compared with conventional formulations.

The incorporation of corticosteroids in SLNs, PLGA, microemulsions and liposomes may demonstrate to be more efficient than the commercial corticosteroid formulations in skin penetration and reduction of inflammation. NLPs loaded with an analog of vitamin D_3, calcipotriol, and methotrexate are showing good skin infiltration and no significant skin irritation. Also, scientific efforts have been made to generate NPs encapsulating cyclosporin A or tacrolimus for topical administration to improve the penetration of the skin, reduce the dosage and the systemic effects. Numerous MTX incorporating nano formulations are being produced and tested man cadavers, animal models and in clinical trials. Generally, increased efficiency of drug absorption through the skin, reduction of diseased areas and decrease of the disease severity index have been observed (Prosperi et al, 2017). Hydrogel (Carbopol® Ultrez 10 National Formulatory) containing dexamethasone as the active ingredient has shown potential use in controlled drug delivery for the treatment of psoriasis. The most recent studies are represented briefly in Table 11 while some clinical trials and patents for novel psoriasis's therapy are shown in Table 12 and 13, respectively.

Table 11: Recent studies for psoriasis's treatment

Nanoparticle	Drug	Outcome	Reference
AuNPs	Methotrexate	↓ keratinocyte hyperproliferation, epidermal thickness and ↓ inflammatory infiltration was observed in in vivo studies	Frattodi et al, 2019
Dendrimers	Dithranol	↑ permeability across the skin and prolonged release of the drug	Tripathi et al, 2019
Ethosomal gel	Methotrexate-salicylic acid	Slow, prolonged release of methotrexate	Chandra et al, 2019
PLGA nps	Apremilast	↑bio availability, half-life, and sustained release	Anwer et al, 2019
(MPEG-dihexPLA) diblock copolymer	Tacrolimus	↑deposition into the hair follicle	Lapteva et al, 2014
SLNs and NLCs	Cyclosporine	prolonged release of the drug	Essaghraoui et al, 2019
Cationic liposomes	Cyclosporine	↑stability and entrapment efficiency	Walunj et al, 2020
HA-conjugated propylene glycol ethosomes	Curcumin	N/A	Zhang et al, 2019
Nanoemulsion	8-methoxy psoralen	autooxidation of chignolin	Oliveira et al, 2018
Niosomes	Vitamin-A analogue	↑ permeability in the viable skin layers compared with acitretin gel and ↑antiproliferative activity in HaCaT cell culture	Abu Hashim et al 2018

Table 12: Recent clinical trials for psoriasis' s treatment (Clinicaltrials.gov., 2021)

Delivery system	Drug	Clinical phase	NCT number
JAK inhibitor	Tofacitinib	Phase III	*NCT03736161*
TNF-α Inhibitor	Infliximab (subcutaneous)	Phase IV	*NCT00686595*
Blocks IL-17R	Brodalumab (210 mg, subcutaneous)	Phase IV	*NCT04183881*
PDE4 inhibitor	Apremilast	Phase III	*NCT04175613*
Vitamin D and corticosteroid	Calcipotriene (0.005)/betamethasone	Phase II	*NCT03731091*
Pefcalcitol ointment, 0.005%	PDE4 inhibitor	Phase II	*NCT02970331*

Table 13: Patented nano formulations for psoriasis's treatment (Rapalli et al, 2020)

Delivery system	Drug	Patent number
Water-dispersible NPs	Tretinoin, isotretinoin, adapalene, tazarotene	EP3108875A1
NP comprising alginate, aerosol OT, and therapeutic agent	Methotrexate, cyclosporine, and steroid	US20110020457A1
Topical preparation	Apremilast	WO2017168433A
Oil-in-water emulsion	Ruxolitinib	WO2011146808A2
PLGA NPs	Calcitonin, cyclosporine	EP2667844A2
Pefcalcitol ointment, 0.005%	PDE4 inhibitor	NCT02970331
Liposomes	clobetasol propionate	CA 2416731 C

7. Atopic Dermatitis and nanotechnology

Nanotechnology gives many potentials minimizing the several side effects of topical conventional AD therapy and optimizing the therapeutic outcomes. Innovative drug nano delivery systems are exhibiting great results as they obtain the capacity to penetrate the stratum corneum (SC), to reduce adverse effects and increase drug targeting. So, formulations based on nanoparticles (NPs) like liposomes, ethosomes, SLNs, nano emulsion and polymeric NPs as well as the process of iontophoresis are being expected to

overcome all the above-mentioned limitations for AD's therapy. The most indicative studies for novel AD's therapy are represented briefly in Table 14 while some clinical trials and patents are shown in Table 15 and 16, respectively.

Table 14: Recent studies for AD's treatment

Nanoparticle	Drug	Outcome	Reference
SLNs	Tacrolimus	↑release and penetration of drug into the deepest skin layers compared to Protopic®	Kang et al, 2019
SLNs	Capsaicin-siTNFα	↑ penetrability, % of drug retained in target tissues, ↓dermatitis index and lesser SC thickness	Pinaki et al, 2013
Lipid Nps	Tacrolimus	↑in vitro permeation compared to Protopic®	Singh & People, 2011
Chitosan	HA-Tacrolimus	↑Drug release kinetics, permeation, and efficacy	Zhuo et al,
ethosome	certirizine	↓ scores, skin hyperplasia and scratching	Goindi et al, 2014
Transfersomes	tacrolimus	↑ release compared to Protopic®	Lei et al, 2013
+ charged nanoemulsion	amphotericin B	↑permeation across human skin	Hussain et al, 2013
nanoemulsion	ceramide 3B	↑skin elasticity and hydration level on humans compared to Corneometer® 825, Cutometer® SEM 575 and Mexameter® 18	Yilmaz et al, 2006
guar gum nanoparticle	oxazolone	↓ cellular infiltration and epidermal thickness (in vivo study)	Ghosh et al, 2018
cationic chitosan	Hydrocortisone - hydroxytyrosol	optimal epidermal and dermal permeation, reaching the deepest skin layers	Siddique et al, 2019
Chitosan (nanocapsules)	betamethsone valerate	↑Drug permeation efficiency and amount of BMV retained into the epidermis and the dermis	Md et al, 2018
NLC	microsilver	↑antimicrobial and anti-inflammatory activity	Keck et al, 2014

Table 15: Recent clinical trials for AD' s treatment (Clinicaltrials.gov., 2021)

Delivery system	Drug	Clinical phase	NCT number
Topical preparation	Pimecrolimus	Phase IV	*NCT00484003*
infusion intravenously	Rituximab	Phase IV	*NCT00267826*
N/A	NF-kappaB Decoy	Phase II	*NCT00125333*
N/A	Photocil	Phase IV	*NCT02780167*
N/A	Ustekinumab	Phase II	*NCT01806662*
N/A	Alefacept	Phase IV	*NCT00376129*
N/A	Vitamin D3	Phase II	*NCT01337635*
N/A	Paclitaxel	Phase I	*NCT02013154*

Table 16: Patented nano formulations for AD's treatment (Akhtar et al, 2017)

Delivery system	Drug	Patent number
Water-dispersible NPs	Interleukin-11	US 20030147849 A1
liposomes	PVP-iodine	WO 2004073683 A1
N/A	Corticosteroid and antihistamine	US 8003127 B2
METADICHOL R liquid and gel Nanoparticle formulations	Ruxolitinib	CN 105188687 A
Chitosan nanoparticle	Hydrocortisone - hydroxytyrosol	WO 2015072846 A1
Nanocapsule	HDL	WO 2016011049 A2
Colloidal nanoscale carriers	Active hydrophilic substances	EP 2583671 A1

8. Vitiligo and nanotechnology

Since vitiligo's management is usually a long process ranging from months to years, the patient inevitably displays a variety of side effects like skin atrophy, acne and burning sensation. The development of nano-drug delivery systems like microemulsions, nano emulsions, nanoparticles, lipid carriers has already been shown some prominent advantages over conventional methods. Even though existing literature focused on vitiligo's nano treatment is small, these novel methods facilitate the ability for drugs to possess sustained or controlled release behavior, enhance the therapeutic efficiency and reduce side effects. There have been already patented synergistic therapeutic options such as local application of bFGF peptide(s) lotions in association with psoralens and UV-

A, or steroids or surgical procedures (US9457064B2) and disclosed herein excimer laser to restore pigmentation to skin areas (US20050273142A1) The most interesting treatment studies are presenting in Table 17 while some recent clinical trials regarding new therapeutic interventions for the vitiligo are shown in Table 18.

Table 17: Recent studies for Vitiligo's treatment

Nanoparticle	Drug	Outcome	Reference
Liposomes	8-methoxypsoralen	↑release and permeation of 8-MOP	Sinico et al, 2006
Liposomes	Baicalin and berberine	antioxidant - photoprotective activity	Mir-Palomo et al, 2019
Cationic noisome	Tyrosinase plasmid pMEL34	gene topical delivery	Jiradej et al, 2010
Pd/Pt NPs	Polydopamine	efficient transdermal delivery	Huang et al, 2017

Table 18: Recent clinical trials for Vitiligo' s treatment (Clinicaltrials.gov., 2021)

Drug	Clinical phase	NCT number
INCB054707	Phase II	*NCT04818346*
Topical ruxolitinib (Janus Kinase inhibitor)	Phase III	*NCT04052425*
N/A	Phase I	*NCT02797574*

9. Lupus and nanotechnology

Similarly, with the previous ADs, novel nano modalities could show a better therapeutic outcome for Lupus as they facilitate the SC drug penetration. In fact, since currently available drugs must be taken continually by the patients, and some are quite toxic, leading to a high rate of treatment noncompliance, nanoparticle-based drug delivery systems may be the new therapeutic key. These new vesicles can selectively deliver most of the conventional drugs to inflamed tissue or specific cells. The utilization of polar solvents such as dimethyl sulfoxide (DMSO) and liposomal encapsulation is the most mainstream and prevalent since both modalities take advantage of the lipophilicity of the

stratum corneum lipid bilayers (Ting et al, 2001). The development of inhibitors for specific targeting via targeted immunotherapy in different mechanisms such as B-cell depletion, targeting B-cell survival factors, B-cell tolerization, anti-cytokine therapies are also other significant therapeutic approach (Rostamzadeh et al, 2016; Look et al, 2013). To date, there is no FDA nanomedicine approved therapeutic approach for SLE, so many more studies are needed to be declared. It is important to note though that both siRNAs conjugated with lipids or encapsulated in liposomes and anti-IgD monoclonal antibodies (mAbs) conjugated with dextran molecules are considered good therapeutic approaches. It should also be declared that scientists at Yale University (New Haven, CT) have reported successful treatment of a mouse model of SLE using nanogel technology (biodegradable nanoparticles) to deliver relatively low but effective doses of the immunosuppressant mycophenolic acid (MPA), a form of which is already used to treat SLE in humans. MPA-loaded nanogels extended mean survival time by 3 months when administered before the onset of disease and by 2 months when administered to mice that had already developed renal failure. (Look et al, 2013). GlaxoSmithKline and scientists from Singapore are conducting a PHASE IV clinical trial (NCT number: NCT04447053 for SLE patients via Belimumab Injection [Benlysta] and T cell therapy. (Sheikh et al, 2019). Although there are realizing many trials worldwide for lupus therapy, there is not yet a significant outcome since there is low minority participation leading to a lack of data.

10. Urticaria and nanotechnology

The conventional drugs sometimes are unsatisfactory due to low efficacy, increased drug resistance, short half-life, potential or harmful fatal toxic side effects, and drug incompetence to reach the site of parasite infection so, recent research is showing some satisfactory results regarding new therapeutic strategies. These strategies include a) the development of more efficient antibodies targeting IgE and IgE receptor, b) Blocking the recruitment and activation of inflammatory cells, c) Inhibiting mast cell activation by blocking signaling pathways – and neuropeptides, d) targeting complement C5a and C5a receptor and e) supplementing vitamin D. (Radonjic-Hoesli et al, 2017). Undoubtfully, if the previous ones are correlated with nano technology, the outcomes would be promising. However, there are only a few experiments and trials about them since urticaria etiopathogenesis is not fully decrypted. There are some drugs under

development that may lead to better therapeutic outcomes (Hon et al, 2019; Martina et al, 2020; Godse et al,2015). Table 19 shows some significant clinical trials for urticaria's therapy while Table 20 some patented therapeutic and diagnostic tools used.

Table 19: Recent clinical trials for Urticarias' s treatment (Clinicaltrials.gov., 2021)

Mechanism	Drug	Clinical phase	NCT number
Anti-IgE	Quilizumab	Phase II	NCT01987947
Syk (Spleen tyrosine kinase) inhibitor	GSK2646264	Phase I	NCT02424799
Anti-IL 1β antibody	Canakinumab	Phase II	NCT01635127
N/A	Vitamin D_3	Phase III	NCT02873364
Anti-IgE	UB-221	Phase I	NCT03632291
H_4R antagonist	JNJ 39758979	Phase I	NCT01068223

Table 20: Patented treating and diagnostic methods for Urticaria's treatment (Hon et al, 2019)

Mechanism	Patent number
Method for IL-3 blocking	US20150017180
Administration of dexpramipexole	US20160193186
Diagnostic test kit of the CU	US20130183248
Administration of pramipexole	US20160271112
Administration of dexpramipexole	US20180015073

11. Pemphigus and nanotechnology

It is well known that Pemphigus is one of the best-characterized human autoimmune diseases, particularly regarding the pathogenic contributions of B cell and T cell populations. Scientists are using several new techniques for inducing antigen-specific tolerance, including a) autoantigen vaccination and antigen-coupled cell tolerance to induce desmoglein specific tolerance, b) the generation of antigen-specific T regulatory cells to suppress anti-desmoglein autoimmunity, and c) the generation of chimeric autoantibody receptor T cells (CAARTs) to eliminate desmoglein-specific B cells.

Veltuzumab, a humanized anti-CD20 monoclonal antibody, has shown promise in refractory pemphigus and has received FDA orphan drug status for this indication in 2015. (Kasperkiewicz et al, 2017). In addition, since measures aimed at managing cutaneous wounds are an important aspect in patient's care, innovative dressings such as hydrogel, polymeric membrane, hydrocolloid, and nano silver wound dressings have already been created (Marashian et al, 2015; Grada et al, 2019; Khalaf, 2019). Understanding the benefits of nanotechnology, nowadays, scientists will surely create new sufficient techniques regarding Pemphigus' treatment. Table 21 shows the three most important clinical trials so far.

Table 21: Recent clinical trials for Pemphigus' s treatment (Clinicaltrials.gov., 2021)

Drug	Clinical phase	NCT number
Rituximab	Phase I	NCT02383589
PRN1008, an inhibitor of tyrosine-protein kinase BTK	Phase II	NCT02704429
VAY736 (monoclonal antibody that blocks BAAFr receptors)	Phase II	NCT01930175

12. Bullous and nanotechnology

Even though bullous diseases are well described, unfortunately, scientists have not realized any sufficient studies regarding their therapeutics via novel nanotechnological vesicles as they have realized in other skin disorders. Dupilumab, rituximab and omalizumab in combination or not, are showing great results in recent *in vivo* trials. (Lernia et al, 2020) Their combination with liposomes or dendrimers in the future may lead to promising drug delivery systems – a fact that it's only now in the imagination.

13. Acne and nanotechnology

Acne is a well described skin disorder. Scientists have discovered a lot of ways so that patients have an effective treatment. Nanotechnological carriers like liposomes, niosomes, microemulsions, microsponge, microspheres, and nanoparticles have already proved their capability to improve anti-acne therapy by improving conventional drugs' efficacy and reducing their side effects. Also, these carriers show controlled drug release

and improved drug penetration even up to pilosebaceous unit of skin. (Patel & Prabhu, 2020) The most indicative studies for novel acne's therapy are represented briefly in Table 22 while some clinical trials and patents are shown in Table 23 and 24, respectively.

Table 22: Recent studies for Acne's treatment

Nanoparticle	Drug	Outcome	Reference
Liposomal gel	azelaic acid	good localization of drug in stratum corneum and skin compatibility	Burchacka et al, 2016
Ethosomal cream	azelaic acid	superior antibacterial activity than marketed Zelface® cream	Apriani et al, 2019
Niosomes	dapsone	High entrapment efficiency	El-Nabarawi et al, 2018
PEG-PCL micelles	lauric acid	High bacterial efficacy	Tran et al, 2018
Chitosan-alginate Nanoparticles	Benzoyl Peroxide	antibacterial and anti-inflammatory properties	Friedman et al, 2013
Nano sponges	tazarotene	Penetration into deeper skin layers	Aggarwal et al, 2016
SLNs	Benzoyl Peroxide	High entrapment efficiency and slow release	Pokharkar et al, 2014
SLNs	isotretinoin	superior efficacy and better tolerance than marketed product	Raza et al, 2013

Table 23: Recent clinical trials for Acne' s treatment (Clinicaltrials.gov., 2021; Patel & Prabhu, 2020)

Delivery system	Drug	Clinical phase	NCT number
Topical cream	JNJ 10229570-AAA	Phase II	NCT01326780
Red and blue light mask	Benzoyl Peroxide	Phase I	NCT02698436
Gold photothermal therapy	N/A	Phase I	N/A
Chitosan/TPP NPs	N/A	Phase I	N/A
Nano emulsion gel	clindamycin	Phase II	N/A

Table 24: Patented nano formulations for Acne's treatment (Akhtar et al, 2017)

Delivery system	Drug	Patent number
Topical stable gel formulation	N/A	*US25509494A*
Oil in water nanoemulsion	Non-ionic amphiphilic lipids	US5753241 A
Topical application	Cetirizine and loratadine	*US20030129209A1*
N/A	Emu-oil	*WO2001013956A2*
Liposomes	Phosphatidylcholine/nitric oxide	*US20140079761 A1*
Microspheres	Isotretinoin	*US20140271875 A1*
Lipid NPs	N/A	WO 2011116963 A2

14. DISCUSSION

Along with the advances in drug development, nanotechnology is gaining great attention in the therapeutic field nowadays. Drug delivery is by far the most important therapeutic intervention. Most drugs available nowadays are limited by their poor solubility, number of side effects, frequent dosing, and nonspecific delivery. Therefore, scientists are shifting their research to use nanoparticles for the delivery of drugs to avoid those limitations. Nanoparticles represent a new generation of drug delivery systems that can be engineered to harness optimal target selectivity for specific cells and tissues and high drug loading capacity, allowing improved pharmacokinetics and enhanced bioavailability of therapeutics.

Psoriasis, atopic dermatitis, vitiligo, lupus, urticaria, pemphigus, and bullous represent the most important autoimmune skin diseases. Acne is another skin dermatological category equally significant. Searching the relative scientific literature, someone can easily understand that despite the nanotechnological development, there is still limited data available for the therapy of most of these diseases. Psoriatic, dermatitis, and acne conditions hold the highest position in the therapeutic field due to their high incidence in the general population.

Liposomes, niosomes, tranfersomes, ethosomes, SLNs, NLCs, polymers, micelles, dendrimers, QDots, metal nanoparticles as well as nanosponges, and nanofibers play an important role in skin drug delivery due to their special characteristics. Not all of them have been studied for each skin disease though. Depending on the skin condition there is an optimal nanoparticle that facilitates its therapeutics. Correlating all the mentioned knowledge, the above conclusions could be drawn:

- Combination therapies (the use of corticosteroids along with non-corticosteroids with PUVA therapy) play an important role in the treatment of psoriasis. Liposomal and polymeric formulations are the most sufficient drug vesicles so perhaps hybrid nanosystems could be a potential therapeutic candidate later.
- Lipid-based nanoparticles have great potentials for the novel therapy of atopic dermatitis. Their combination with tacrolimus may also be beneficial for patients who suffer severely.

- Vitiligo's nanoformulations also have been broadly explored so far. Liposomal drug vesicles in topical forms could potentially facilitate patients' life as it is already shown from various studies.
- The modulation of T-cells along with nanoparticles like lipid-based ones may lead to an amelioration of the therapeutic index of lupus. Also, rituximab combined with dendrimers may be a future perspective as some steps in this direction have already been done.
- Vitamin D analogs can be used therapeutically in urticaria's management as many research groups have already indicated their potentials.
- Nano silver wound dressings may be the most appropriate therapeutic candidate for pemphigus's management so far. Polymeric fiber mats may act also as potential drug delivery systems.
- The bullous pemphigoid nanotechnological therapeutic approach is still new in the research of nanomedicine.
- Acne is a well-described skin disease. From all the research been done, polymers combined with severe corticosteroids are the most suitable drug delivery systems for the future.

In any case, there is still a lot to be studied and patented so that nanotechnological approaches can have a therapeutic impact on each patient in their everyday life.

15. CONCLUSION

In this work, there was an attempt at the overall presentation of nanotechnology therapeutic contribution in the most important skin diseases. Also, the advantages of nanotechnology in dermatology and the different kinds of skin NPs available were presented.

Autoimmune skin diseases (AD) are a significant category of dermatological illnesses affecting a large part of the world population. Conventional AD treatments like corticosteroids do not fulfill the expectations of both patients and physicians and there is an unmet need for a new kind of therapies that will increase drug delivery to the specific tissues. Nanotechnology may be the key for this as it is proving continually to be an encouraging strategy in the healthcare system and the medical field. Nanocarriers hold great promise to improve the therapy of all skin autoimmune diseases. Their ultra-fine size and easy modulation facilitating their ability to pass through metabolic barriers and target deliver drugs to the required sites without affecting healthy cells and tissues highlights their utility for AD treatments. So, nanocarriers as drug delivery systems designed to improve the pharmacological and therapeutic properties of conventional drugs, could play an important role in nano-dermatology applications. Unfortunately, up to now, very few nanocarrier based formulations are available in market for topical use. Most of the mentioned nano formulations related to the therapy of skin disorders are only in experimental stage with promising results.

So, both autoimmune skin disorders and acne can eventually be better controlled, managed, and even cured considering the significant progress that has been made and the ongoing development of new insightful nanotechnological strategies to tackle this situation. However, even though the small size of nanomaterials allows them to penetrate deeper areas of biological systems that are inaccessible to larger particles, they should not be forgotten for their toxicity, tissue deposition, and long-term oncological potentials. Their therapeutic application, especially the effect on the immune system, requires further caution and detailed investigation. Therefore, future nano-drug delivery studies are recommended, focusing on toxicity, route of administration, physicochemical properties, and composition of NPs. Finding the correlation between what makes a nanoparticle beneficial in one model and toxic in another model is critical. This will aid

drug delivery formulation scientists in choosing appropriate nanoparticle carriers and enhance the rapidly growing field of nanotechnology.

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