Journal of Integrated Pharmaceutical Sciences (JIPS)
www.journals.bmusurat.ac.in
ISSN: 0000-0000

Review Article

Nanopharmaceuticals For Psoriasis

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ABSTRACT

Psoriasis is a chronic disease with erythematous scaly patches, which typically affects the open surfaces of the body and scalp. Various factors like bacterial infection, genetic and environmental factors, and immune disorders play a major role in causing psoriasis. Various types of psoriasis can be observed, such as guttate psoriasis, inverse psoriasis, pustular psoriasis, and psoriatic arthritis. Various ancient approaches have been used to control the disorder, but have failed to achieve a complete reduction of the disease, besides causing toxic effects. Therefore, our main aim in this review article is to introduce the different advanced nanotechnological approaches for effective treatment of psoriasis.

Key Words*: *Drug delivery, Nanostructured Lipid Carriers, Ethosomes, Liposomes, Psoriasis

Received Date: 11-19-2020 Revised Date: 12-12-2020 Acceptance Date:30-12-2020

INTRODUCTION

Psoriasis common immune modulated inflammatory disease affecting nearly 15 million people in approximately 2.5% of the population, both males and females are equally affected. Psoriasis is an autoimmune T-cell mediated disease of the skin accompanied by constrained, red, thickened plaques with an overlying silver-white scale and relapsing episodes of inflammation and hyperkeratosis. (dubet 2017) Psoriasis tends to have onset at two peak times during life: 1) between the ages of 20-30 or 2) between 50-60 years old, with 80% of patients having onset before 45 years of age[2].

It is an autoimmune disorder caused by the inflammation of skin cells which can multiple up to 10 times faster than the normal skin cells. Although the primary causes of psoriasis are not clearly identified so it is believed as a disorder of keratinocytes[2,3,4].

Psoriasis results from a complex interplay between genetic and environmental factors influences. When patients with genetic pre-dispositions encounter a precipitating factor, there is the potential for an outbreak of psoriasis. Some of the common precipitating and environmental factors are injury to the skin, infections, drugs (beta blockers, nonsteroidal anti-inflammatory drugs, lithium, and antimalarials), smoking, alcohol consumption, obesity, and psychological stress. Psoriasis vulgaris is the most common form of the disease affecting 85–90 % of the patients and is also known as plaque psoriasis (raut 2018). The present article gives an overview on various targeted nanomedicines for effective treatment of psoriasis. Pathophysiology involved in psoriasis, available therapies, and their challenges are also covered[7].

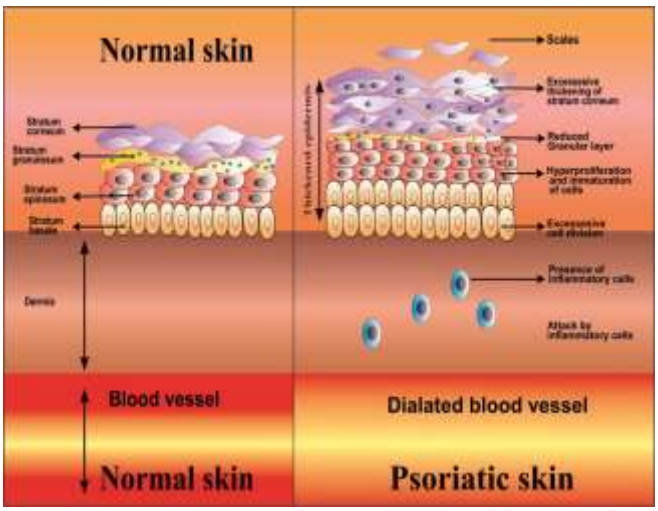

Figure 1. Comparison between Normal skin and Psoriatic skin

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Table 1. Types of psoriasis

Types of psoriasis	Signs & symptoms	Causes
Plaque psoriasis: The most prevalent form of the disease. About 70–85% of those who have psoriasis have this type. It is typically develop on the elbows, knees, scalp, and lower back.	The plaques are pinkish-red, round, and covered with white silvery scales. The plaques tingling or may be painful	Rubbing of skin, infection, medicines, alcohol, mental stress, smoking, and sunlight.
Flexural psoriasis: It is also known as inverse psoriasis. Inverse psoriasis is found in the armpits, groin, under the breasts, and in other skin folds around the genitals and the buttocks. About 20% of those who have psoriasis have this type.	Bright red scrapes those are smooth and shiny. Irritation from rubbing and sweating.	Yeast overgrowth, high sensitivity to friction or sweating.
Guttate psoriasis: Guttate psoriasis is usually triggered by a bacterial/viral infection such as strep throat. This form of psoriasis that often begins in childhood or young adulthood. It often comes on quite suddenly.	Itching on skin. The spots may be covered with silvery, flaky skin called scales. It is marked by small water-drop-shaped sores on the trunk, arms, legs and scalp.	Streptococcal infection, bacterial or viral infections, injury to skin, e.g., cuts, burns, and insect bites, medicines, Mental stress, sunburn, and alcohol consumption.
Nail psoriasis: Psoriasis can affect finger-nails and toe-nails, causing pitting, abnormal nail growth, and discoloration.	Change in nail color, little pits in nails, lines across the nails, white area on nail plate, thickening of skin under nails, loosening of nails.	Combination of genetic, environmental, and immune causes
Psoriatic arthritis: Psoriatic arthritis (PSA) is an inflammatory condition that affects the joints of children and adults with psoriasis.	Red, swollen, tender, warm, and stiff joints, stroke, arthrosclerosis, myocardial infarction.	Trauma or injury on skin, like cuts or burns, medicines, alcohol, skin irritants, smoking
Erythrodermic psoriasis: It is a particularly inflammatory form of psoriasis that affects most of the body surface. It is characterized by periodic, predominant, fiery redness of the skin and the superfluous of scales in sheets, rather than smaller flakes.	Increase in Heart rate, fluctuating body temperature, reddening and superfluous of the skin	Use of steroid, sun burn, emotional stress, alcoholism, infections, allergy
Pustular psoriasis: This type of psoriasis can form in widespread patches or in smaller areas on the hands, fingertips or feet.	Reddening of the skin, followed by formation of pustules and scaling. Severe irritation or light sensitivity.	Over-exposure to UV light, pregnancy, steroids, infections, mental stress, and sudden withdrawal of systemic medications or potent topical steroids

1.1 Types of psoriasis

On the basis of causes, signs and symptoms, and characteristics, psoriasis is classified into 7 major categories. Each type of psoriasis will appear in response to a trigger. Typically, an individual has only one type of psoriasis at a time, and the signs and symptoms, which are typically identified by their hallmark appearance (Table I), vary from person to person[8].

2. PATHOPHYSIOLOGY AND PHARMACOTHERAPY FOR PSORIASIS

Activation of T lymphocyte is a principle pathway involved in pathogenesis of psoriasis. Epidermis and dermis are populated with antigen-presenting cells which can pick up the antigen and present it on their cellular surface in the context of major histocompatibility complex (MHC) molecules.[16,17]

Antigen is ultimately transported to lymph nodes and binding with T lymphocyte receptors and produces T cell activation and further formation of synapses such as cluster differentiation 2 (CD2) and lymphocyte functional antigen (LFA-3), 18,19etc. Thus, an activated T cell rapidly enters into systemic circulation and further migrates to various skin layers, which ultimately produces various cytokines and chemokines.[20] This process is responsible for hyperkeratosis and neovascularization in psoriasis.[21] Dendritic cells (DCs) and macrophages are associated with CD4 and CD8 T-cells, which are profound in psoriatic lesions.[22,23] They are responsible for cytokines production such as IL-12, IL-23, and TNF- a and b. These cytokines regulate the production of T helper (Th1) and Th17/Th22 cells, which further leads to production of IL-4, IL-13, IL-5 IL-17A, and IL- 23R. Among all, IL-17A and IL-23R were reported as leading biomarkers for keratinocyte hyper-proliferation in psoriasis.[24,25] Moreover, there are many predisposing factors in the pathogenesis of psoriasis which include eicosanoid metabolism, lymphokine secretion, and free radical generation. Current pharmacotherapy for psoriasis includes vitamin D analogs, corticosteroids, coal tar, retinoids, tacrolimus, babchi oil, and 8-methoxypsoralen with UVA radiation (PUVA), which is delivered either topically or through the systemic route. Topical therapies gained wider popularity in psoriasis treatment, but they suffer from limited absorption of drugs through skin, limiting their therapeutic effectiveness. But these have numerous limitations such as immunosuppression suboptimal therapeutic effects, poor patient compliance, and significant toxicity. Other than these therapies, biological agents have been employed in psoriasis treatment. Biological agents are proteins which are obtained from microorganisms and exhibit fewer side effects. However, they are not common in clinical practice due to their immunosuppressive effects, high cost, and availability in only injection form which leads to poor patient compliance.[26,27]

2.1 Challenges in the treatment of psoriasis psychosocial aspect

Chronic nature of psoriasis spectacularly deteriorates the quality of life of psoriasis patient as they experience great psychological, financial and also social burdens. That's why before the initiation of any psoriasis treatment, addressing patients: psychosocial needs is a great challenge. Psoriasis patients apparently experience 1.5 times more depression than those lacking the disease[28]. Evidence suggests that clinical outcome especially adherence concern could be optimized if the patients emotional needs are dealt wisely. Furthermore, the execution of depression screening into medical practice might facilitate the detection and management of the disease[29].

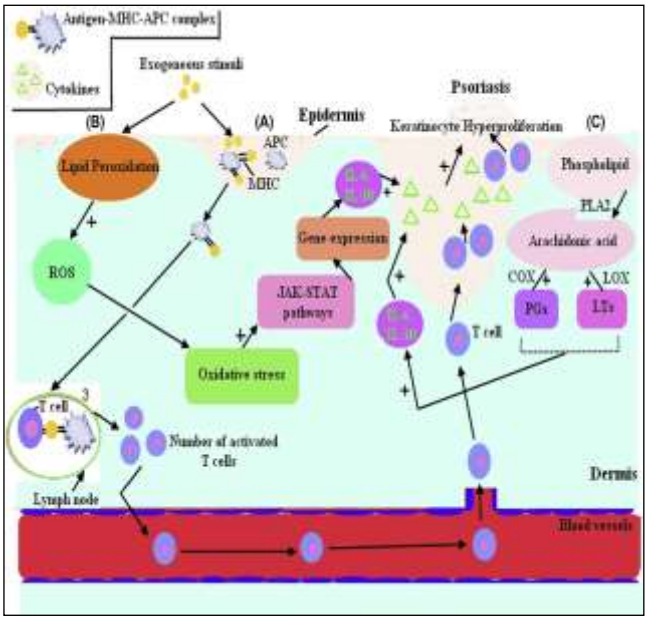

Figure 2. Pathophysiology of Psoriasis

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2.2 Therapeutic aspect

At presently, many therapeutic options are available for psoriasis treatment, but getting a innocuous and effectual therapy is still a significant challenge. Topical therapy remains a widely employed option for this, and about 80% of the psoriasis population depends on topical therapy[28,29]. However, topical therapy using conventional formulation possesses its limitation of poor drug penetration and absorption due to barrier properties of skin. This barrier results in slow penetration rates and restricted uptake of therapeutic moiety. Moreover, in psoriasis, skin becomes very tough and rigid owing to epidermal hyperplasia, hyperkeratosis and lack of common moisturizing elements like water. All these phenotypic changes over skin also limit sufficient drug penetration across the psoriatic skin. Thus, the therapeutic effectiveness of conventional topical therapy remains a considerable issue. Although phototherapy, which remains the following treatment choice after topical therapy, is useful it possesses many disadvantages which add to underutilization of phototherapy[29]. In a broad sense, underutilization is a consequence of numerous factors mainly patient and physician. From the patient's standpoint, phototherapy is time usually taking 3–5 sessions per week, and it is expensive too. Also, patients fret regarding the destructive toxicities linked phototherapies such as photoaging, sunburn, and erythema. From the physician's point of view, phototherapy unit is expensive to set up due to high equipment, space, and maintenance costs with the additional need of skilled and qualified phototherapy personnel. Furthermore, as per the report of the National Psoriasis Foundation (NPF), only 1/3 patient of psoriasis participates in phototherapy. As far as the systemic therapy is concerned, it is convenient to receive, but the use of systemic agents is restricted due to adverse effects associated with systemic anti-psoriatic agents. Systemic agents display common ill effects including renal toxicity, hypertension, hepatotoxicity, skin cancer, hyperlipidemia, etc. therefore challenges are numerous which must be addressed to attain a better therapeutic effect for the treatment of psoriasis.[28,29,30]

3. TREATMENT APPROACHES FOR PSORIASIS

Numerous ancient approaches have been used for initial stage or mild psoriasis; typically, topical approaches are used for mild disease, phototherapy for moderate disease, and systemic agents for severe disease. Complete reduction of psoriasis is not achieved by using the above approaches, therefore various nanotechnological approaches are mainly considered by the research scientists to achieve complete eradication of the disease worldwide.[31,32]

Topical therapy, phototherapy, and systemic therapy are the existing therapeutic alternative for psoriasis. In order choose active therapy patients are needed to divide into mild-to-moderate and moderate-to-severe disease categories.[33] Moderate-to-severe psoriasis is usually defined as the participation of more than 5–10 percent of the body surface area (the entire surface of the palm, together with fingers of one hand constitutes about 1 percent of the body surface area) or engagement of the palm, sole or face. However, patients having involvement of less than 5 percent body surface area fall under the category of mild to moderate psoriasis. For the management of limited or mild-to-moderate psoriasis, topical agents are considered, while for moderate-to-severe disease phototherapy or systemic therapy is taken into account. Nevertheless, patients on systemic therapy would also need to keep on some topical agent.[34]

3.1 Ancient approaches

Various ancient approaches such as acupuncture (inserting needles at various depths at meridians), ayurveda, manipulation (massage), herbal treatment (garlic, jasmine, guggul, neem, turmeric, bogbean, Guaiacum), environmental or atmospheric treatment (sunlight), use of dietary supplements (vitamins, minerals), meditation, moisturizing treatments (aloe vera, neem oil, emu

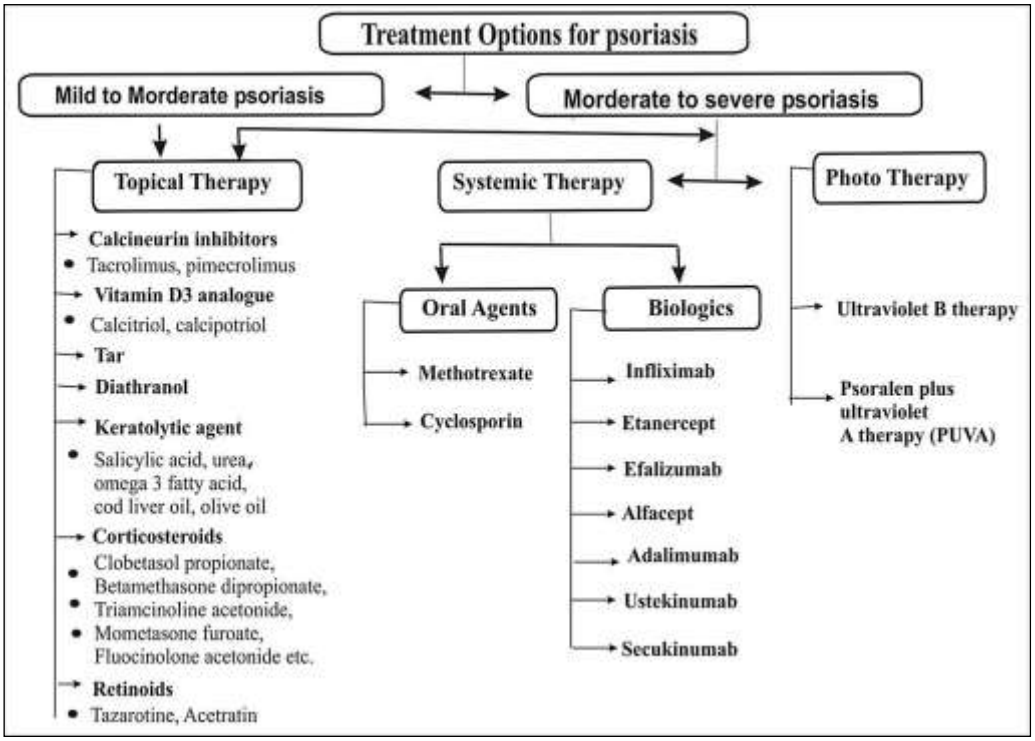

Figure 3. Treatment options for psoriasis

oil), water therapy, and other therapy (exercise, swimming) were used to control the various stages of psoriasis. The major limitations of these approaches are that they can be used only for mild disease. The other limitations are that they could causes allergic reactions, irritation, or darkening of skin, stain clothing, increase chances of infections as well as scarring, show limited efficacy and high toxicity, such as renal toxicity, and require patient monitoring. Miroddi et al. (2015) conducted a systematic review of clinical trials assessing the effectiveness and safety of aloe for the treatment of psoriasis[35]. Xiong et al. (2015) investigated the effect of glycyrrhizin (GL) on psoriasis and explored the mechanisms involved. The results showed that GL treatment significantly reduced the levels of ICAM-1 in TNF-a-stimulated HaCaT cells, inhibited subsequent monocyte adhesion to keratinocytes, and suppressed the nuclear translation and phosphorylation of p65following the degradation of inhibitor kB (IkB). GL treatment blocked the phosphorylation of extracellular signal regulated kinase (ERK)/p38 MAPK. GL effectively delayed the onset of IPI in mice and ameliorated ongoing IPI, thereby reducing ICAM-1 expression in epidermal tissues. A conclusion is that GL treatment ameliorates skin inflammation by inhibiting ICAM-1 expression via interference with the ERK/p38 MAPK and NF-kB signaling pathways in keratinocytes. Therefore, GL can be used as an anti-psoriatic drug.[36]

3.2 Topical approaches

Topical agents such as Epsom salts, moisturizers, mineral oil, and petroleum jelly may offer support by soothing inflamed or elevated skin and diminishing the dryness which accompanies the build-up of skin on psoriatic plaques. They also help to normalize skin cell production and reduce inflammation. Typically, topical approaches are mainly used for control and treatment of the mild form of the disease.[37] Various anti-psoriatic drugs such as tacrolimus, clocortolone pivalate, zinc pyrithione, methotrexate (MTX), betamethasone dipropionate, Acitretin, adalimumab, dapsone, valrubicin, etc. are successfully delivered to the target site through different dosage forms such as cream, gel, paste, lotion, ointment, and spray. The major advantages of topical approaches are that they are safe, effective, cause minimum inflammation, reduce skin turnover, remove built-up scale, and can be applied directly to the target site. However, they suffer from various limitations such as having a greasy feel, staining clothes and bedding, having an unpleasant odor like coal tar,[38] and being time consuming. Del Rosso and Colombo et al. (2012) prepared Dovobet gel

incorporating calcipotriol and betamethasone dipropionate, and the results showed better overall adherence and treatment of patients with mild-to-moderate psoriasis.[38]

3.3 Systemic approaches

Systemic approaches are mainly used in severe conditions or when the psoriasis is resistant to topical treatment. The three main traditional systemic treatments are the use of MTX, cyclosporine, and retinoids. The main mechanisms of systemic approaches are to suppress the immune system and slow the growth of skin cells.[39] Various anti-psoriatic drugs such as dithranol, ammonium glycyrrhizinate, ketoprofen, betamethasone 17-valerate, bortezomib, simvastatin, cyclosporine, retinoids, etc. are successfully administered through the systemic route to the target site. The major advantages of systemic treatment are good skin tolerability, effectiveness against various types of psoriasis, and activity in severe conditions.[40] Despite their advantages, they suffer from some limitations such as causing nausea or fatigue, abdominal pain, diarrhea and headaches, damaging the liver and blood cells, impairing kidney function, and increasing blood pressure. Hazarika (2009) developed a cyclosporine-incorporated solution and administered it to psoriatic patients by the systemic route. The result showed an excellent management of pustular psoriasis of pregnancy or psoriasis with postulation in pregnancy.[41]

3.4 Nanotechnological approaches

An ancient approach has been used for initial stage or mild psoriasis, but has not been successful in the case of moderate and severe conditions of psoriasis. Topical and systemic approaches provide effective control of various types of disease, but show number of side-effects and toxicity.[42] So various nanotechnological colloidal carriers including vesicular and particulate systems like liposomes,[43] transfersomes,[44] niosomes,[45] ethosomes,[44] solid lipid nanoparticles,[46] microspheres, micelles, dendrimers,[45,46] etc. are widely used for the prevention and control of psoriasis, because of their unique characteristics.[34] These nanotechnological approaches can be delivered by various routes such as topical, or systemic, in a single form or a combined form.[46-48]

3.5 Characteristics of nanocarriers

Nanocarriers play a critical role in drug delivery to the target site for control[43] and prevention of the disease[46]. Currently, these carriers have become the first choice to deliver anti-psoriatic drugs, due to their various characteristics such as:

- Pre-eminent biocompatibility as well as biodegradability
- Free from unfavourable inflammatory reactions
- Non-toxic and degradable in nature
- Easily eliminated from the body
- Stable at physiological and atmospheric conditions
- Stability retained for a prolonged duration of time
- Adequate porosity, pore size distribution, and interconnectivity
- Reproducible microscopic and macroscopic composition
- Provide protection of encapsulated substances from physiological and climatic conditions
- Sustained and controlled drug release to the target site
- Prevent dose dumping and associated adverse effects

3.5.1. Advantages of lipid based nanoparticles

- Large surface area due to small size allows wider and better interaction with the stratum corneum increasing the proportion of drug penetrating the skin.[42,49]
- Negligible irritation and biocompatible carriers as it incorporates physiologically tolerated, non-irritative, and non-toxic lipid.[50]
- SLN protected the drug from degradation and offers sustained and controlled-release profile avoiding drug dosing, toxicity, and dose fluctuations.[49,50]
- Biphasic drug release can be achieved. It involves initial burst of the drug present in the shell followed by sustained and prolonged release from solid core.[51]
- SLN possesses occlusive properties upon transdermal application which prohibits water loss and favors drug penetration into the skin.[52]

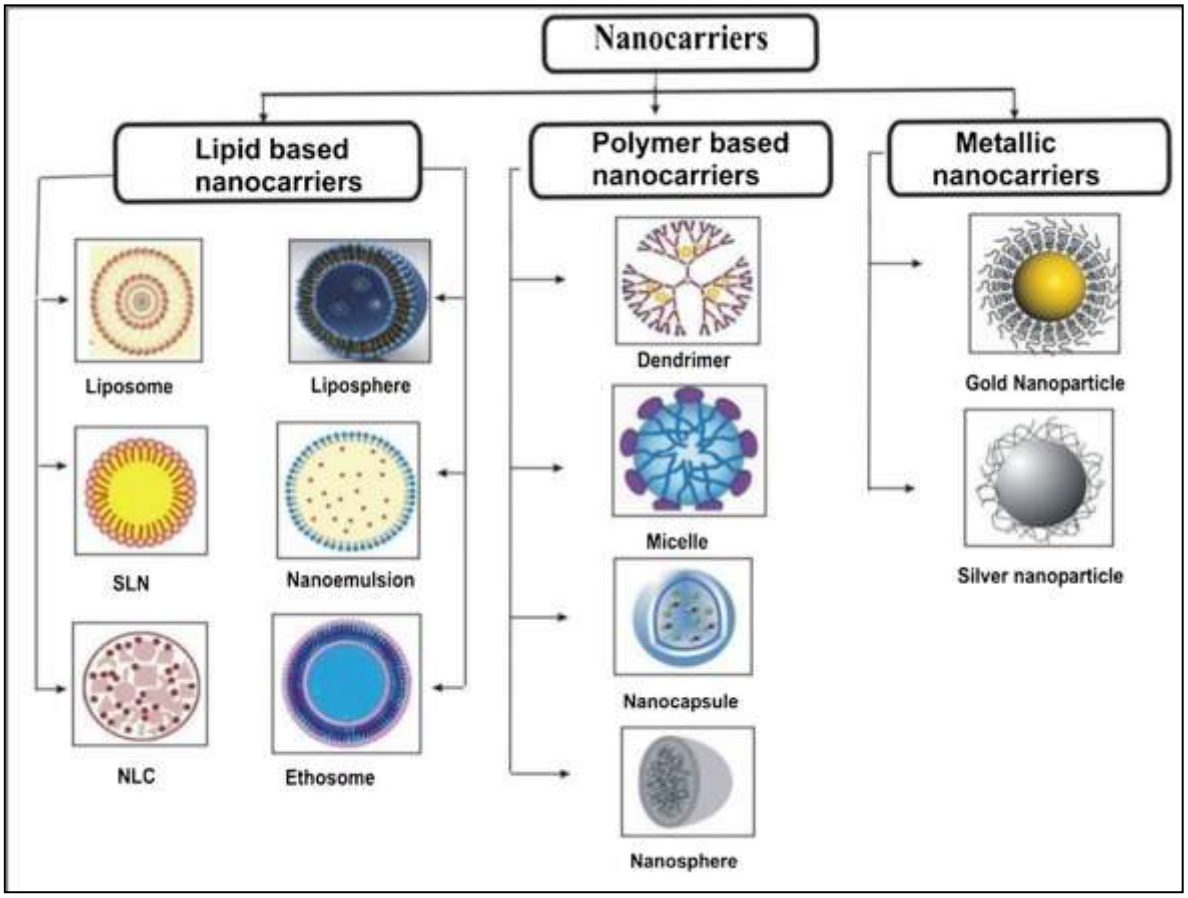

Figure 4. Nanotechnological approaches (Nanocarriers)

- Production of SLN can be carried out organic solvent free and can be easily scaled up, for example, by high-pressure homogenization[53]

3.6 Types of nanocarrier

Liposome

Liposomes are microscopic phospholipid bilayered vesicles comprising of one or more concentric lipid bilayer enclosing an aqueous chamber. Cholesterol is included for providing integrity to the bilayer by increasing microviscosity and reducing permeability of the membrane to water-soluble molecules, thereby providing rigidity to the membrane and stabilizing the vesicles.[49]

Liposomes are most preferred carriers for the transdermal formulation and are superior to conventional transdermal formulation because[49,54] (1) they are capable of carrying drugs with opposing solubilities, that is, lipophilic and hydrophilic and (2) the major structural component of liposomal carrier, phospholipid, gets easily integrated with the skin lipids and assures the desired hydration conditions to get better penetration and localization of drug in the layers of the skin.[49-53] Liposome-based formulations are used for the treatment of variety of dermatological conditions including psoriasis. Liposomal formulations have also been found to be promising for providing improved therapeutic effect and reduced side effect of the topical antipsoriatic drugs for example; liposomal encapsulation of retenoids, such as vitamin A acid or tretinoin reduced the local irritation.[54,55] Skin deposition of liposomal formulation depends on lipid composition, method of preparation, and thermodynamic state of the bilayers of liposomes.[51,53]

Liposomes offer enhanced the topical therapeutic by number of mechanisms which are: (1) intact vesicular skin penetration, (2) the penetration enhancing effect, (3) the adsorption effect, and (4) the penetration of liposomes through the transappendageal route.[56]

Mezei and Gulasekharam (1982) were first to report the concept of intact vesicular skin penetration and suggested that liposomes act as reservoir at the site of action and large size of

liposomes excludes their entry into the capillary circulation. They also reported that the liposomes composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol (CH) (1.1:0.5, molar ratio) reduced the percutaneous absorption along with the 5–6 times in raise in the concentration of triamcinolone acetonide in the epidermis and dermis as compared to standard ointment.[52]

A second possible mode of action is the penetration enhancing effect was supported by the finding that a fluorescent lipid bilayer marker showed ameliorate delivery into deep stratum corneum after skin treatment with empty vesicles which was parallel to that obtained from carriers encapsulating the marker. This suggested that upgraded delivery was not due to intact vesicular penetration, supporting a second possible mode of action, the penetration enhancing effect.[53] Liposomes have the potentiality to act as a penetration enhancer by causing loosening of the lipidic stratum corneum overcoming the barrier property of the skin with the subsequent partitioning of the drug in skin. Liposome forming lipid adheres to the surface of the skin followed by the destabilization and fusion or mixing with the lipid matrix of stratum corneum leading to penetration of liposome through skin. Therefore it is suggested that the liposomes made of lipid similar to skin lipids (like ceramides, cholesterol, free fatty acids, and cholesteryl sulfate) are more effective for dermal delivery than the phosholipid vesicles.[54] For example, skin-lipid liposomes are prepared to improve corticosteroid dermal delivery and hence, their therapeutic effectiveness, which provided highest drug disposition within the deeper skin layers, especially in the epidermis and dermis.[55] It has been found that pre-treatment of the skin with liposomes did not promote the absorption of hydrophobic/hydrophilic drugs concluding that liposomes stratum corneum interaction hypothesis was invalid. Hence, it has been suggested that liposomes must be applied concurrently with the drug or the drug must be encapsulated within them.

Solid lipid Nanoparticles (SLNs)

SLNs are submicron sized (50–1000 nm) lipid particles comprising of lipid core made from high melting lipid and coated by surfactant or co-surfactant. Physiological and nontoxic lipids are basically used for the preparation of SLNs which makes them extensively acceptable for topical drug delivery. SLNs are formed by dissolving or dispersing the hydrophobic drug into the lipid matrix or by dispersing the drug into the outer coating around the solid lipid core.

Despite of the aforementioned advantages SLN suffers from the potential limitations of low drug loading capability and discharge of drug from the matrix over the period of time during storage.[56] The reason for such behavior is the transformation of less orders arrangement of the lipid in the particle matrix to the well-ordered β-modification during the storage after production. Such ordered arrangement consists of perfect and compact crystal lattice with little space for the settlement of the drug and hence drug leaches out.

Nanostructured Lipid Carriers

NLC matrix is made up of the mixture of spatially different lipid molecules, which includes mixture of solid and liquid lipid and an aqueous phase containing a surfactant or a mixture of surfactants. Usually, the solid and liquid lipid are mixed in the ratio of 70:30 upto 99.9:0.1 and amount of surfactant included may range from 1.5% to 5% (w/v). Unstructured solid and liquid lipids matrix creates more deformity in the matrix to house larger number of drug molecules than SLN. Regardless of the presence of liquid lipid, NLC matrix is solid at room/body temperature.[57] Imperfections in NLC results in loosely arranged crystal lattice than SLN thereby increasing the drug loading capacity and minimizing drug expulsion during storage. Drug-release profile can be easily modulated by varying the lipid matrix composition.[58]

Niosomes

Niosomes (non-ionic surfactant-based liposomes) are microscopic lamellar structures obtained on hydration of non-ionic surfactant, cholesterol, and other lipids.[59] The vesicle holds hydrophilic and hydrophobic drugs within the space enclosed in the vesicle, and within the bilayer itself, respectively.[60] Based on the size of the vesicle, niosomes can be classified into three groups: (i)

small unilamellar vesicles, (SUV) (ii) multilamellar vesicles (MLV) and (iii) large unilamellar vesicles (LUV).[61] They can be used for oral, parenteral, as well as topical administration, and can enhance the oral bioavailability and the skin penetration of drugs.[62] They are biodegradable, biocompatible, non-immunogenic, and do not require any special condition for handling or storage. They provide protection from the biological environment and improve the therapeutic performance of the drug.[63] Marianecci et al. (2012) investigated the potential application of niosomes for the delivery of ammonium glycyrrhizinate (AG), useful for the treatment of various inflammatory diseases such as psoriasis. The results showed that the AG-loaded non-ionic surfactant vesicles showed no toxicity, good skin tolerability, and were able to improve the drug's anti-inflammatory activity in mice.[64] Abdelbary and AbouGhaly (2015) designed topical MTX-loaded niosomes for management of psoriasis to avoid systemic toxicity. An *in vivo* skin deposition study showed that the highest values for percentage of drug deposited (22.45%) and AUC0-10 (1.15 mg.h/cm^2) of MTX were significantly larger with the use of niosomes than those seen with the drug solution (13.87% and 0.49 mg.h/cm2, respectively). Moreover, *in vivo* histopathological studies confirmed the safety of topically applied niosomes. Summing up, the results showed that targeted MTX delivery might be achieved using topically applied niosomes for enhanced treatment of psoriasis.[65]

Transferosomes

Transferosomes are highly elastic lipid vesicles capable of penetrating intact skin and are used for non-invasive or needle-free delivery of therapeutic agent. The conventional liposomes rarely provide transdermal effect and mainly elicit localizing effects while transferosomes are several orders of magnitudes more elastic than the standard liposomes capable of carrying therapeutic effect to the deeper layer of skin. These are self-aggregate vesicles having great flexiblilty and deformability, which permits them to overcome the mechanical barrier generated by the stratum corneum when applied to nonocclusive skin. Transferosomes are metastable vesicles, which makes them capable of permeating intact skin by squeezing through the intracellular sealing lipid or the pores present in the stratum corneum. They squeeze through the skin by the process of diffusion by following the natural water gradient across the epidermis thereby minimizing the possibility of vesicle rupture in the skin. They are capable of shrinking to one-tenth of the original size and therefore, vesicles upto the size of 200–300 nm can penetrate easily.[66] They are composed of phospholipids (soya phosphatidylcholine, egg phosphatidylcholine, dipalmityl phosphatidylcholine, etc.) as the main component and 10%–25% single chain surfactant as an edge activator (sodium cholate, tween 80, span-80), alcohol as solvent (3%–10%), and saline phosphate buffer (pH 6.5–7).[67]

Ethosomes

Ethosomes are recently developed non-invasive novel colloidal carriers for topical application and accredit drugs to reach the deep skin layers and/or the systemic circulation. They are made of phospholipids, ethanol, and water. Main constituent of ethosome which renders easy availability to the skin is presence of high concentration of ethanol which creates disturbances of the lipid present in skin making pathway for penetration of vesicles into the skin.[68] Although the exact process of drug delivery by ethosomes remains a matter of speculation,[69] most likely, a combination of processes contributes to the enhancing effect. However, previous studies[69] that compared permeation enhancement of drugs from ethosomal systems versus hydroethanolic solutions showed that permeation enhancement from ethosomes was much greater than would be expected from ethanol alone. A synergistic mechanism was suggested between ethanol, vesicles, and skin lipids. The drug absorption probably occurs in following two phases ethanol effect and ethosomes effect. The mechanism of its penetration enhancing effect is well known and is dependent on the following effects.[68,69]

Effects of ethanol: Ethanol may provide the vesicles with soft flexible characteristics, which allow them to more easily penetrate into deeper layers of the skin. Ethanol acts as a penetration enhancer through the skin, penetrates into

intercellular lipids, and decreases the density of lipid multilayer of cell membrane.[70]

Ethosome effects: Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. So, the ethosomes permeates very easily inside the deep skin layers, where it gets fused with skin lipids and releases the drugs into deep layer of skin.[71] It was also proposed that phospholipid vesicles with ethanol may penetrate into the skin and influence the bilayer structure of the stratum corneum and this may lead to enhancement of drug penetration.[70,71]

Lipospheres

Lipospheres are lipid-based nanoparticulate carrier constituted from stabilization of an aquaphobic solid lipid core by coating phospholipid molecules (coat lipid) on their surface. Lipospheres present numerous advantages over other lipid-based systems regarding economic reagents, stability concern, and increased dispersibility in aqueous media, trouble-free manufacture and sustained release rate offered by phospholipid coating as well as a carrier.[72] Lipospheres have been successfully used for an oral, intravenous and topical route for the treatment of various ailments. They have also been used effectively for the treatment of psoriasis.

Nanoemulsion

Nanoemulsions are biphasic dispersion constituted from two immiscible liquids (oil and water), existing in either water in oil (W/O) droplets or oil in water (O/W) droplets.[73] These are ultrafine dispersions offering a varying degree of drug loading, visco-elasticity, and visual properties, which impart multi-functionality to nanoemulsion including drug delivery. The word nanoemulsion is sporadically used for submicron emulsion or mini-emulsion though it should not be confusing with microemulsion. Nanoemulsions nevertheless of possessing the same range of droplet size like microemulsions diverge immensely in structural characteristics and prolonged thermodynamic stability.[74] Nanoemulsion offers high solubilization capability than simple micellar formulation and superior kinetic than coarse emulsions. Their small droplet size offers extended physical stability and avoids traditional instability causing events like creaming, coalescence, and sedimentation.[75] Nanoemulsions have been productively employed in drug delivery for microbial infections, wound healing, glaucoma, fungal infection and oxidative stress. They have also attained a unique position in the field of anti-psoriatic drug delivery.[76,77]

Polymer based nanocarriers

Polymers have been investigated over decades as a chief formulation constituent in drug delivery systems for delivery of various therapeutic constituents such as synthetic drugs, herbal drugs, vitamins, peptides, etc. Polymer-based nanocarriers are usually fabricated from environmental friendly polymers falling in size range of usually 10–1000 nm, where the therapeutic constituent might be captured or bound to the matrix of nanocarrier.[78,79] Polymer-based nano-formulations have been emerged as an excellent delivery vehicles due to ease of preparation, target specific delivery, and safety concern. Furthermore, they are structurally stable and capable of preserving their structure for a longer duration, when applied topically owing to their tough matrix. Most frequently used polymer-based nanocarriers for dermatological application are a polymeric micelle, nanoemulsions, dendrimers, nanospheres, and nanocapsules. Nano-formulations have been successfully employed for the treatment of various disorders such as cancer, diabetes, neurodegenerative diseases, skin diseases, microbial infections, cardiovascular diseases, ocular therapy, etc. They have also achieved great success in clinical trials.[35] Recent advances and applications of various nanoformulations anti-psoriatic drug delivery have been discussed in the following section of the review.

Polymeric micelle

These are self-assembled nanocarriers (5–100 nm) constituted from amphiphiles, above the critical micelle concentration (CMC) giving a specific structure 'core-corona'. Micelles create a shielded slot for aquaphobic drugs in the core, which is subsequently surrounded by an aquaphilic margin constituting rigid guard. This

formation of a rigid guard protects the therapeutic moiety from opsonization thereby providing long circulation life. Micelles offer many advantages such as increased bioavailability, high drug loading, low degradation of drugs and decreased side effects. Recently polymeric micelles have also been used for delivery of the therapeutic gene for the cure of psoriasis.[80,81]

Polymeric nanosphere

Nanospheres are constituted by entrapment or homogeneous dispersion of the drug in the polymer matrix. Polymers employed could be biodegradable as well as non-biodegradable in nature. Nanospheres offer enhanced solubility, increased chemical and physical protection of therapeutic moiety, improved drug absorption and controlled/ sustain drug release. Nanospheres (tyrospheres) have been successfully employed for drug delivery to the skin.[82] In this context Batheja et al., developed lipophilic drug loaded tyrosine-derived nanospheres for topical application. They further loaded developed nanospheres in a gel formulation and evaluated its permeation potential. Permeation studies using human cadaver skin exhibited enhanced drug permeation from tyrosphere as compared to aqueous nanosphere formulation. Conclusively, they reported tyrosphere to be a promising delivery cargo for lipophilic drugs used in the treatment of acne, psoriasis and other dermatological disorders. Furthermore, tyrosphere has recently been applied for topical delivery of Vitamin D3, very widely used the drug for the treatment of psoriasis.[83]

Nanocapsules

Nanocapsules are capsular nanostructures, where the drug is restricted to a cavity (core) enclosed by an exclusive protective polymer matrix (shell). They have acquired huge attention because of their excellent skin permeation potential and capability to direct the rate of drug release across skin. However, these features can be adjusted through alteration of compositions of formulations. Additionally, polymeric nanocapsules protect the residing active constituent from degradation by acting as a guard. Watery suspensions of polymer-based nanocapsules could be applied as intermediary products for semisolid preparations or even used directly over the skin in the form of hydrogels and emulgels. Polymeric nanocapsules are a precious tool for dermal applications.[84]

Dendrimers

Dendrimers are multivalent, monodisperse, typically spherical macromolecules having a regular and hyperbranched organization. They own a distinct three-dimensional architecture with unique physicochemical features such as high reactivity, good solubility and biocompatibility. Furthermore, they can carry an active drug constituent in an encapsulated or covalently conjugated form, which shields the drug from biological and chemical degradation. Thus, it assists to conquer a variety of resistance mechanisms and facilitate the liberation of the activated form of active constituent.[85] These features make them an efficient nanocarrier for therapeutic application. Dendrimers have established tremendous applications in the field of drug delivery as they offer numerous advantages such as increased solubilization, controlled drug release and formation of drugpolymer conjugates (pro-drugs). Most notably, the highly dense surface functionalities make it available for targeted cell-specific interactions. Furthermore, viscosity generation property of dendrimer solution permits direct and smooth application of very concentrated dendrimer formulations over skin. Therefore dendrimers have been successfully used for delivery of antiviral, nonsteroidal anti-inflammatory, antihypertensive, anticancer and antipsoriatic drugs.[86]

Metallic nanocarriers

Metallic nanocarriers have been extensively evaluated as suitable cargoes for biomedical applications. They have attained an exceptional position in the field of diagnosis, and drug delivery is owing to their inimitable properties such as small size, very high surface area, capability for surface modification and high reactivity towards living cells. Typical used metallic nanoparticles for biomedical applications are gold, silicon and silver nanoparticles.

Gold nanoparticles

Gold nanoparticles (AuNPs) falling in the particle size range of 1–100 nm are broadly employed for gene and drug delivery because they are inert, low toxic and offer excellent control on their size. Also, versatility is presented by surface functionalization, which is compulsory to target specific disease and permit nanoparticles to selectively interrelate with cells.[87] Functionalization of AuNPs with various compounds such as PEG, RNA, DNA peptides, lipids, antibodies and small drug molecules is frequently done to achieve targeted action as functionalized AuNPs increases the binding and interactions of nanoparticles with biological molecules and cells. Furthermore, their photophysical property could turn on drug release in the distant region. Surface modified AuNPs have been extensively used for diagnosis and therapy of cancer; however, they have recently been employed for the therapy of psoriasis.[88]

Silver nanoparticles

Silver nanoparticles (AgNPs) are amongst most imperative and attractive metallic nanoparticles, which are concerned with biomedical applications. AgNPs are very widely used in the field of nanomedicine especially for the diagnosis and therapy of cancer. Nevertheless, the potential of AgNPs for delivery of antimicrobial, antibacterial, antifungal and anti-material agents have also been explored. Also, AgNPs have been productively employed as a delivery carrier for the successful deliverance of antipsoriatic drugs.[89,90,91]

4. FUTURE PROSPECT

Psoriasis presents a progressively emerging clinical problem in the human population worldwide. The available treatment strategies based on conventional formulations are non-specific and associated with considerable systemic toxicity. Novel drug delivery approach, using nano-formulation could provide an inimitable prospect for the development of highly competent and low toxic treatment modalities. Furthermore, nano-formulations hold easy entry into the skin and offer deeper penetration to the skin. These nanocarriers are also used for targeted drug delivery with the improved benefit-risk ratio. However, the clinical significance of nanocarrier-based formulation in the treatment of psoriasis remains in its early stage as compared to other targeted nano-formulation delivery methods. Through an advanced understanding of the pathophysiology of psoriasis, new strategies could be expanded to by developing novel economic, biological agents with high therapeutic value. In future, apart from drug delivery, nano-formulations could also be exploited for delivery of a therapeutic gene to achieve more successful and targeted therapy. Also, applicability of metallic nanocarriers for anti-psoriatic drug delivery is needed to be explored.

Patents are a crucial parameter to justify the ultimate success of any research. Thus huge attention and effort are required to get patented any method or product, to establish a great success in the field of nanotherapeutics development for psoriasis.

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How to cite: Chauhan Velenti , Ramani Vinod, Dedania Ronak, Sailor Girish. Nanopharmaceuticals for Psoriasis. Journal of Integrated Pharmaceutical Sciences 2021;1(1):7-22.