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Nanoformulations in the treatment of psoriasis: An overview

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ABSTRACT:

Psoriasis is an inflammatory, autoimmune skin disorder that recurs frequently, affecting approximately 2–5% of the global population. No therapeutic agent is totally safe and effective to treat psoriasis without compromising patient compliance, despite the fact that there are numerous accessible for the condition. Furthermore, the medications that are now on the market focus on controlling the condition and reducing symptoms rather than offering a full cure; that is, they aim to limit the illness and lessen its signs and symptoms. Investigating innovative pharmacological moiety or delivery mechanism that could safely and efficiently manage psoriasis without compromising patient compliance is therefore a major task. Nanocarrier-based novel formulations present a promising solution to address the drawbacks of traditional formulations by reducing dosage, frequency of dosing, and dose-dependent side effects while improving efficacy. In the modern day, psoriasis can be effectively and safely be treated with nano-formulations and we can get the promising results. Due to the nanosized molecules' bioavailability, these innovative drug delivery methods enable the targeted region to be smoothly reached by the weakly soluble active medicinal components.This study mainly focuses on the latest advancements in anti-psoriatic drug compositions that are lipid-based, polymer-based, and metallic, as well as the effects and tactics of traditional therapy.The feasibility of several nanocarrier systems, including liposomes, transferosomes, ethosomes, nanostructured lipid carriers, nanoemulsion, solid lipid nanoparticles, nanocapsules, micelles, dendrimers, gold, and silver nanoparticles, has been thoroughly discussed. In summary, nano-formulations are still recognized as a potentially effective therapy option for psoriasis.

Keywords: Nanoformulations, pathogenesis, psoriasis,

I. INTRODUCTION

About 0.5-0.1% of children and 2-3% of adults are known to suffer with psoriasis, a recurring, chronic, autoimmune inflammatory condition. Another feature of psoriasis is constant skin irritation that results in erythematous, scaling, and confined plaques [1]. In addition to worsening the skin, psoriasis is linked to comorbid conditions such diabetes, hyperlipidemia, asthma, ischemic heart disease, psoriatic arthritis, peptic ulcer, hepatitis B or C, endocrine disorders, metabolic disorders, and cardiovascular diseases [2]. Psoriasis patients experience physical stigmatization, which exacerbates psychological problems in their emotional, social, and professional lives. The main therapeutic options topical therapy, phototherapy, and systemic therapy are available for the treatment of psoriasis. Topical therapy is typically advised as the first line of treatment for minor diseases. On the other hand, systemic therapy or phototherapy is recommended for a severe problem [3]. Even while there are numerous ways to treat psoriasis today, none of them are effective enough to fully eradicate the condition. Conventional formulations for topical treatments have a number of drawbacks, including poor patient compliance, increased frequency of dosages, restricted drug penetration, and severe effects [4]. Additionally, a number of adverse effects, such as skin cancer, liver toxicity, renal toxicity, and high blood pressure, are manifested by phototherapy and systemic medications. The use of currently available conventional therapies for psoriasis is restricted by all these problems.

1.1 Pathogenesis of psoriasis

Psoriasis is a severe autoimmune cellular T-mediated dermatitis that is characterized by dominant Th1 and Th17 cells, aberrant epithelial stratification, and epithelial hypertrophy [5]. Rather than being a skin condition, it is suggested to be a clinical syndrome [6]. Psoriasis is generally considered to be an autoimmune illness in which

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several T cells and lymphocytes are important players. Psoriasis results in skin problems and HaCaT hyperproliferation by activating pathogenic T lymphocytes and innate immune cells. B cells' significance in the development has typically gone unnoticed. Although T cell activation is a crucial factor in the development of psoriasis, it is not a comprehensive explanation of all the disease's features. PSO is the end product of a complex series of events that include several mediators and the biological participation of various cells, including keratinocytes, neutrophils, macrophages, and B cells [7]. Platelet interactions with lymphocytes have been observed in experimental animals with psoriasis and are typical in many other inflammatory diseases. There is no known role for platelets in the lesions of psoriasis patients [8]. However, a notable correlation between platelet and monocyte aggregation in blood circulation and skin illnesses supports the systemic inflammatory component of psoriasis. The modulation of pro-inflammatory cytokines, such as tumor necrosis factor (TNF-1), interleukin-1 (IL-1), and class I interferons (IFN), is linked to psoriasis lesions. [9]. The forms and degrees of severity of the various forms of psoriasis vary. The most prevalent kind of psoriasis is known as plaque psoriasis, or common psoriasis.

Lesions that are red and elevated are its hallmark; each person will have a different lession's length and size. Although it can affect any part of the body, the scalp, lumbar region, elbows, and knees tend to be the most affected skin areas. Approximately 85–90% of instances of psoriasis are caused by it.[11] Guttate psoriasis is a less common kind of psoriasis that manifests abruptly and primarily affects children and adolescents. The tiny (2–10 mm) psoriatic lesions have a drop-like appearance. They can progress to more chronic plaque psoriasis, however they often have a centripetal distribution.[12] is frequently linked to a streptococcal infection. Reddish, shining, and well-defined psoriatic lesions, primarily on the skin folds such as the armpits, groin, and infra-mammary region, are the hallmarks of inverse psoriasis.[11] All body parts are affected by erythrodermic psoriasis, which can develop when plaque psoriasis advances or as an indication of unstable psoriasis brought on by an infection, other medications, or stopping the use of corticosteroids.[9] Pustules, or pus-filled bubbles, are the outward sign of pustular psoriasis. The most common type is called palmoplantar pustulosis; it is characterized by yellow pustules that eventually turn brownish, and the palms and soles of the hands are the most commonly affected areas.[13]

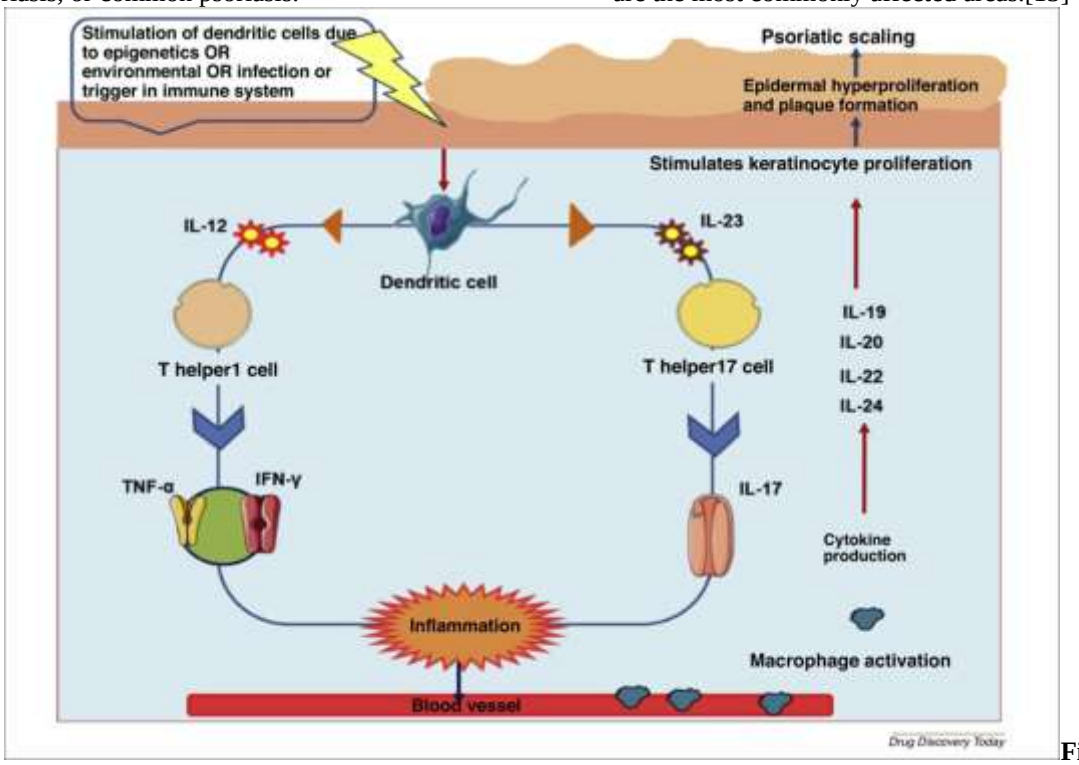

Fig. 2. Pathophysiological mechanism of psoriasis.[10]

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1.2 Mechanism of percutaneous absorption and treatment

Topical treatment is typically used to treat mild to severe psoriasis. It allows for targeted therapy of the particular skin condition while avoiding systemic negative effects. Patient satisfaction with current treatments is still low, though one essential component of topical treatment is cutaneous availability[15]. Topical drug distribution is influenced by the properties of the skin, the physicochemical properties of the drug and its carrier, and the way the drug and its vehicle interact with the layers of skin. Often penetrating intact skin are hydrophilic substances with a molecular mass of less than 500 Daltons. This explains why molecules with a higher molecular weight and those that are particularly lipophilic or hydrophilic are less suited for therapy with conventional topical medications [16]. The dermis, the outermost layer of skin, plays a vital role in skin metabolism due to its diverse cellular proliferation, vascular structure, and production of biochemical mediators that are linked to the preservation of extracellular matrices and the regulation of immune responses. As seen in Figure 2, transdermal delivery can occur via either trans epidermal or trans appendageal channel [17]. Triacylglycerols, which make up the sidewalls of nanopores, enclose hydrophilic regions of a skin cell's transcytosis pathway. Materials traveling via this channel use defects that create holes filled with water to enter corneocyte groups. The majority of substances or fragments penetrate the epidermis through intercellular diffusion inside corneocytes of the stratum corneum (SC). A chemical must travel through a convoluted path to pass between corneocytes since they are not stacked perpendicularly in strata. It is proposed that this channel permits free-volume transfer via the phospholipid bilayer that separates cells [18].

II. CONVENTIAL TREATMENT FOR PSORIASIS

For treating psoriasis, topical treatments are by far the most popular. These days, topical corticosteroids, calcineurin inhibitors, topical retinoids, and vitamin D analogs serve as its foundation.[19,20] As vitamin D analogs, calcitriol and calcipotriol (or calcipotriene), tacrolimus as a calcineurin inhibitor, and tazarotene as a topical retinoid are a few examples.

For more than 50 years, methotrexate has been used to treat psoriasis.It functions similarly to folic acid and is based on competitive inhibition of the dihydrofolate reductase enzyme. Consequently, it will prevent the synthesis of cofactors required for the synthesis of nucleic acids, which will impair the synthesis of T lymphocytes and keratinocytes. Cyclosporin turned out to be a very successful antipsoriatic medication after it was first prescribed as an immunosuppressant to prevent organ rejection following transplantation. Its action results from calcineurin inhibition, which prevents the release of pro-inflammatory cytokines and suppresses T cell activation.[21] A very old technique for treating dermatosis is phototherapy consists of regulated and repeated exposure to UV light from artificial sources; the UV light is absorbed by skin-localized endogenous chromophores. UVA or UVB radiation may be employed.[22] UVA radiation (320–400 nm) is inefficient when used alone; but, when combined with photosensitizing drugs, either topical or systemic (psoralen), it can be highly effective. This combination of treatments is known as PUVA (psoralen + UVA radiation). This treatment suppresses cytokine release and reduces epidermic proliferation.[23, 22]The biological impact of UVB light (290–320 nm) is greater and modifies cellular processes. Example: Clobetasol tablet is used in the treatment of psoriasis and it has sustain release pattern. Soriatane is another example which is in the form of capsule for treatment of psoriasis.

III. NANOTECHNOLOGY-BASED STRATEGIES FOR TOPICAL TREATMENT OF PSORIASIS:

A novel family of approaches with a diameter of less than 100 nm is known as nanocarriers, and they have been explored for the treatment of skin conditions.[24] Comparing nanotechnology to conventional formulations, there are many advantages and a growing amount of interest in this field. [25, 26] The reduction of side effects brought on by conventional treatments, along with improved drug penetration and increased drug release profiles to meet the therapeutic goal, are the main benefits of these nano-based formulations. [27] Nonetheless, it is necessary to solve certain drawbacks.[28, 29] (Fig. 3),

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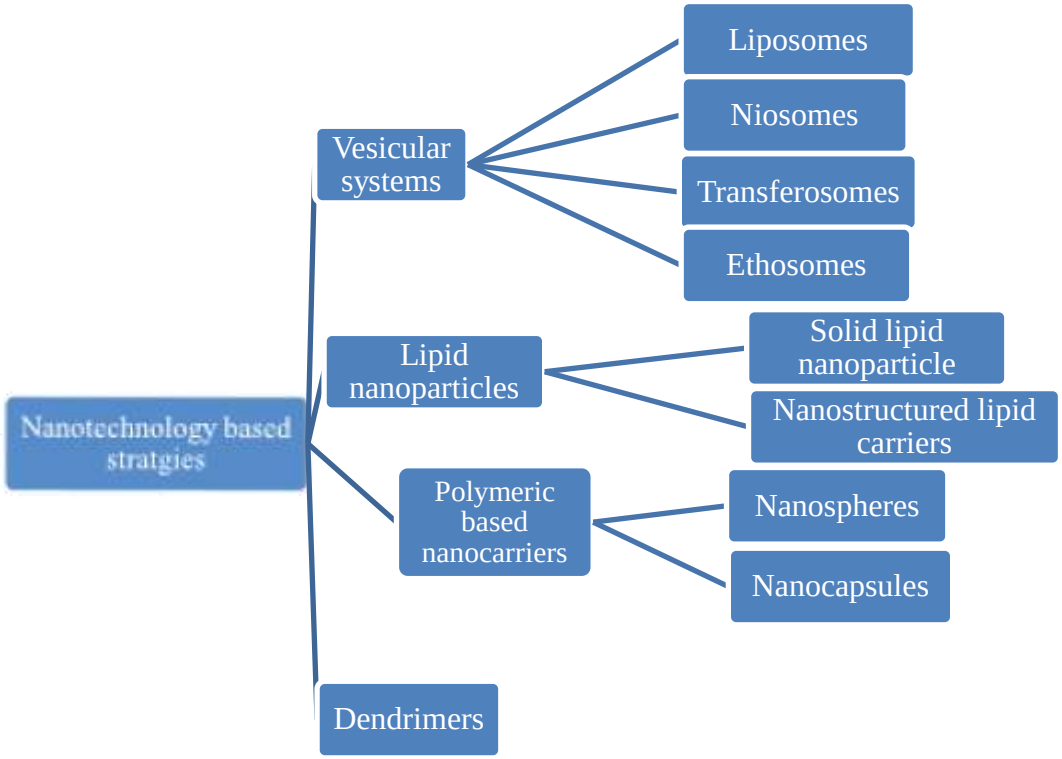

Fig. 3. Different nanotechnology-based strategies for topical treatment of psoriasis.

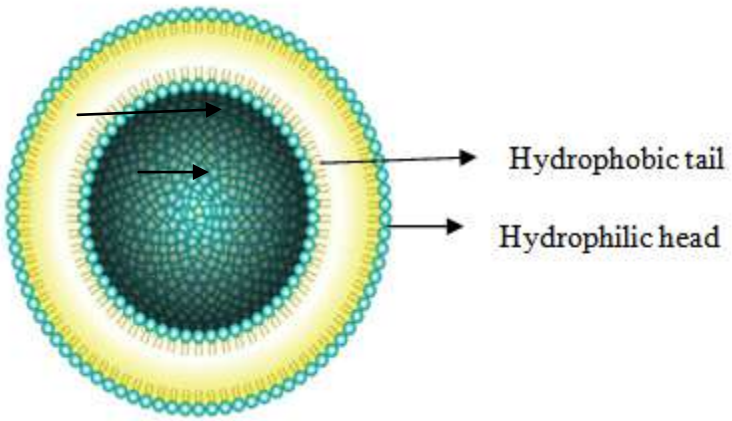

Fig: Structure of Liposome

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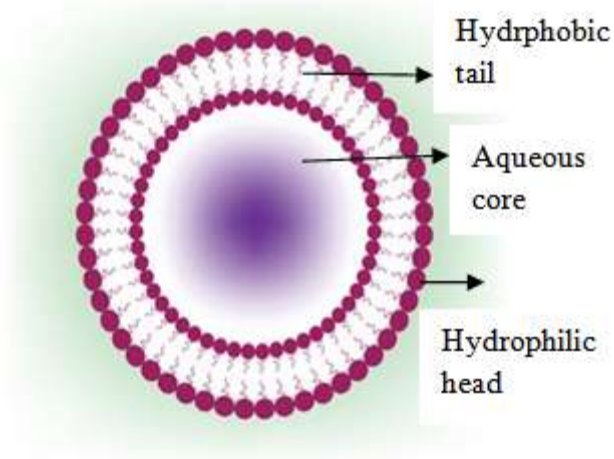

Fig: Structure of Niosome

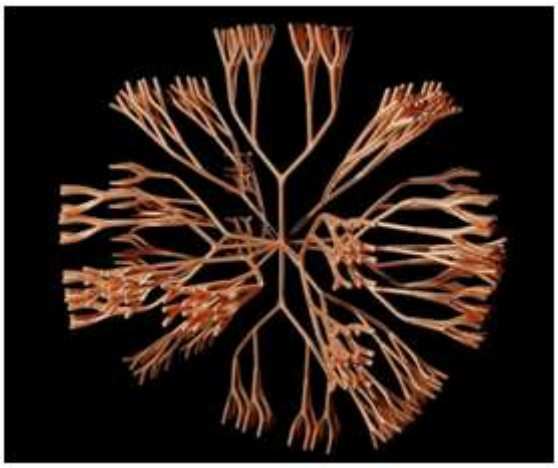

Fig: Structure of Dendrimer

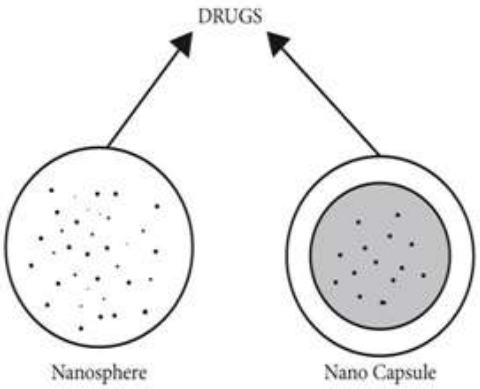

Fig: Nanosphere and Nanocapsule

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A. VESICULAR SYSTEMS:

A.1 Liposomes:

Liposomes (LIPs) are derived from phospholipids, cholesterol, and long-chain fatty acids. They can be unilamellar or multilamellar vesicles.[30] This nanosystem is made up of a lipophilic environment sandwiched between layers of phospholipids and a hydrophilic environment surrounding the vesicle core.[31] Lipids were specifically created to improve medicine administration and manage inflammatory conditions, such as psoriasis, because of their moisturizing qualities. They can contain both hydrophilic and lipophilic compounds, and their use has been effectively linked to an improvement in medication penetration and skin permeation. [31]. Overall, some of the primary benefits of lipids are their capacity to deliver both hydrophilic and lipophilic medicines through the skin[32,33], their improved regulated drug release[34], and their ability to block systemic drug absorption. Through serving as a barrier and promoting the drug's absorption into the skin's layers. [36] On the other hand, a few drawbacks include the purity of phospholipids, high cost, and challenges with large-scale production [36][35]. Example: Patent No: US5834016- Active ingredient used are vitamin D compounds calcitriol or 1 α-hydroxycholecalciferol. Compounds are useful in treating disorders including psoriasis, eczema, dry skin. Liposome composition generally contain about 300 to 5000µg of vitamin D per 100 gram of composition. Composition used is vitamin D , lecithin, cholesterol, alcohol.

A.2 Niosomes:

Niosomes (NIOs) are lipid structures that are produced through the hydration of cholesterol, other lipids, and non-ionic surfactants[37]. The niosomes vesicle may include hydrophilic or hydrophobic medications, as well as niosomes can be categorized into three classes according to the capacity of this vesicle: large unilamellar vesicles (LUV, size 0.10 mm), multilamellar vesicles (MLV, size 0.05 mm), and small unilamellar vesicles (SUV, size 0.025–0.05 mm)[37] niosomes, like LIPs, have multiple modes of administration, including topical application. They have the ability to improve medication penetration and release. Because they are osmotically active, biodegradable, and biocompatible, they don't need particular storage conditions[37]. There have been reports of several niosome preparation techniques, including as thin-film hydration, emulsion, reverse phase evaporation, ether injection, and micro-fluidization technology, each of which may produce vesicles with varying diameters[38, 39, 40]. It is indicated that by taking into account the nonionic surfactants' hydrophilic lipophilic balance (HLB) value, which ranges from 4 to 8, a favorable amphiphilic bilayer niosome for optimal entrapment effectiveness may be generated[39, 41]. The range of nonionic surfactants that are commonly used is comprised of Tween, Span, and Brij. Furthermore, the utilization of lengthy hydrocarbon chains devoid of a double bond can result in a stable niosome formation for improved drug loading. Example: Niosomal methotrexate gel. Methotrexate niosomes were prepared by lipid layer hydration method. Characterized niosomes were incorporated in chitosan gel. It is used to treat localized psoriasis.

A.3 Transferosomes:

Transfersomes (TRAs) are nanocarriers that have an aqueous compartment that is easily malleable and is surrounded by lipids and surfactants. Their most notable benefit is their capacity to must be flexible enough to pass through smaller pores. When medications are hydrophilic, they are trapped in their watery core; when they are lipophilic, they are trapped in the bilayered wall by hydrophobic and electrostatic forces.[42]. Essentially, transfersomes are more elastic and pliable than traditional liposomes, allowing them to effectively enter the skin's tiny channels.[43,44]Because of their membrane's self-optimizing deformability and change in flexibility upon traveling through the pores in the skin might happen on their own as they allow the cells' extracellular routes to open up.[44] EA acts as a permeation enhancer to promote transdermal penetration by rupturing the lipid bilayers of the vesicles and enhancing the fluidity of the stratum corneum lipid. As a result, transdermal administration can be improved by preventing the "first-pass effect," regulated, and extended drug activity duration. The pharmacological and physiological response are enhanced by these pharmacokinetic effects, which also enable the effectiveness of medications with short half-lives[45,46]. The ethanol injection, reverse-phase evaporation, thin-film hydration, and freeze-thaw methods are among the frequently used techniques for preparing transfersomes[47]. In terms of skin penetration, transfersomes are generally thought to be superior to liposomes however they are comparatively less deformable than ethosomes[48,49,50]. Example: Betamethasone

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dipropionate loaded transfersomal formulations was prepared by conventional thin lipid film hydration technique using rotary evaporator. Amount of lipid , surfactant and drug were dissolved in chloroform. Betamethasone gel is used to treat localized plaque psoriasis.

A.4 Ethosomes:

The primary components of ethosomes (ETOs) are alcohol, water, and phospholipids. These nanosystems can range in size from 30 nm to microns. Because of their great flexibility and the ability of formulations based on transferosomes to penetrate pores smaller than their diameter, they are also known as elastic vesicles[51]. Ethosomes might include compounds with unique properties that are lipophilic, hydrophilic, or amphiphilic. Ethosomal carriers offer a number of benefits, including increased substance compliance and penetration, non-toxic ingredients, and easier drug administration.[52] These systems are appropriate for use in biotechnology, pharmacology, veterinary medicine, and cosmetics.[58]. The fundamental mechanism involves the interaction between the polar head group of ethanol and the lipid areas of the skin, leading to an increase in the lipid fluidity of the cell membrane and an improvement in the ethosomes' capacity to penetrate the skin. The system's medication is subsequently released once these ethosomes penetrate the skin and combine with the lipids in cell membranes. The standard cold approach, the hot method, the ethanol injection-sonication, the thin-film hydration, and the reverse phase-evaporation procedures are some of the commonly used ethosomal formulations.[54] Ethosomal systems can be further divided into the following categories based on their makeup: (1) transethosomes (added with an edge activator or chemical surfactant); (2) binary ethosomes (added with isopropyl alcohol or another type of alcohol); and (3) classical ethosomes.[55] Example: Anthraline loaded ethosomes were prepared by cold method. Anthraline and PL-90G were dissolved in the designated amount of absolute ethanol. Anthraline is used to treat long term psoriasis.

A.5 Lipid nanoparticles

Solid lipid nanoparticle:

Introduced in the 1990s, SLNs represent the initial generation of lipid nanocarrier systems. It is a sophisticated drug delivery vehicle in which lipids are distributed in an aqueous surfactant solution to form submicron particles, ranging in size from 40 to 1000 nm.[78] At room temperature and body temperature, lipids such as glycerides, fatty acids, and steroids are solid; this is because the surfactant utilized in SLNs functions as an emulsifier.Depending on the drug's thermal stability, either a cold or hot homogenization process is frequently used to formulate[79] SLNs.Moreover, high-pressure homogenization and ultrasonication techniques can be used to create[80,81] SLNs.Site-specific[80,82] SLNs were created to address the problems with polymeric nanoparticles and liposomes, including drug leakage, cytotoxicity, and phospholipid degradation in the liposome. Compared to liposomes, their dynamic system also permits component customization. For example, the surfactant—which is frequently combined with a co-surfactant to lower particle size—can be either ionic or nonionic.[84]However, well-established research indicates that certain lipid and surfactant components, such as stearic acid (lipid) and sodium dodecyl sulphate (surfactant), in the SLN formulation may have contributed to their high cytotoxicity level and, consequently, their lack of biocompatibility feature[85,86]. Example: Methotrexate and etanercept prepared by hot ultrasonication method. It has a long in vitro release time and doesn't harm human keratinocytes or fibroblasts.[91]

Nanostructured lipid carriers:

Similar preparation techniques used for SLNs and NLCs include hot homogenization, cold homogenization, and ultrasound-heated emulsification.[81] However, the oils in NLC's composition, in contrast to SLNs, stop the medicine from being expelled as much while it is being stored since they impede the process of recrystallization.[87] Lipid defects in their matrix systems also increase drug incorporation.[88] NLCs can thereby produce a regulated release profile and increased drug solubility. NLCs are currently thought to be a better drug carrier than SLNs because of their greater biocompatibility and formulation. Additionally, NLCs are site-specific, and when applied topically, they enhance skin occlusive qualities, skin penetration, and skin retention[89,90]. Mometasone furoate prepared by microemulsion method. Route of administration is topical. Superior skin accumulation, reduced main skin irritation score, and total resolution of parakeratosis in vivo[92].

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A.6 Nanoemulsion:

A significant amount of medicine is dispersed in nanodroplet sizes by two immiscible liquids to form an isotropic, heterogeneous system known as a nanoemulsion. The two liquids can be water in oil (W/O), oil in water (O/W), or double emulsion (W/O/W and O/W/O) stabilized by amphiphilic surfactants, with mean droplets of less than 200 nm, depending on the phase media.[57,58]. It has been demonstrated that the systems essentially encapsulate lipophilic active ingredients for improved topically applied skin distribution[59]. Furthermore, as recent research and the literature have demonstrated, nanoemulsions are also effective carriers for encapsulating natural bioactive substances and essential oils[60].Because of its versatility, the emulsion approach can be applied as a spray, gel, cream, or aerosol[61-64]. Selecting the right surfactants is essential for lowering the ionic or nonionic tension at the oil-water surface and between the two phases. Tween® 80, phospholipids (soy lecithin), polysaccharides, polymers (PEG), and amphiphilic proteins (caseinate) are examples of common surfactants or emulsifying agents[59].Because nonionic surfactants induce less local irritation than anionic surfactants, they are generally thought to be safer for use in pharmaceutical applications[65]. They also have a lower CMC value than their ionic counterparts of the same alkyl chain length, suggesting a more stable drug delivery mechanism.[66]. In addition, Ethylene glycol, propylene glycol, ethanol, and propanol are examples of alcohol groups with C3–C8 chain lengths that are commonly added as a co-surfactant to improve entropy and stabilize the colloidal system[67,68]. In general, there are two types of nanoemulsion preparation techniques: high energy and low energy. A reliable technique for creating nanoemulsions is the high-energy method, such as high-pressure homogenization, which breaks big droplets into nanosized particles by using mechanical devices or excess shear[69]. A repeated sequence of cycles is required since the high energy technique, which is more suitable for large-scale production, only produces 1% nanoemulsion while 99% of its heat is dissipated off[69,70]. But since the low interfacial property of the system is exploited to form nanoemulsions, two separate low-energy techniques—phase inversion composition (PIC) and phase inversion temperature (PIT)—are recognized to be energy-saving[71]. Example: To improve topical medication availability and efficacy against plaque psoriasis, apply soy lecithin and vitamin E oil to create a nanoemulsion of tacrolimus and azelaic acid. High speed homogenization was the method employed.

A.7 Polymeric based Nanocarriers:

Nanospheres:

Nanospheres, or nanoparticles, are particles smaller than one micrometer that have a polymer matrix with a uniform drug distribution within them. The polymers used may or may not biodegrade. Nanospheres offer superior stability, increased solubility, improved absorption, and better control over the release of the medicine.[72]. Previous research has shown that NSs' non-cytotoxic properties and their capacity to encapsulate without losing active ingredients make them an intriguing asset for the assessment of these systems in cutaneous applications. Nanospheres have several benefits, including improved skin penetration of lipophilic medicines [72, 73], biocompatibility and biodegradability [73], increased cutaneous penetration, and resistance to degradation.[74] However, nanospheres need to be purified and are not appropriate for transdermal application [72].

A.8 Nanocapsules:

Similar to nanoparticles (NSs), nanocapsules (NCs) are colloidal particles smaller than 1 µm. However, in contrast to nanospheres, nanocapsules have a reservoir system in which a polymeric membrane coats the drug core. Their remarkable ability to penetrate skin has led to their increasing appeal. They prevent the medication from degrading and are regarded as superior materials for use in dermatological treatments. Hydrophobic materials are primarily incorporated into NCs, which are composed of a lipophilic core encircled by a polymeric wall. The benefits of nanocapsules include reduced irritant effects and enhanced skin penetration [75, 76]. The drawbacks include challenges with manufacturing at larger scales.[76].

A.9 Dendrimers:

Typically, dendrimers are multivalent, spheroidal, three-dimensional macromolecules having multiple active terminal groups and a hyperbranched shape. [77] Dendrimers may carry a conjugated medication or one that is encapsulated. They also aid in the diffusion of the active ingredient and aid in the defeat of various resistance mechanisms. Because of these qualities,

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they work well as carriers and can be administered intravenously, orally, transdermally, pulmonaryly, and ocularly.[77] In addition to these benefits, they demonstrated improved drug release control, enhanced solubility, and the production of pro-drugs (drug-polymers).

These characteristics indicate that dendrimers have showed tremendous promise as antipsoriatic medications.[77]. Example: Using a poly(amido) amine dendrimer to apply dithranol topically. Effect of dithranol in psoriasis is reflected by inhibition of granulocyte function, keratinocyte hyperproliferation as well as immunosuppression.

IV. CONCLUSION:

Skin illness psoriasis is caused by cell hyperproliferation and is known to be influenced by a number of recognized causes, including hereditary and environmental factors. Topical, systemic nonbiologic, systemic biologic, and phototherapy treatments are available for psoriasis among other alternatives. The most practical method of delivering the therapies across the skin barrier is through topical treatment, even with the abundance of antipsoriatic medications with various modes of action. Lipid-based nanoparticles hold great potential as innovative nano delivery methods to enhance the delivery of APIs to their intended location. According to current research, liposomes and nanoemulsions have been the focus of the majority of effective nano-based psoriasis treatments, despite the fact that numerous APIs can be encapsulated into different lipid nanocarriers. Furthermore, because of their huge surface area at the nanoscale size, the therapies also demonstrate very positive results in the alleviation of psoriasis lesions by improving skin penetration, retention, and extended release. Nevertheless, further research and development, including alternative lipid-based nanocarrier configurations like ethosomes, transfersomes, and niosomes, are necessary to completely examine their enormous potential in the topical delivery of antipsoriatic uses.

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