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Review Article

Revolutionary nanocarriers-based drug delivery system for antipsoriatic agents: an overview.

Vikash Jauhari*, Rajan Kothari.

Shivdan Singh Institute of Technology and Management, Mathura Road, Aligarh, Uttar Pradesh, India.

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ABSTRACT

Psoriasis is an unremitting, inflammatory, autoimmune disorder of the skin disease. It is characterized by excessive growth and aberrant differentiation of keratinocytes. Although psoriasis occurs worldwide is 2-5%. The study found that 35% of people have moderate to severe psoriasis. Several approaches have been explored by researchers with different anti-psoriasis drugs for their successful treatment. But psoriasis is a challenge to treat due to its chronic recurring nature and lack of a perfect carrier for safe and effective delivery of antipsoriatic drugs. Novel nanocarriers have been thoroughly investigated like liposomes, transferosomes, niosomes, ethosomes, SLN, NLC, microspheres, micelles, nanocapsules, dendrimers, etc. Presently nanocarriers have gained widespread application for effective and safe treatment of psoriasis. The present review focuses on currently existing treatment options and recent developments in the delivery of various antipsoriatic drugs through revolutionary nano carriers categorized as lipid-based carriers and polymer-based carriers.

*Author for Correspondence: vikas_jauhari@yahoo.com

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INTRODUCTION

Psoriasis is a chronic inflammatory, autoimmune disorder of the dermis and epidermis. Although psoriasis occurs worldwide is 2-5% [1]. The disease is usually characterized by skin thickening, and excessive growth of red scaly patches appears on the skin. The disease involves a sequence of cellular changes in the skin like hyperplasia of epidermal keratinocytes, vascular hyperplasia, ectasia, and penetration of T-lymphocytes, neutrophils, and other types of leucocytes in the affected skin. The classification of types of psoriasis is done based on the extent of the inflammatory process, localization of rash, the severity of the patient condition, and other clinical traits into chronic plaque, guttate, pustular, and erythroderma [2]. Amongst these, chronic plaque psoriasis (CPP) represents a major occurrence proportion with the equivalent likelihood in both sexes and early onset before the age of 40 years. The classification of types of psoriasis is shown in Table 1.

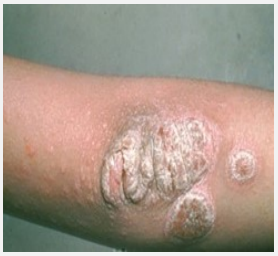
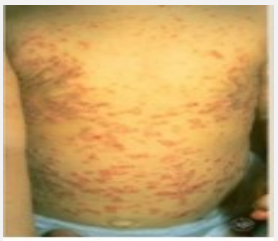
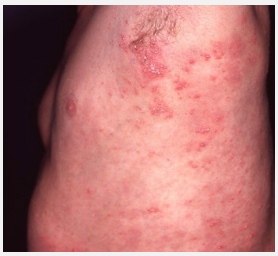
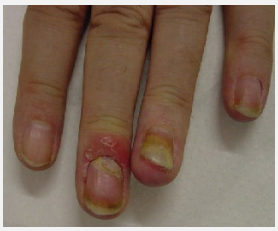
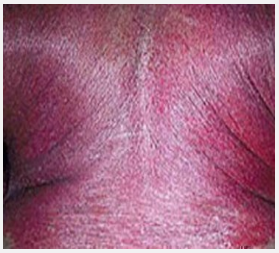
Challenges in psoriasis treatment

The major challenges in psoriasis treatment are elaborated on below.

Deficiency of competent carrier for delivery of anti-psoriatic drugs

The main problems are physicochemical properties of the carrier with drug moiety and their incorporation leading to alteration in drug absorption behaviors and the drug efficacy. Novel carriers could be an option to overcome the problems associated with conventional vehicles [3].

Table 1. Types of psoriasis disease.

Types	Signs and Symptoms	
Plaque psoriasis		Most people have plaque psoriasis. It is characterized by a silvery-white scale affecting elbows, knees, lower back, and scalp. Chronic plaque psoriasis is the most common variety of psoriasis, representing about 70% to 80% of psoriatic patients.
Guttate psoriasis		Guttate psoriasis is especially common in children or young. He Small red scaly patches dotted across the skin. These patches can cover quite a large area of the skin.
Pustular psoriasis		It is a severe type of psoriasis where lots of small bumps appear on your skin. Bumps usually appear only on the palms and soles. Soreness and pain where the bumps appear. Pus-filled bumps will dry, and leave behind brown dots and/or scale on the skin.
Flexural psoriasis		Psoriasis can be more difficult to treat on some parts of the body. Flexural psoriasis happens in skin folds, armpits, under the breast, and between the buttocks. It can also affect the genitals. It is not usually scaly.
Erythrodermic psoriasis		It is the least common type of psoriasis and may occur only in 1-2% of people. The skin looks like it is burned. The body cannot maintain its normal temperature of 98.6° F. Person gets very hot or very cold. The heart beats too fast. Intense itching and pain.

Pathophysiology of psoriasis

The difference between the standard and psoriatic epidermal skin has been shown in Fig. 1. There are different events in the pathogenesis of psoriasis:

Binding of antigen to antigen-presenting cells (APC)

↓

Migration of antigen carrying APC to the lymph nodes

↓

Antigen presentation by APC to T cell and co-stimulation

↓

Migration of clones of activated T cells to blood vessels

↓

Migration of activated T cells to epidermis and release of cytokines

↓

Formation of psoriatic skin by the influence of cytokines.

Figure 1. There are different events in the pathogenesis of psoriasis.

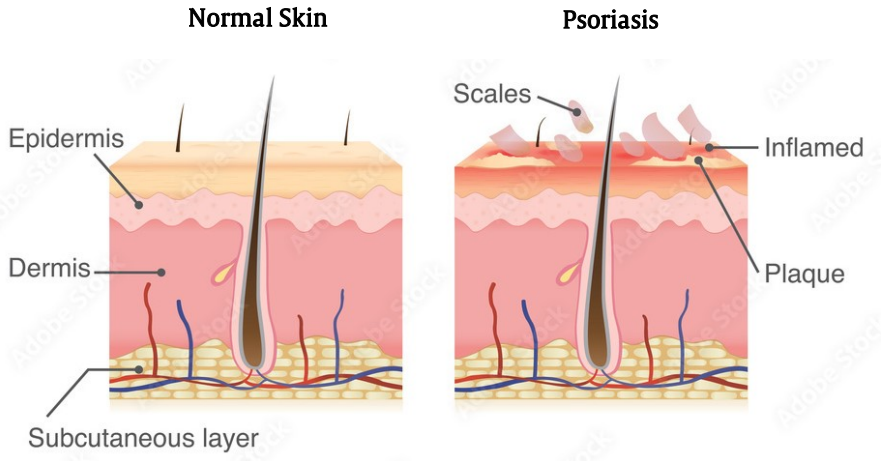


Figure 2. Difference between the standard and psoriatic skin.

Lack of appropriate animal model

Another challenge in the development of an ideal drug and delivery carrier for the psoriasis is lack of an appropriate animal model. Although numerous immunological and genetic animal models have been developed, none of these models display all the characteristics of psoriasis with limitations [4].

Various treatment options for psoriasis

Generally, there are three main modes:

a) Topical therapy
b) Phototherapy
c) Systemic therapy.

Firstly, topical therapies are considered. Phototherapy is suggested when topical therapy is ineffective which is followed by systemic medications. Detailed descriptions of antipsoriatic drugs are given in Table 2.

Conventional topical medication is used for mild psoriasis, but the absorption rate is low. In the last stages of psoriasis, systemic therapies are preferred. However, in systemic therapy, drug moieties are needed at high doses which maybe produce adverse effects. In addition, biologics employed as an immense therapeutic option for moderate-to-severe psoriasis, are very costly for patients and the healthcare system. The conventional topical treatments that have been used in past, but their chronic recurrent nature, psoriasis are a challenge to treat by traditionally (topical, oral, and systemic) treatment. The overuse of highly potent corticosteroids can cause thinning of the skin and side effects, while coal tar and dithranol have

low efficacy, and poor aesthetic and cosmetics appeal leading to poor patient compliance while systemic therapies such as methotrexate, cyclosporine, and acitretin produce significant side effects [5].

The currently available treatments based on the conventional formulation for psoriasis are related to problems like increased dosing frequency, increased side effects, and decreased safety and efficacy. Among the currently available treatments, none of the psoriasis treatment is found to be safe, effective, and able to completely cure the disease. Further, available treatment options are associated with both inappropriate cosmetic appearance and related toxicities leading to poor patient compliance in long-term use [6]. Therefore, a novel drug delivery approach came into existence. Presently great and wide research is being done to achieve a safe and effective therapy of psoriasis using novel carriers.18 A novel drug delivery approach using novel carriers offers several advantages such as improved encapsulation efficiency, increased biocompatibility, and desired drug concentration at the targeted site. Consequently, reduction of dose & dosing frequency and then side effects thereby improved effectiveness and patient compliance [7].

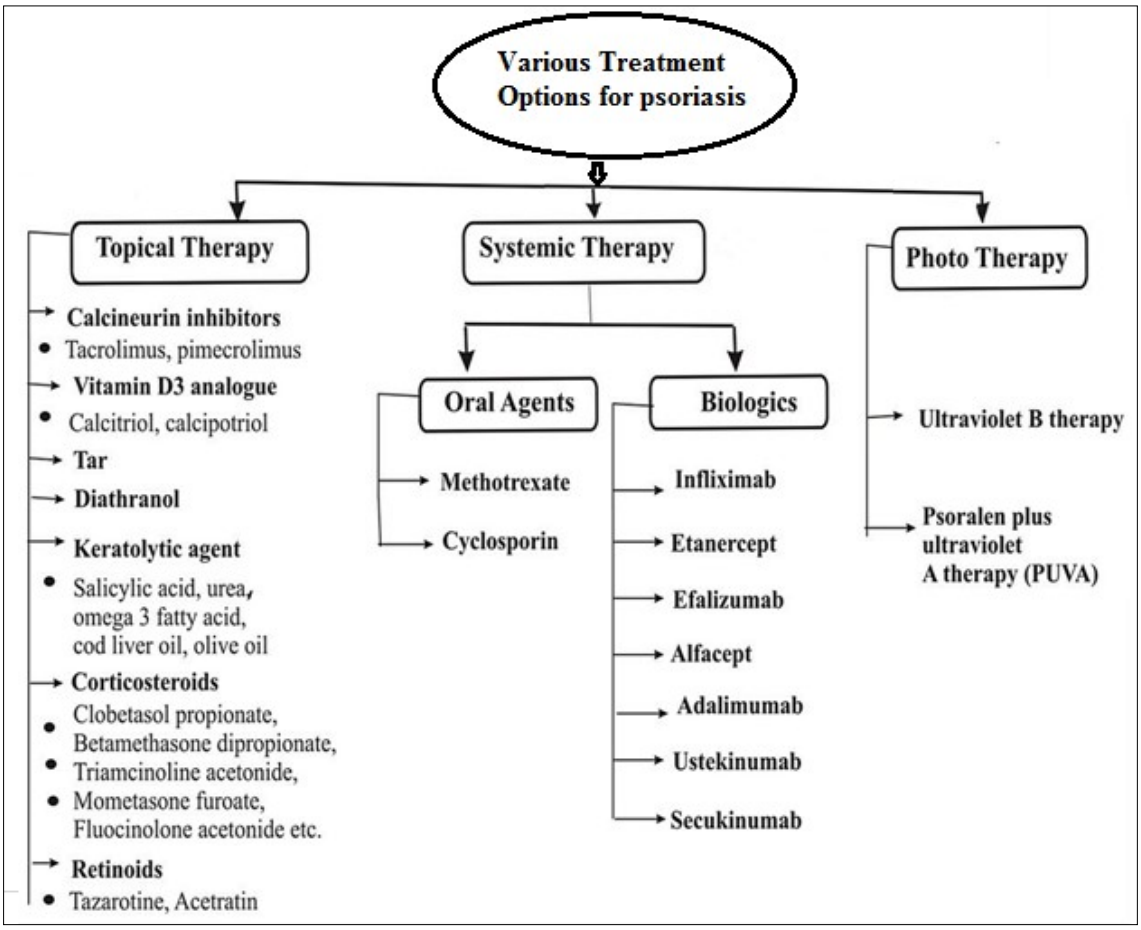


Figure 3. Various treatment options for psoriasis.

Current and future management of psoriasis

There are several recent attempts to utilize the NDDS approach to improve the accessible topical drug formulations in psoriasis. The most widely used drug delivery systems include lipid-based nanoparticles *i.e.* nanoemulsion, solid lipid nanoparticles, lipid nanocapsules, nanosuspensions, liposomes, liquid crystalline nanoparticles, lipid-drug conjugates) or polymer-based nanocarriers (polymeric nanoparticles, polymeric micelles, polymer-drug conjugates) as shown in Table 2 [8].

Classification of novel nanocarriers

Numerous versatile and smart nanocarriers have been developed as advanced drug delivery systems for dermal application [9]. The nanocarriers included in this review fall into four main classes. They are classified as follows:

1) **Polymer-based nanocarriers** : micelles, polymeric nanoparticles, dendrimers, nanosphere, and nanocapsule.

Table 2. List of some antipsoriatic drugs with their novel drug delivery systems.

S. No.	Novel drug delivery carrier	Antipsoriatic drug	Method of preparation
1.	Liposome	Tacrolimus	Self-assembly of the triblock copolymer
2	Liposomes	Capsaicin	Thin film hydration
3	Ethosomes	Methotrexate	Extrusion method
4	Liposomes	Tretinoin	Fusion method
5	Nanoemulsion	Clobetasol propionate	Aqueous phase titration method
6	Solid lipid nanoparticle	Mometasone Furoate	Solvent injection method
7	Dendrimers	8-methoxypsoralene	Divergent method
8	Microemulsion	8-Methoxsalen	Hot homogenization
9	Nanostructured lipid carrier	Cyclosporine	The modified hot Homogenization method
10	Polymeric nanocapsules	Dexamethasone	Interfacial deposition of preformed polymer
11	PEGylated liposomes	Calcipotriol	Thin film hydration method
12	Nanostructured lipid carriers	Fluticasone propionate	Modified microemulsion method
13	Nanostructured lipid carrier	Triamcinolone acetonide	Modified emulsification ultrasonication

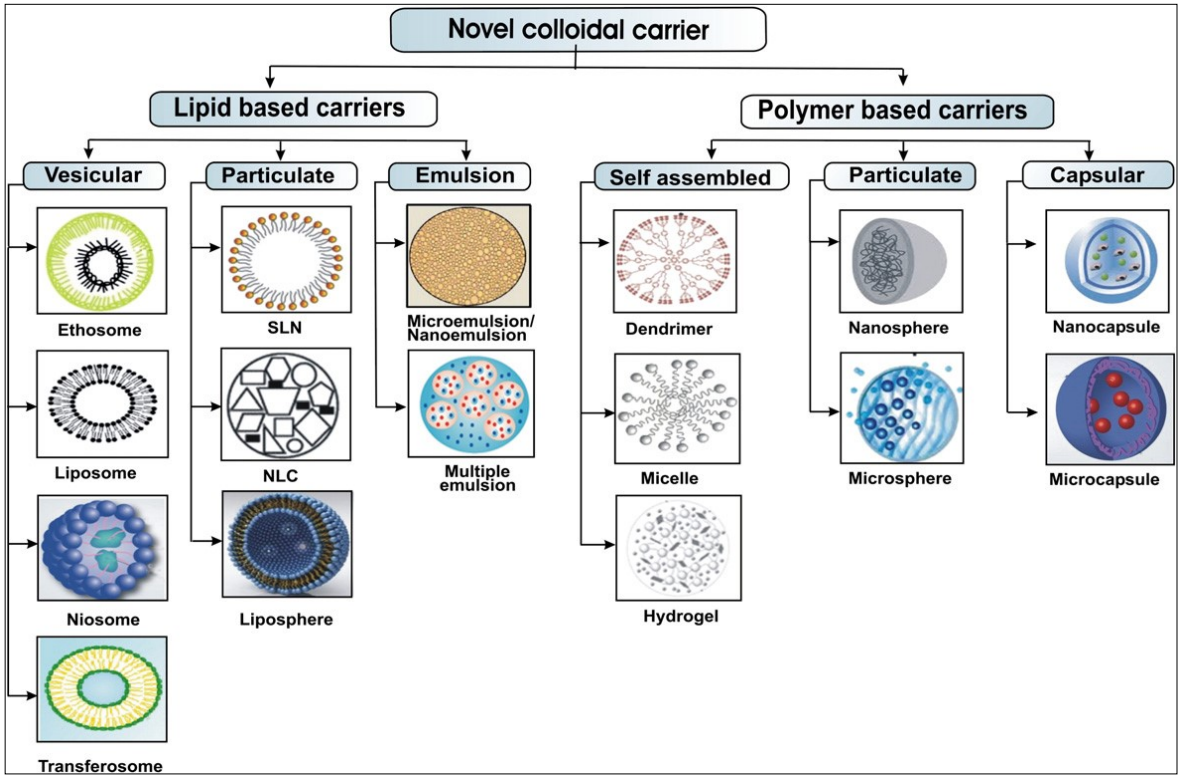


Figure 4. Various types of nanocarriers used in the treatment of psoriasis.

Polymer-based nanocarriers

Polymers are used in the delivery of various therapeutic agents such as synthetic drugs, herbal drugs, vitamins, peptides, etc. Polymer-based nanocarriers are usually made up of environmentally friendly polymers the size range varies from 10–1000 nm. [10, 12]. Polymer-based nano-formulations have emerged as tremendous delivery vehicles due to ease of preparation, targeted delivery, and safety concerns point of view. Additionally, they are structurally stable and able of preserving their structure for a longer duration, when topically applied to the skin [11, 12].

Recent advances and applications of various nano-formulations anti-psoriatic drug delivery have been discussed in the following section of the review.

Polymeric micelles

These are self-assembling nano-sized (5–100 nm) colloidal particles with a hydrophobic core and hydrophilic shell, used as pharmaceutical carriers for water-insoluble drugs. These carriers have a high degree of drug loading capacity, reduced drug degradation, side effects, and increased bioavailability. Drug loading in a micelle can be achieved by drug-polymer covalent attachment or by physical entrapment [13].

These micelles nanocarriers have applications in the delivery of the anticancer drug, antifungal agents, gene delivery, and also for the delivery of antipsoriatic agents. Recently polymeric micelles have also been used for delivery of the therapeutic gene for the cure of psoriasis. In this context, Fan et al., developed modified c-Rel specific siRNA (siRel) loaded poly (ethylene glycol)-b-poly(L-lysine)-b-poly(L-leucine) (PEG-PLL-PLLeu) micelles [14].

Polymeric nanoparticle

Nanoparticles generally vary in size from 10 to 1000 nm. Polymeric nanoparticles are of two types – nanospheres and nanocapsules depending on the arrangement of the drug in the polymer system. In the nanosphere, the drug is entrapped or dispersed in the polymer matrix. Polymers used can be either biodegradable or non-biodegradable. Biodegradable polymers are significantly used as potential drug delivery systems in the controlled or site-specific delivery of drugs or bioactive such as DNA, proteins, peptides, and genes through various routes of administration. Drug release either diffusion, erosion of the matrix, or a combination of both depending on the nature of the polymer or method of fabrication.45 Nanocapsules, a characteristic class of nanoparticles, are made up of one or more active materials (core) and a protective matrix (shell) in which the therapeutic substance may be confined [15].

Dendrimers

The core of dendrimer provides a compartment for housing drugs suitably and nanosize allows internalization by endocytosis. Dendrimers provide void space for drug loading as the drug can either reside in the central unit or interact with terminal functional groups via electrostatic or covalent bonds. Drug releases from the dendrimer either by enzymatic degradation of drug dendrimer conjugate or by changes in the physical environment such as pH and temperature. Dendrimers have great applications in the drug delivery system. They have advantages such as increased solubilization, controlled drug release, and the formation of drug-polymer conjugates (pro-drugs). Furthermore, the viscosity generation property of the dendrimer solution permits direct and smooth application of very concentrated dendrimer formulations over the skin [15]. Therefore dendrimers have been successfully used for the delivery of antiviral, NSAIDS, etc. antihypertensive, anticancer, and antipsoriatic drugs [17].

Nanosphere

It is one type of polymeric nanoparticle in which a drug is entrapped or dispersed in the polymer matrix. Polymers used can be either biodegradable or non-biodegradable. Biodegradable polymeric nanoparticles are significantly used as potential drug delivery systems in the controlled or site-specific delivery of drugs or bioactive such as DNA, proteins, peptides and genes [18]. Polymeric nanoparticles delivered the drugs used in various diseases and dermatological diseases including psoriasis. Nanospheres (tyrospheres) have been successfully employed for drug delivery to the skin. Batheja et al. developed lipophilic drug-loaded tyrosine-derived nanospheres for topical application. They further developed nanospheres in a gel formulation and evaluated its permeation potential by using human cadaver skin exhibited enhanced drug permeation from tyrosphere as compared to aqueous nanosphere formulation. Furthermore, tyrosphere has recently been applied for topical delivery of Vitamin D3, a very widely used drug for the treatment of psoriasis [19].

Nanocapsules

Nanocapsules are polymeric nanoparticles in which one or more active core material is surrounded by polymeric matrix (shell). Nanocapsule can provide nano drug carriers to achieve controlled release as well as proficient drug targeting. Polymeric nanocapsules are a valuable means for dermal applications. The main advantages of nanocapsules include sustained release, increased drug selectivity and effectiveness, improved drug bioavailability, and reduced drug toxicity. The release properties and degradation mostly depend on the polymer properties, drug used and method of preparation [18].

Liposomes

Liposomes are phospholipid bilayered vesicular structures enclosing an aqueous compartment. Liposomes are suitable for carrying both hydrophilic (in aqueous core) and lipophilic drugs (in lipid bilayer) due to their amphiphilic nature. Dermal delivery of drugs through liposomes is favored by its small size, lamellar, elastic, and fluid properties. Phospholipids, being the major component of liposomal systems, are

easily integrated with the skin lipids and maintain the desired hydration conditions to improve drug penetration and localization in the skin layers [20]. Liposomes are uniquely used in topical/ transdermal drug delivery for a variety of dermal disorders including psoriasis. They are considered unique because they play the role of organic solvent for solubilizing poorly soluble drugs; act as a local depot contributing to sustained drug release; act as penetration enhancers due to diffusion of phospholipid molecules or nonionic surfactants into the lipid covering of the stratum corneum; promotes localized higher drug concentrations. Calcipotriol, a vitamin D analog was successfully delivered in lipopolymer poly(ethylene glycol)-di-stearoyl phosphoethanolamine (PEG-DSPE) liposomes with a significant increase in drug deposition into the stratum corneum. Doppalapudi et al. developed liposomal nanocarriers containing psoralen for safe and effective PUVA therapy of psoriasis with better skin penetration [21].

Solid lipid nanoparticles

Solid lipid nanoparticles are nanoparticle systems in sizes ranging from 50 to 1000 nm. They are composed of physiological lipids and surfactants.66 which make to form SLN on dispersion in water. SLN offers unique properties such as tiny size with large surface area, high drug loading capacity, and extended drug release profile due to slow degradation of lipid matrices. SLNs have been successfully used in various cosmetic and dermatological preparations. Shah and co-workers developed the SLN of tretinoin for its improved photostability using the simple emulsification–solvent diffusion (ESD) method. In comparison with other vehicles such as solutions, creams, and emulsions, SLNs combine several advantages including controlled drug release minimal skin irritation, and protection of active constituents [22, 23].

Nanostructured lipid carriers

Nanostructured Lipid Carriers (NLCs) represent an advanced form of solid lipid nanoparticles (SLNs) with improved properties of drug loading, modulation of the release profile, and stable drug incorporation during storage [24]. NLCs are promising drug carriers for topical application because of their improved skin retention properties. Compared with other topical vehicles like creams, tinctures, lotions, and emulsions, the NLCs have several advantages such as controlled drug release, negligible skin irritation, protection of active compounds, and targeted drug delivery. NLCs are produced by mixing solid lipids (stearic acid, palmitic acid, carnauba wax, cetyl palmitate) with liquid lipids (oleic acid, isopropyl myristate) and form a lipid matrix with a specific structure [25, 26].

Liposphere

Lipospheres are lipid-based nanoparticulate carrier that is composed of a solid lipid core surrounded by a single unit phospholipid layer that may entrap the drug or coat with the drug. The emulsifying agent or stabilizing agent is used to forming a uniform coating around the core material and to facilitate the partitioning of the drug between the lipid and aqueous phases [27]. Lipospheres have been successfully used for an oral, intravenous, and transdermal route for the treatment of various ailments [28, 29]. They have also been used effectively for the treatment of psoriasis.

Nanoemulsion

Nanoemulsions are biphasic dispersion of two immiscible liquids having droplet size on the order of 100 nm, which is existing in either water in oil (W/O) droplets or oil in water (O/W) droplets. Nanoemulsions despite having the same droplet size range as microemulsions differ tremendously in structural aspects and long-term thermodynamic stability [30]. The small droplet size can resist the physical destabilization caused by gravitational separation, flocculation, and/or coalescence. It also avoids the creaming process because the droplet′s Brownian motion is enough to overcome the gravitational separation force. Nanoemulsions can be rendered into several dosage forms, like liquids, creams, spray, gels, aerosols, foams and can be administered by equally varying routes like topical, oral, intravenous, intranasal, pulmonary, and ocular [31].

Ethosomes

Ethosomes are soft, flexible, and noninvasive delivery carriers. It is mainly composed of phospholipids, ethanol and water. The characteristic feature of ethosome is due to its high ethanol concentration which is responsible for disturbing the organization of skin lipid bilayer. Thus, these vesicles based on ethanol easily penetrate the stratum corneum and are reported to be safe for pharmaceutical and cosmetic use. Ethosomes are suitable for topical drug delivery as they remain confined to the upper layer of the stratum corneum. They have also been used for dermal, transdermal delivery of numerous drugs for the treatment of several dermal diseases like alopecia, dermatitis, and psoriasis [32, 33].

CONCLUSION

Various topical treatments are available for psoriasis. Yet, none of them are completely secure and effective to treat the disease without compromising patient compliance. Furthermore, already existing drugs are supposed to control the disease and improve the sign

and symptoms with no complete cure. Therefore, there is a challenge to explore new drug delivery carriers which could safely and effectively manage psoriasis and improve patient compliance. Novel drug delivery carriers, especially nanocarriers improved the problems such as minimization of dose, dosing frequency, and side effects, associated with conventional drug delivery systems. Nanocarriers such as liposomes, ethosomes, Lipospheres, SLNs, polymeric nanoparticles, NLCs, nanocapsules, dendrimers, gold nanoparticles, silver nanoparticles, etc. have successfully been employed for antipsoriatic drug delivery. These carriers present a tool to overcome the many challenges associated with topical antipsoriatic drug therapy.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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