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An Overview on Management of Psoriasis Using Calcipotriene and Its Amalgamation as Nano Based Drug Delivery System †

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Abstract: A skin ailment known as psoriasis, which affects 2–5% of people worldwide, is characterised by excessive keratinocyte proliferation and abnormal differentiation. Calcipotriene, a synthetic vitamin D analogue, is the first-line treatment for psoriasis. It may be used in combination with methotrexate, tazarotene, acitretin, cyclosporine, and corticosteroids. It reduces the number of T cells and regulates the inflammatory response in psoriatic lesions. However, the effectiveness of pharmacotherapy based on conventional formulations for treating patients is only partially favourable. Recent developments in nanotechnology-based nanomedicines may allow us to improve the efficacy and safety of pharmacotherapeutic treatments for psoriasis. Enhancing therapeutic efficacy while lowering toxicity through overall dose reduction are two spectacular effects of using nanomedicine as a medication carrier. This novel method efficiently ensures the site-specific administration of medications throughout the skin to treat psoriatic lesions. The present manuscript aims to discuss the chemistry and pharmacology of calcipotriene, conventional pharmacotherapy and contemporary research on calcipotriene, and the combinations of it that are used as nanomedicines for the better management of psoriasis. This review primarily focuses on the nanoemulsion loaded gel of calcipotriene and clobitasol propionate as it offers high drug loading and retention in the skin, improving the local concentration of both drugs and reducing their systemic side effects. Calcipotriene and methotrexate combined in a nanostructured lipid carrier are also the most recent generation of solid lipid nanoparticles, with better drug loading, controlled release, and enhanced bioavailability.

Keywords: psoriasis; calcipotriene; nanomedicine; therapeutic; nanoemulsion

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1. Introduction

Psoriasis is a chronic autoimmune inflammatory disease, affecting 2–5% of the world's population, and is characterized by macules and plaques on the skin due to hyperproliferation and abnormal keratinocyte differentiation [1,2]. The primary clinical sign of psoriasis is an erythematous and scaly skin lesion, which is generally located in the joints (elbows, knees) and scalp, but any localization is possible. The pathogenesis of this illness reveals three key characteristics: vascular alterations, keratinocyte proliferation, and aberrant differentiation, Inflammatory cells infiltrate the skin and produce cytokines [3]. Psoriasis patients have higher rates of obesity, cardiovascular disease, non-alcoholic fatty liver disease, diabetes, and metabolic syndrome than the general population. These risks are particularly high in patients with more severe psoriasis. Its origin is currently unknown, but it seems to be triggered by a combination of genetic (family history) and environmental factors (alcohol, tobacco, infections, medications, stress). Psoriasis can be categorised into

guttate, inverted, plaque, erythrodermic, and pustular forms according to its clinical manifestations [3–5]. The first-line treatment for psoriasis is calcipotriene, also called calcipotriol, a synthetic vitamin D analogue that was invented in 1985 and given clinical approval in 1991. The rationale for the use of a vitamin D analogue in psoriasis is based on the role played by the active form of vitamin D in regulating epidermal proliferation and differentiation in normal epidermis and in modulating the immune response. Calcipotriene is the first of the vitamin D_3 analogues to find widespread application in dermatology [6].

The current breakthrough in psoriasis therapies comes from the use of innovative drug carrier systems or nanotechnology-based techniques that increase therapeutic efficacy and long-term effects [7]. Enhancing therapeutic efficacy and lowering toxicity through overall dose reduction are two excellent effects of using nanomedicine as a medication carrier. This novel method efficiently ensures the site-specific administration of medications throughout the skin to treat psoriatic lesions. Nanotechnology is one of the most promising technologies with various possibilities and great potential to contribute to innovative option treatments [8–10]. The present manuscript aims to discuss the chemistry and pharmacology of calcipotriene, conventional pharmacotherapy and contemporary research on calcipotriene, and its combinations used as nanomedicines for the better management of psoriasis.

2. Conventional Pharmacotherapy for Management for Psoriasis

The choice of psoriasis treatment is influenced by a number of variables, such as the severity of the condition, its effect on a patient's life, and the patient's perception of their illness [2]. Treatments prescribed in psoriasis are effective only to stop the disease progression. Psoriasis cannot be cured, although treatment can improve quality of life [3]. Therapeutic options for psoriasis include topical therapy, phototherapy, or systemic treatment. Topical therapy is the standard of care for treatment of mild to moderate disease. Topical psoriasis treatments include: topical corticosteroids, vitamin D analogues, anthralin, topical retinoids, calcineurin inhibitors, salicylic acid, and coal tar. Individuals with moderate to severe disease typically need systemic medications (such as cyclosporin, methotrexate, oral retinoids, and fumaric acid esters) to appropriately control their condition. Phototherapy includes exposing the skin to UV rays, which might lessen the visibility and associated itchiness of plaques. Narrowband UV-B, broadband UV-B, psoralen, and UV-A (PUVA) are the three main phototherapy modalities used to treat psoriasis [11–14].

3. Drug Profile

Calcipotriene is a synthetic 1,25-dihydroxy vitamin D analog containing a double bond and a cyclopropane ring in the side chain. The crystalline substance calcipotriene has a molecular weight of 412.6 g/mol and the chemical formula $C_{27}H_{40}O_3$. The IUPAC Name is (1R,3S,5E)-5-{2-[(1R,3aS,4Z,7aR)-1-[(2R,3E)-5-cyclopropyl-5-hydroxypent-3-en-2-yl]-7a-methyl-octahydro-1H-inden-4-ylidene]ethylidene}-4-methylidenecyclohexane-1,3-Diol [15,16]. The structure of calcipotriene is shown in Figure 1.

3.1. Mechanism of Action

Calcipotriene has been found to have similar affinity to calcitriol for the vitamin D receptor (VDR), but has less than 1% of calcitriol's activity in controlling calcium metabolism. The vitamin D receptor belongs to the steroid/thyroid receptor superfamily, and is found on the cells of many different tissues including the thyroid, bone, kidney, and T cells of the immune system. T cells are known to play a role in psoriasis, and it is thought that the binding of calcipotriene to the VDR modulates the T cells' gene transcription of cell differentiation and proliferation-related genes [15].

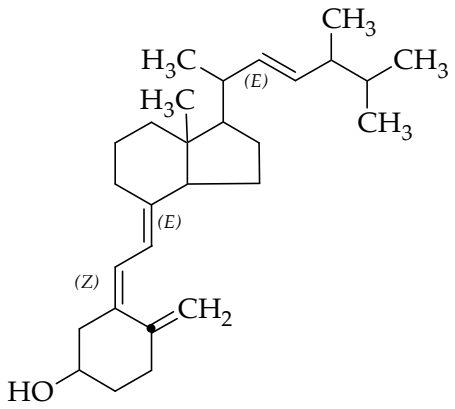

Figure 1. Structure of Calcipotriene.

3.2. Pharmacology

Calcipotriene has pharmacodynamic properties similar to those of calcitriol (1,25-dihydroxy-cholecalciferol), the active metabolite of vitamin D_3. Calcipotriene and calcitriol significantly decrease cell proliferation and improve cell differentiation in a number of in vitro models at doses ranging from roughly 10^{-10} to 10^{-6} mol/L. Both medications, for instance, increase both the quantity of human keratinocytes with cornified envelopes and the activity of the enzyme responsible for protein cross-linking in the envelopes while decreasing cell counts, total DNA content, and incorporation of radiolabelled thymidine into DNA. Calcipotriene binds to intestinal calcitriol receptors with affinity similar to that of calcitriol, but is 100 to 200 times less potent than calcitriol in its effect on in vivo calcium metabolism. Calcipotriene binds to the vitamin D receptor in a number of different cell types with the same affinity as calcitriol [17,18].

4. Combination Approach for Management of Psoriasis

Combination therapy, also known as polytherapy, is the use of several treatments or medications to treat the same ailment while ensuring that each therapeutic agent is administered at low doses and with minimal toxicity. The primary benefit of combination therapy is the potential to lower dosages of the individual agents while still achieving an additive or synergistic impact, which helps to lessen adverse effects. It is crucial that suggestions for combination therapies with the most popular forms of treatment be made in order to improve long-term illness management while lowering the dangers connected with required long-term medication. Calcipotriene may be used in combination with methotrexate, tazarotene, acitretin, cyclosporine, and corticosteroid [10,19].

5. Nano Based Drug Delivery System for Psoriasis

Nanocarriers are a class of innovative strategies with particle structure starting from roughly 1–100 nm [20] and have been considered for the treatment of skin diseases. The potential to increase the safety and efficacy of pharmacotherapeutic drugs for psoriasis has been raised by recent developments in nanotechnology-based drug delivery systems [13]. There are several different kinds of nanocarriers that are used to treat psoriasis, including liposomes, niosomes, transmitters, microspheres, micelles, dendrimers, glycosomes, solid lipid nanoparticles, ethosomes, nanoemulsion, nanocapsules, and so on. Numerous studies in recent decades have demonstrated that nanocarriers as a drug carrier can enhance the efficacy and reduce side effects of drug agents through increased skin retention and sustained drug release. Through the use of nanomedicine, nanoparticles are created to lengthen the drug's half-life, making it easier for the API to be delivered via nanocarriers to its intended action site [14]. The present manuscript primarily focuses on calcipotriene and its amalgamation's nanoscale pharmacotherapy.

5.1. Nanoemulsion

Nanoemulsions are liquid systems with a size of tens to hundreds of nanometers that are made up of water, emulsifier (co-emulsifier), and oil in the proper ratios. Nanoemulsion formulations have a high capacity for drug loading and are thermodynamically stable. They are highly helpful in many dermatological applications due to their excellent kinetic stability, low viscosity, and optical clarity. High pressure homogenization, microfluidization, sonication, the phase inversion temperature procedure, the solvent displacement method, and spontaneous emulsification are some of the techniques that can be used to prepare nanoemulsions [21].

Kaur et al. reported the development and optimization of clobitasol propionate and calcipotriol-loaded nanoemulsion-based gel for the topical treatment of psoriasis. Nanoemulsion was formed by the spontaneous emulsification method. It was reported that the developed formulation improved the local concentration of the two drugs, reducing their systemic side effects in the process of specific higher penetration of the skin layers where conventional formulations had limited skin access. Nanoemulsion shows reduction in skin irritation due to the sustained release and the controlled exposure of drugs to the skin. Drugs were reported to have increased bioavailability and anti-psoriatic effects [22].

5.2. Solid Lipid Nanoparticle (SLN)

Solid lipid nanoparticles (SLN), a unique class of nanoparticulate active substance carriers for topical application, are gaining significant attention. SLNs are lipids that are physiologically tolerated and are in the solid state at room temperature. They are in the submicron size range. They provide benefits including a huge drug integrating capacity, increased surface area, and high phase communion at the interphases. These are made by combining an emulsifier, a solid lipid, and a solvent. The risk of toxicity is reduced as they are made of physiological lipids [10,11].

Sonawane et al. prepared gel formulation containing calcipotriol and betamethasone dipropionate loaded SLNs to achieve effective treatment of psoriasis using the hot high shear homogenization method and exhibited higher in vitro and in vivo antipsoriatic efficacy [23]. According to Arora et al., solid lipid nanoparticles loaded with cyclosporine A and calcipotriol have a greater capacity for skin penetration. Incorporating these medications into solid lipid nanocarriers increased their local concentration in the skin and enabled effective psoriasis treatment [24].

5.3. Nanostructured Lipid Carriers (NLC)

NLCs are next-generation solid lipid nanoparticles that combine liquid and solid lipids to produce a disordered matrix that impedes recrystallization and provides more room for drug storage. Within NLCs system, the drug is encapsulated in the mixture of unsaturated, amorphous, or liquid lipids (oils) to the solid lipids. As a drug carrier system, NLCs provide a number of benefits, including increased stability, simplicity in preparation and scaling up, improved entrapment efficacy of hydrophilic and lipophilic drugs, increased skin occlusion, increased hydration and elasticity, improved storage stability, fewer side effects, and a longer half-life [25,26].

Lin et al. developed nanostructured lipid carriers (NLCs) loaded with lipophilic calcipotriol and hydrophilic methotrexate as topical remedy. Confocal laser scanning microscopy (CLSM) analysis revealed a strong correlation between the outcomes of in vitro and in vivo research. The local administration of antipsoriatic medications can be carried out using dual drug-loaded NLCs due to their increased drug absorption and the reduced adverse effects of both drugs [27].

6. Conclusions

Psoriasis is a prevalent skin condition that requires long-term therapy due to both its high prevalence and its significant negative effects on quality of life. Clinically recommended antipsoriatic medication only works to stop the disease's progression. Despite

the wide range of conventional therapy choices for disease management, there is a need to investigate novel emerging therapeutic approach for the management of psoriasis. The current manuscript covered the chemistry, pharmacology, and nanoscale pharmacotherapy of calcipotriene and its amalgamation. The nano-based method results in reduced adverse effects, low dose, and dosing frequency, as well as better patient compliance. The future of calcipotriene as an anti-psoriatic drug is bright. Despite the good effects of current research on the pathophysiology of psoriasis and available treatments, this condition is still very confusing and difficult to cure, necessitating intense focus and continual updating in order to develop effective psoriasis nanotherapeutics.

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