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Advances in Vesicular Drug Delivery and Insitugel Systems for the Effective Management of Psorasis: A Review

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Abstract: Keratinocyte hyperproliferation and aberrant differentiation are hallmarks of psoriasis, a long-term, immune mediated inflammatory skin condition. Achieving prolonged remission is still a clinical problem despite the availability of numerous therapy modalities because of limited drug penetration, systemic side effects, and patient non-compliance. In situ gel formulations, which provide regulated and extended release of therapies at the target location, have become a potential platform for both parenteral and non-parenteral drug delivery methods. Under physiological settings, these systems go through a sol-to-gel transition that improves patient adherence and drug bioavailability. Sphingosomes-lipid vesicles containing sphingolipids-have drawn interest as novel vesicular drug delivery methods because of their structural stability, biocompatibility, and capacity to alter inflammatory pathways and skin barrier function. The paper examines sphingosome preparation techniques and emphasizes their use in targeted distribution for the treatment of psoriasis. Additionally, by working together to target immune responses and keratinocyte dysfunction, the combination of nanomedicine and combinational therapy offers a novel way to address the multifactorial character of psoriasis. While comparative studies of commercial formulations and FDA-approved psoriasis medications shed light on recent therapeutic developments, case studies on sphingolipids clarify their role in the pathophysiology of psoriasis. All things considered, this review highlights the therapeutic potential of sphingosome-based nanocarriers and in situ gels as next-generation approaches for efficient and long-lasting psoriasis treatment.

Keywords: *Psoriasis, targeted drug delivery, sphingolipids, nanomedicine, in situ gel, sphingosomes, and vesicular drug delivery systems.*

1. Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by rapid epidermal proliferation, erythematous plaques, scaling, and compromised skin barrier function. It affects millions of individuals worldwide, significantly impairing quality of life due to its persistent, relapsing nature and associated psychosocial burden [1]. Conventional topical and systemic therapies, including corticosteroids, vitamin D analogs, retinoids, and systemic immunosuppressants, are widely employed to alleviate the symptoms of psoriasis [2]. However, these treatments often encounter limitations such as poor drug penetration through the stratum corneum, short residence time, suboptimal bioavailability, frequent dosing requirements, and undesirable systemic side effects. As a result, there has been a growing emphasis on developing advanced drug delivery strategies to enhance therapeutic outcomes while minimizing adverse effects. One promising approach involves the use of vesicular drug delivery systems, such as liposomes, ethosomes, niosomes, transferosomes, and other nanovesicular carriers [3]. These vesicles consist of lipid bilayers or surfactant assemblages capable of encapsulating hydrophilic and lipophilic drugs simultaneously, protecting labile molecules, and facilitating deeper skin penetration. Vesicular carriers can enhance drug permeability across the skin by interacting with epidermal lipids and by altering local skin structures to improve drug deposition in the dermis [4]. For example, liposomes—spherical vesicles composed of phospholipid bilayers—have been widely explored for topical delivery in dermatological disorders due to their structural similarity to biological membranes, excellent biocompatibility, and ability to carry a broad range of therapeutic agents. Studies have demonstrated that liposomal formulations can improve drug retention in psoriatic skin and enhance clinical efficacy compared to conventional formulations. In addition to liposomes, ethosomes-vesicular carriers composed of phospholipids and high concentrations of ethanol—have shown superior skin penetration by increasing lipid fluidity in the stratum corneum. Ethosomes can squeeze through narrow skin channels due to their highly flexible structure, leading to enhanced drug permeation and deeper dermal delivery compared to traditional liposomal systems. Other vesicular systems such as niosomes and transferosomes have also been investigated for psoriatic therapy, showing improved drug localization, reduced side effects, and sustained therapeutic effects due to their ability to navigate through skin barriers more efficiently than conventional topical preparations [5]. While vesicular systems effectively enhance drug delivery to psoriatic lesions, another emerging strategy is the use of in situ gel systems. In situ gels are liquid formulations that transform into a gel state upon administration in response to physiological stimuli such as temperature changes, pH shifts, ionic interactions, or solvent exchange [6]. This sol-to-gel transition prolongs drug residence time at the application site, enables sustained drug release, and reduces dosing frequency, leading to improved patient compliance and therapeutic outcomes [7,8]. In situ gels can be formulated using natural and synthetic polymers with gelation properties, such as poloxamers, gellan gum, chitosan, and hydroxypropyl methylcellulose, which allow controlled gelation and drug release kinetics

tailored to specific therapeutic needs [9]. Such systems are particularly advantageous in topical applications, where prolonged contact with psoriatic plaques is required to maximize drug absorption and modulate local inflammation effectively. The integration of vesicular carriers within in situ gel matrices, sometimes termed vesicle-in-gel systems, combines the advantages of both technologies. These hybrid systems leverage the deep penetration and protective features of vesicular carriers alongside the prolonged retention and controlled release provided by in situ gels. By entrapping vesicles within a gel network, drug diffusion can be further regulated, ensuring sustained therapeutic levels at the target site while minimizing systemic exposure. Moreover, gels can improve the physical stability of vesicles, enhance spreadability, and promote patient comfort during application—attributes especially beneficial for chronic skin conditions like psoriasis where long-term therapy is required [10,11]

Overall, recent advances in both vesicular drug delivery and in situ gel technologies offer significant potential to overcome the limitations of traditional antipsoriatic treatments. By enhancing drug penetration, prolonging site residence time, and enabling controlled release, these innovative delivery platforms hold promise for achieving better clinical outcomes with fewer side effects. Continued research and formulation optimization are critical for translating these advanced systems into effective, patient-friendly psoriasis therapies.

2. In-Situ Injectable Gels

The intriguing feature of polymeric delivery systems [12] is the capacity to regulate pharmacological ingredient release to reach desired blood levels over a predetermined period of time. This ability might be quite beneficial in some situations. For example, long-term delivery systems are frequently used to increase patient compliance with permanent medications. For persistent treatment and a variety of additional applications in people and animals, proper depot systems are required. Injectable in-situ forming depots are a type of polymeric delivery method that has the advantages of simple manufacture, even for sensitive compounds, and convenience of application as a liquid, which solidifies after application via phase separation. When made of a polymer such as poly (d,l-lactide-co-glycolide) (PLGA), the depot is biodegradable in vivo. Currently, the market has two injectable in-situ forming depots: Atridox® and Eligard®. Both devices are based on Dunn Atrigel technology. This method uses PLGA dissolved in N-methyl-2-pyrrolidinone (NMP), a water miscible solvent, with a drug powder dispersed in the solution before application [13,14]. Semi-solid drug depots that can be injected in situ are being developed as an alternate delivery mechanism. These implants are made of biodegradable products that can be injected into the body with a syringe and then solidify to form a semi-solid depot [15]. The solvent of an injectable in-situ depot system must have strong polymer solubility properties, be chemically compatible, biocompatible, and overall stable. Furthermore, an appropriate solvent for subcutaneous (s.c.) or intramuscular (i.m.) injection should cause minimum irritation to the injection site, and its metabolic products should have no negative effects on the organism. The International council for harmonisation (ICH) classification of solvents in medicinal products limits their usage to the allowed daily exposure of excepients [15]. This approach has numerous advantages over traditional ways of medicine delivery such as tablets, capsules, etc. This includes:

Injectable in-situ systems are compatible with a wide range of pharmaceutical molecules, including water-soluble and insoluble compounds, as well as high and low molecular weight substances such as peptides and proteins, vaccines, and natural products and many advantages include are given in **Figure.1,2**

A protein-based in-situ drug delivery method aids in the protection of peptide medicines. The injectable in-situ system is composed of biodegradable polymers and biocompatible solvents, so it does not require removal. In case of Economic factors microspheres must be cleansed and segregated after preparation; production costs for in-situ forming applications are minimal, cutting investment and manufacturing costs [13-15].

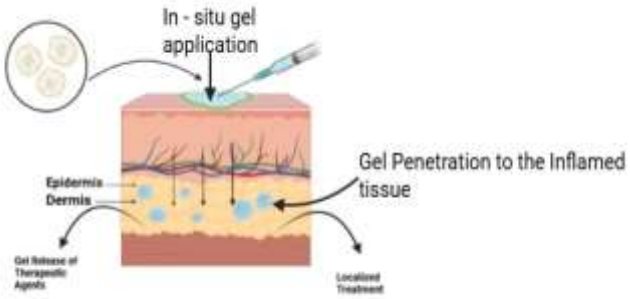


Figure 1: Illustrates increased medication concentration at the desired site of action, reducing systemic side effects.

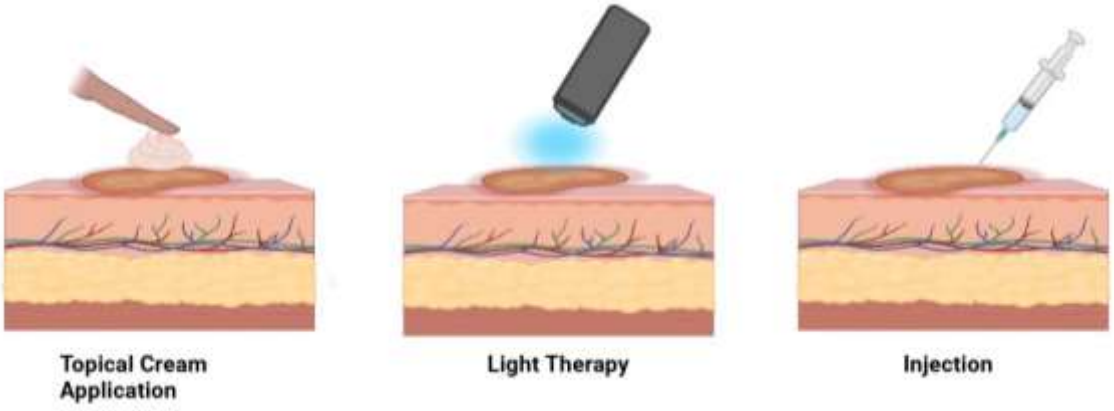


Figure 2: Shows that it is less intrusive and painful than implants, which call only a small amount of surgery and local anaesthesia.

3. NON-PARENTRAL ROUTE

Non-parenteral routes of drug administration refer to delivery methods that do not involve injections. These routes include oral, topical, transdermal, nasal, ocular, buccal, rectal, and vaginal administration. They are generally preferred due to ease of use, better patient compliance, and reduced risk of infection compared to parenteral routes. Non-parenteral systems are particularly suitable for chronic conditions requiring long-term therapy. Advanced delivery systems such as vesicular carriers and in situ gels have significantly improved drug absorption and controlled release through these routes.

3.1. Ocular formulation

The unique anatomical and physiological features of the ocular cavity, along with efficient protective mechanisms such as blinking, tear turnover, and nasolacrimal drainage, make ocular drug delivery highly challenging and often result in low therapeutic response [16]. To overcome these barriers, advanced ophthalmic formulations aim to enhance drug availability and improve therapeutic efficacy. In situ gelling systems have emerged as a promising approach, as they prolong pre-corneal residence time and maintain optimal drug concentration at the target site [16]. These systems are administered as liquids and undergo a sol-to-gel phase transition in response to environmental triggers such as temperature, tear fluid ions, and pH changes [17]. After topical administration, gel formation in the conjunctival cul-de-sac allows sustained drug release, leading to prolonged therapeutic action, reduced dosing frequency, and improved patient compliance. The polymers used in such systems are typically biocompatible, well tolerated, and often mucoadhesive in nature. Pseudoplastic behavior is desirable, as viscosity decreases with increasing shear rate, thereby minimizing discomfort during blinking [18]. In addition to liquid systems, solid in situ gelling formulations such as polymeric films [19] and electrospun nanofibers [20] have been explored for ocular therapy. These solid systems offer advantages including easier handling, better storage stability, and enhanced ocular bioavailability. Upon application, they rapidly hydrate and form a transparent gel layer illustrated in **Figure 3** that resists ocular clearance mechanisms [21].

Figure 3: The drug-resin thermosensitive in situ gelling system for ocular application is depicted in the picture

3.2. The Nasal Route

The nasal cavity has emerged as an attractive multi-site targeting route for delivering a wide range of therapeutics, from small molecules to biological macromolecules such as peptides, proteins, and vaccines [22]. It is particularly suitable for the topical treatment of local nasal and paranasal conditions including sinusitis, rhinosinusitis, allergic or infectious rhinitis, and nasal epithelial lesions [23,24]. Moreover, the highly vascularized nasal mucosa provides a non-invasive alternative for systemic drug delivery, especially for drugs with poor oral bioavailability due to first-pass metabolism or gastric degradation [24]. The nasal route also enables direct drug transport to the brain by bypassing the blood–brain barrier (BBB), facilitating rapid nose-to-brain delivery through the olfactory neuroepithelium [23,25]. Despite its advantages in accessibility, tolerability, and patient compliance, mucociliary clearance significantly reduces drug residence time in the nasal cavity, leading to rapid drug elimination [22–24]. To overcome this limitation, viscosity-enhancing strategies have been proposed to prolong nasal residence time. Nasal in situ gelling formulations offer a superior alternative to conventional nasal solutions [22]. These systems are administered as low-viscosity

polymeric solutions that undergo sol–gel transition upon exposure to physiological stimuli such as temperature, pH, or ionic strength shown in **Figure 4**. The in vivo formation of a gel network prolongs drug–mucosa contact and ensures sustained drug release [26]. Additionally, for locally acting drugs such as corticosteroids, rapid gel formation reduces mucociliary clearance and limits systemic absorption, enhancing therapeutic efficacy [27].

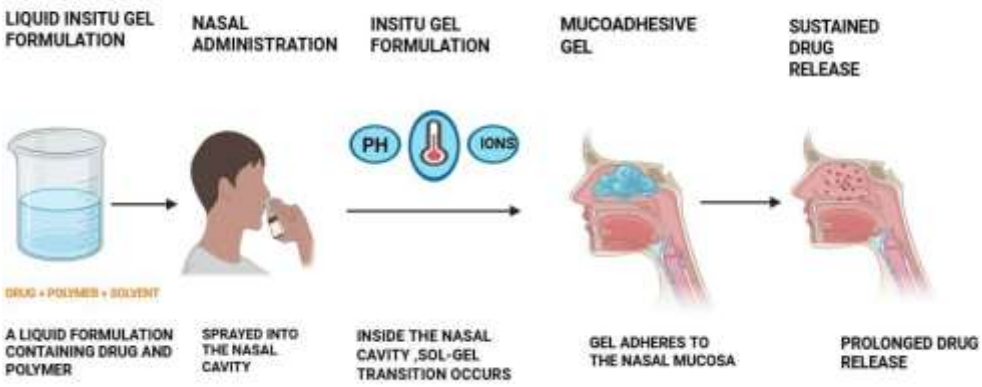


Figure 4: The image depicts nasal administration of an in-situ gel formulation containing nanocarriers, which spreads over the nasal mucosa and undergoes gelation due to physiological conditions

3.3. Buccal Route

In the past decade, in situ gelling systems in the oral cavity have gained importance, particularly for the local management of oral mucositis, offering benefits such as pain relief, modulation of inflammation, enhanced wound healing, and prevention of bacterial and fungal infections. Oral mucositis is a common and serious complication of chemotherapy and radiotherapy in patients with head and neck cancer, characterized by epithelial damage, inflammation, ulceration, pain, and bleeding. This condition significantly compromises nutritional intake, quality of life, and may even necessitate dose reduction or temporary discontinuation of anticancer therapy in severe cases [28,29]. Currently, oral rinses containing local anesthetics such as lidocaine are widely used in clinical practice; however, their analgesic effect is short-lived (less than 30 minutes) due to limited retention at the lesion site. Frequent administration may also cause generalized numbness of healthy oral tissues. Conventional formulations such as mouthwashes and polymeric gels for anti-inflammatory or antifungal therapy often fail because of rapid removal by saliva and tongue movement, resulting in reduced residence time and poor therapeutic efficacy [30]. Mucoadhesive in situ gelling systems offer a promising alternative by transforming from a liquid to a gel upon exposure to physiological stimuli such as temperature changes or divalent ions illustrated in **Figure 5**. After application, they form a protective gel layer over ulcerative lesions, reducing microbial invasion and promoting healing. Their unique composition ensures prolonged residence time and sustained drug release at the site of injury, minimizing the need for repeated dosing and improving patient compliance [31].

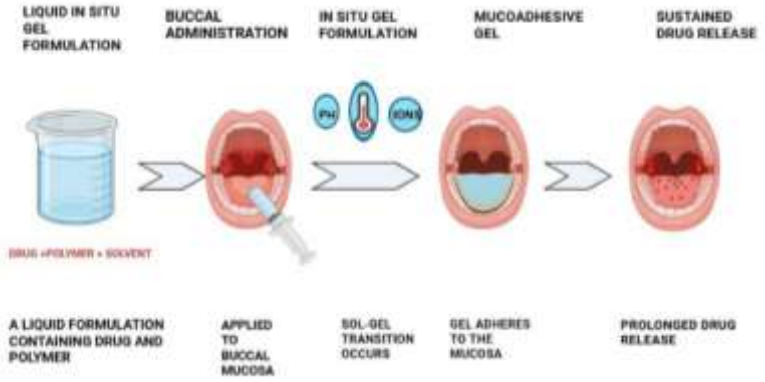


Figure 5: Illustrates the mechanism of in situ-gel based buccal drug delivery using nanocarriers

3.4. Gastrointestinal Route

In the recent decade, researchers have reported on the creation of in situ gelling formulations for local (rectal-colonic) medication administration. An increase in pH, temperature, or ion concentration caused the sol-gel transition. Several studies employed a variety of methods, leading to formulations composed of polymers that are sensitive to pH, temperature, and/or ions. We list a few notable cases below studied the ability of collagen-genipin solutions for endoscopic treatments of gastrointestinal ulcers [32]. In situ gelling ALG formulation for long-term dextromethorphan (DX) release in the gastrointestinal system. A micronized solid matrix consisting of DX and Eudragit S 100 was distributed in an ALG solution (2% w/w). The ALG vehicle was responsible for the production of a gel Shown in **Figure 6** in the presence of the gastric medium [33].

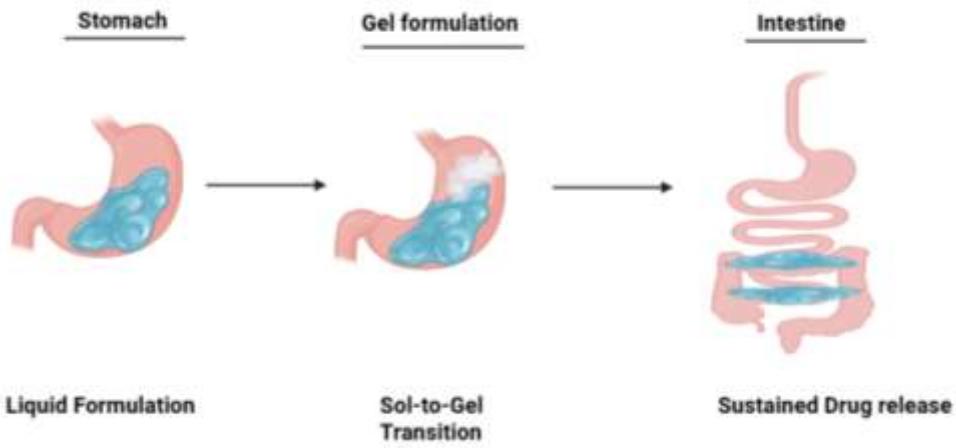


Figure 6: Illustrates an in situ- gel based buccal drug delivery system where a nanocarrier-loaded gel is applied to the inner cheek and undergoes gelation at the site

4. PSORIASIS

Psoriasis in **Figure 7** is a skin disorder in which skin cells grow ten times faster than normal, resulting in red bumpy patches with whitish scales on the head, lower back, elbows, and knees, but they can also arise elsewhere. Psoriasis is not transmitted from one person to another, however members from the same family may have it [34]. Psoriasis generally affects young adults. Psoriasis often affects only a few body locations. Large areas are impacted in extreme situations, though. Patches often heal and reappear over the course of a person's lifetime [35].

Figure 7: The image shows a psoriatic skin lesion characterized by erythematous plaques with silvery-white scales.

4.1. Causes of Psoriasis

Although the cause is unknown, scientists think it is related to a number of factors. A disruption in the immune system causes new cells to appear quickly. Typically, old skin cells are replaced with new ones. Instead of 10 to 30 days, new cells in psoriasis start to form in 3 to 4 days. When new cells take the place of old ones, silvery gray scales appear [36]. Psoriasis is normally passed on via families; however, it can also skip generations. For example, a grandparent and a grandchild may be impacted, but not the grandchild's parent [37]. Surgery, cuts or scrapes, strep infections, emotional stress, medications like lithium and other mood stabilizers, blood pressure meds, NSAIDs, and antibiotics can all lead to psoriasis breakouts [38, 39]. Every individual with this illness has a distinct set of triggers. What causes a flare-up in one sufferer might not affect another. The patient may be able to avoid the flare and symptoms if the trigger is accurately identified. Stress, cold, and dry weather all worsen psoriasis symptoms since the immune system is weakened. Additionally, nervous patients are at a higher risk of outbreak [40]. Infections like strep throat and tonsillitis can promote a psoriasis flare. The red tiny drop-like spots appear mostly on the chest and limbs. Minor scrapes, burns, and bruises might exacerbate the issue for certain people. It has also been demonstrated that HIV infection exacerbates the condition. A fresh lesion may also arise from insect bites and tattoos [41]. Heavy drinking, particularly among young men, can interfere with treatment and exacerbate symptoms. Certain psoriasis treatments might have serious side effects when used with alcohol, especially in women of reproductive age. Tobacco use or passive smoking raises the likelihood of getting psoriasis and worsens existing diseases [42]. Although psoriasis can affect people of all skin colours, it manifests differently in dark skin tones. Purplish-coloured patches with grey scales on very black skin have been observed in the African American population. On darker skin tones, brown psoriasis spots are less noticeable. His panic skin, which is slightly lighter, shows vivid pink psoriasis with silvery white scales. When psoriasis on certain skin types heals, depigmentation occurs. Patches with lighter or darker tint than the surrounding area may persist for some time. This depigmentation fades with time, typically between a few months to a year or longer, depending on severity. The dermatologist's treatment may help eliminate the areas sooner [43,44]. Genes are little fragments of DNA that act as instructions for cells. They control eye and hair colour, taste for certain foods, and other body functions. Some genes are only active during specific times of the day. A person with psoriasis has scrambled genes, which influence immune system signals. Rather than defending the body from external antigens, the genes stimulate the skin cells, causing inflammation. Researchers found that approximately 25 genes are faulty in psoriasis and pathophysiology of psoriasis is given in **Figure 8.**

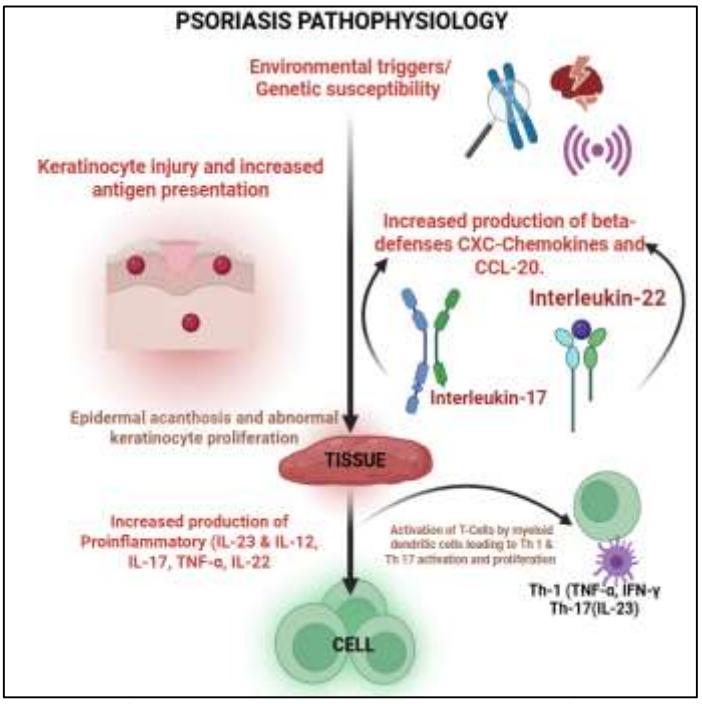
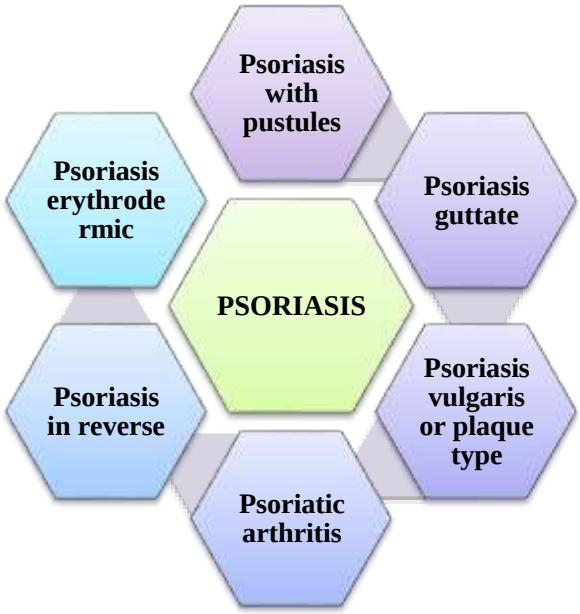


Figure 8: The picture depicts the pathophysiology of psoriasis, demonstrating how immune cells and inflammatory cytokines are activated by hereditary and environmental factors

4.2. Types of Psoriasis [45-50]



5. Systems of Vesicles:

"Vesicles have become the choice in drug delivery system called Vesicular Drug Delivery System." For instance, pharmacosomes, niosomes, and liposomes [51,52]. When specific amphiphilic building blocks are exposed to water, a highly ordered assembly of concentric lipid bilayers known as the vesicular system is created. The origin of biological vesicles was first described by Bingham in 1965. Conventional chemotherapy for intracellular infections is ineffective due to limited drug absorption into cells. To improve bioavailability at the site of illnesses decreases adverse side effects of traditional and controlled release drug delivery methods, overcomes the problem of drug degradation and/or drug dose [57].

5.1. Advantages:

- Prolongs the drug's presence in systemic circulation and may lessen toxicity if selective absorption is achieved by delivering the drug straight to the site of action.
- Delays clearance of rapidly digested medicines, therefore functioning as sustained release systems [53].
- Reduces the expense of therapy [54, 55].
- Drugs with hydrophilic and lipophilic properties can be added
- Delayed elimination of quickly metabolized medicines

5.2. Disadvantages:

- Drugs passively, which may result in limited drug loading efficiency and drug leakage during preparation, preservation, and transport in vivo.
- The need for intense sonication causes medication leakages during storage [56].

5.3. **Types of Vesicular DDS:**

The targeted vesicles are characterized according to their composition [58]. There are two types of biocarriers: lipoidal and non-lipoidal.

a. Lipoidal biocarriers
- Liposomes, Emulosomes, Enzymosomes, Sphingosomes, Ethosomes, Transferosomes, Pharmacosomes, Virosomes

b. Non-lipoidal biocarriers
- Niosomes, Bilosomes, Aquasomes [59]

5.3.1. **LIPOSOMES:**

Liposomes are small, concentric bilayer vesicles that can load strong drugs together with phospholipids to target drugs. When phospholipids are disseminated in aqueous solution, they rapidly form multi-lamellar concentric bilayer vesicles with diameters ranging from 0.05 to 5.0 μm. Another name for it is a colloidal barrier or microparticulate barrier [60].

5.3.2. **NIOSOMES:**

The fundamental goal of developing niosomes is to solve challenges related to sterilization, large-scale production, and stability. Niosomes are thermodynamically vesicles comparable to liposomes, with minuscule size ranges on a nanometric scale, making them excellent for transdermal distribution. It is made up of hydrated cholesterol compounds, charge-inducing chemicals, and nonionic surfactants such as monoalkyl and dialkyl polyoxyethylene ether, which are mostly utilized as transporters for lipophilic and amphiphilic medicines. It delivers the medication to the intended place while minimizing side effects and toxicity. Surfactants form lipid bilayers when they interact with watery environments [61,62].

5.3.3. **AQUASOMES:**

It is a self-assembling system composed of triple-layered particles with a huge surface area. It is also known as "Bodies of Water" and serves as a protein and peptide transporter. These are spherical in shape, with a diameter of 60–300 nm. Aquasomes ensure molecular confirmation and maximum pharmaceutical activity. It delivers the medicine to a specific target spot through molecular shielding and a prolonged release mechanism. It comprises of a ceramic core that is surrounded by polyhydroxy oligomers, and the active medication is entrapped in the coating by absorption via ionic and non-covalent interactions [63].

5.3.4. TRANSFERSOMES:

These are employed in targeted controlled drug delivery systems that are extremely flexible and have deformable vesicles smaller than 300 nm. It can pass through a pore into the deeper epidermal layers (Stratum corneum to stratum bacile) and subsequently

enter the systemic circulation for possible medication administration. It contains buffer solution, color, a little amount of alcohol, surfactant, and soya phosphotidyl choline. Surfactant works as an edge activator, increasing permeability throughout the skin [64].

5.3.5. INVASOMES:

It is a neutrally charged liposomal vesicle that can transfer both hydrophilic and lipophilic medicines to deeper layers of the epidermis and perform its action [65]. They are excellent potential carriers for transdermal skin delivery. It is constituted of modest amounts of ethanol, terpene or terpene combinations (1-5%) and phosphotidyl choline. As the quantity of terpene in the composition grows, the vesicle size and membrane flexibility increase [66,67].

5.3.6. PHYTOSOMES:

Phytosomes, a form of herbosome, are mostly constituted of phytoconstituents (neutraceuticals like flavonoids and terpenoids) and range in size from 500 nm to 100µm. It is a lipid-based compound that improves the bioavailability, solubility, and absorption of water-soluble phytoconstituents. It is made up of aprotic solvent, phytoconstituents, and phosphotidylcholine. It has the ability to carry anti-ageing agents as well as non-pathogenic diseases. Phytosomal formulation enhances antioxidant properties and protects the cardiovascular system from oxygen residues, preventing ischemic heart disease [68].

5.3.7. ENZYMOSOMES:

Enzymosomes are enzymes that are enclosed in liposomal vesicles and attached by covalent bond/coupled creation. These vesicles are used to treat tumor cells by delivering targeted drugs. This formulation may enhance the anticancer activity of medicines. Enzymes encased in liposomal vesicles include β-lactanase, β-glucosidase, carboxypeptidase, and alkaline phosphate [69,70].

5.3.8. ETHOSOMES:

Ethosomes are lipoidal vesicles that contain high concentrations of ethanol. Ethosomes are sometimes called ethanolic liposomes. It is a soft, innovative vesicular carrier for transdermal drug distribution over deeper layers of skin using a controlled release mechanism. It is made up of water, cholesterol, color, polyglycol, ethanol (20-50%), vehicle, and phospholipid. A high quantity of ethanol increases the capacity of medication penetration through the skin [71].

5.3.9. ELECTROSOMES:

A cutting-edge surface display technology is electrosomes. The protein is transmembrane. It generates and spreads electrical impulses that are useful for environmental sensing. Through fuel oxidation, a series of redox enzymes interact with scaffolding to produce numerous releases. It consists of an oxygen-reducing enzyme that attaches to several copies of cohesion-bearing scaffolding as a hybrid cathode and a dockerin-containing enzyme that binds to the cohesive sites of scaffolding to construct the ethanol oxidation cascade as a hybrid anode [72].

5.3.10. PHARMACOSOMES:

Pharmacosomes are innovative vesicular drug delivery devices that offer distinct benefits over other drug delivery systems[72]. Pharmacosomes are amphiphilic lipoidal colloidal dispersions of pharmaceuticals that are covalently bonded to lipids and have the potential to improve the bioavailability of poorly water soluble and lipophilic medications [73]. Any medication having a free carboxyl group or an active hydrogen atom (-OH, -NH2) can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, resulting in an amphiphilic prodrug. When an amphiphilic prodrug is diluted with water, it converts into pharmacosomes. The prodrug combines hydrophilic and lipophilic qualities (gaining amphiphilic features), decreases interfacial tension, and, at higher concentrations, exhibits mesomorphic behavior. Because of a decrease in interfacial tension, the contact area rises, and hence bioavailability increases [72].

5.3.11. VIROSOMES:

Virosomes are reconstituted viral envelopes made of a lipid bilayer that can contain viral glycoproteins generated from several enveloped viruses. Virosomes are liposomes containing influenza virus hemagglutinin (HA) and neuraminidase (NA) spikes on their surface. Virosomes are quite similar to complete viruses, with the exception that they lack viral reproduction machinery. They retain the virus-derived features of cell entrance and membrane fusion. The two methods by which reconstituted vesicles can enter cells and distribute their contents to the cytoplasm are plasma membrane fusion (Sendai virus) and acid-induced fusion from within endosomes (Influenzavirus). As a result, foreign chemicals enclosed in virosome lumens are successfully delivered to target cells' cytosols.Virosomes can be utilized in vaccination to efficiently induce antibody responses against the virus [74].

5.3.12. EMULSOMES:

Emulsomes is a lipid-based drug delivery method, specifically intended for parenteral delivery of medicines with low aqueous solubility [75]. The internal core of emulsomes is composed of fats and triglycerides that are stabilized in the form of an oil-in-water emulsion by the addition of a high concentration of lecithin. Emulsomes combine the features of liposomes with emulsions. Because of the solidified or semi solidified internal oily core, it provides a better opportunity to load lipophilic drugs in high concentration, simultaneously a controlled release can be expected, and these also have the ability to encapsulate water-soluble medicaments in aqueous compartments of surrounding phospholipid layers [74].

5.3.13. SPHINGOSOMES:

Liposomes have stability difficulties such as oxidation, hydrolysis, degradation, leaching, sedimentation, and drug aggregation. As a result, in order to improve their stability, researchers developed Sphingosomes [76,77]. They are concentric, bilayered vesicles made up of an aqueous core surrounded by a membranous lipid bilayer is given in **Figure 9**, primarily consisting of natural or synthesized sphingolipid. Sphingosomes are made up of sphingolipids and cholesterol, and the inside aqueous environment has a lower pH than the exterior [78]. Sphingosomes are an essential targeted lipid vesicular drug delivery

mechanism. Sphingosomes comprise a membranous lipid bilayer that encloses an aqueous area within which the medicine can be contained. Sphingosomes alleviate the shortcomings of liposomes and niosomes by being very stable to acid hydrolysis and having better drug retention capabilities. Sphingosomes can be delivered into the body through a variety of routes, including parenteral, inhalation, oral, and transdermal. Sphingosomes are made up of sphingolipid, which is primarily composed of amide and ester linkages [79,80].

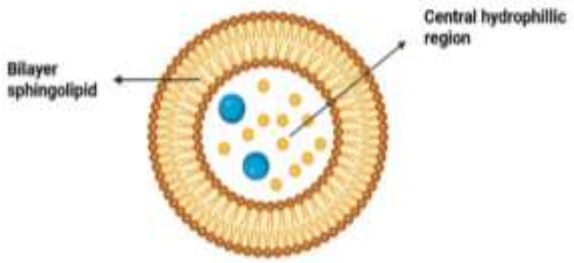


Figure 9: The image illustrates sphingosomes, spherical lipid vesicles composed of a sphingolipid bilayer enclosing an aqueous core

Sphingosomes is more stable than the liposome because of the following reason, it consists only of amide and ether linkages, which are more resistant to hydrolysis than lecithin's ester linkages. They also include fewer double bonds than lecithin, making them less susceptible to rancidity. Sphingosomes absorb less oil than lecithin, and as a result, their geometry and diameter alter.

5.4. CLASSIFICATION:

Sphingosomes are characterized according to the number of lipid bilayers generated and the size of the vesicle. Sphingosomes had an average diameter of 0.05-0.45µm. The optimal diameter range was 0.05-0.2µ.

- Small unilamellar vesicles (SUV): These vesicles are made up of a single lipid bilayer with a diameter of 10 nm to 100 nm
- Large unilamellar vesicles (LUV): LUVs have a larger diameter than SUVs and are made up of a single lipid bilayer. It has a size range of 100 nanometers to one metre.
- Multilamellar vesicles (MLV): These vesicles are made up of many lipid bilayers and vary in size from 100 nm to 20 µm
- Oligolamellar vesicles (OLV): OLVs have more than one bilayer but fewer than MLVs. With a size range of 0.1 µm to 1 µm.
- Vesicles above 1µm are called as Giant vesicles (GV): GVs are vesicles that are longer than 1 µm [81,76].

5.5. Composition Of Sphingosomes:

Sphingosomes are vesicular systems composed mainly of sphingolipids (sphingomyelin) and cholesterol, typically formulated at an acidic intraliposomal pH with sphingomyelin: cholesterol ratios ranging from 75:25 mol% to 55:45 mol%, the latter being considered optimal [78]. Sphingolipids are essential membrane components consisting of a hydrophobic backbone and a polar head group, biosynthesized from acyl-CoA and serine to form ceramides and other complex lipid species [82]. Cholesterol plays a crucial role in sphingosome formation by modulating bilayer structure and stability. The incorporation of sterols significantly alters the organization of the sphingosomal bilayer membrane. In sphingosomes, cholesterol and sphingolipids are commonly combined in ratios of 1:1 or 2:1, which increases spacing between choline groups and disrupts typical electrostatic and hydrogen bonding interactions [83].

6. METHODS OF PREPARATION OF SPHINGOSOMES:

Different methods used in the preparation are Lipid hydration method, French pressure call method, Solvent spherule method, Calcium –induced fusion method, Sonication method and solvent injection method.

6.1. LIPID FILM FORMATION [HAND SHAKING METHOD]:

Sphingolipids, surfactant/cholesterol, and lipophilic drug were combined and dissolved in an organic solvent (ether) contained in the R.B flask. A rotating flim evaporator is used to extract organic solvents under decreased pressure. The surfactant that has been dried or lipid casted is then hydrated with an aqueous phase at 50-60°C. On hydration, the dried lipid layer swells and detaches from the inner surface of the RB flask, forming multilamellar sphingosomal vesicles. Non-shaking approach in **Figure 10** is also

used to obtain large unilamellar sphingosomal vesicles, in which the film is subjected to a stream of N_2 gas for 15 minutes, followed by expansion of lipid layer in aqueous media without shaking [83,84].

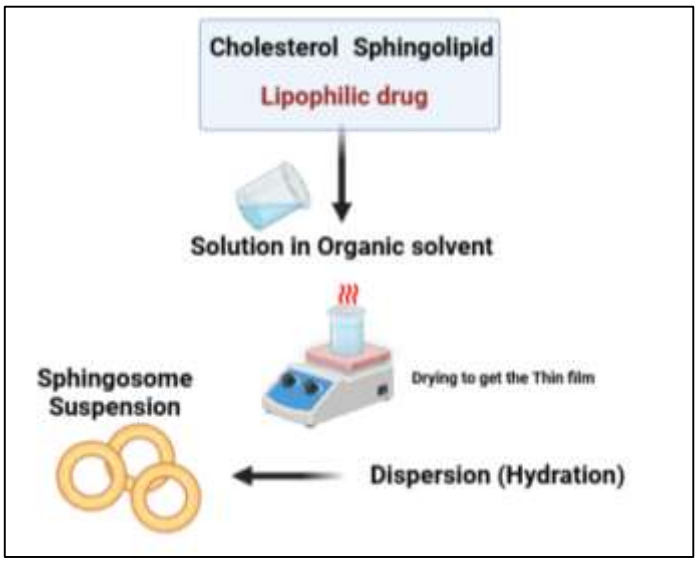


Figure 10: The image depicts the steps involved in the lipid film hydration method for the preparation of sphingosomes

6.2. SONICATION METHOD:

In **Figure 11** Sonication is the most often used method for creating tiny vesicles. Sphingosomes shrink even more when exposed to high quantities of energy. The multilamellar sphingosomal vesicles are subjected to ultrasonic irradiation, which causes the production of tiny vesicles. There are two types of sonication methods: bath and probe-based. The most extensively utilized is the ultrasonic disintegration bath sonicator [85].

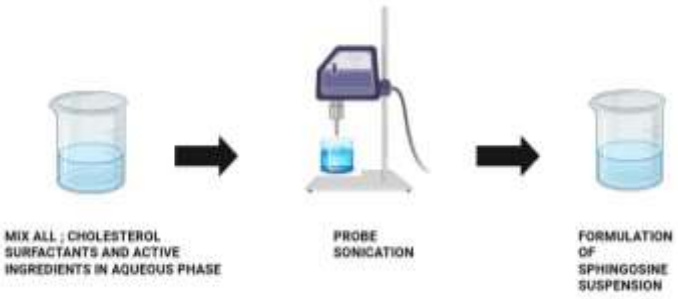


Figure 11: The image shows the hydration of the film followed by sonication produce multilamellar vesicles and small unilamellar sphingosomes

6.3. SOLVENT SPHERULE METHOD:

In solvent spherules, is given in **Figure12** the sphingolipids are dissolved in a volatile hydrophilic solvent which is then dispersed as small spheres in to an aqueous solutions. When the volatile hydrophilic organic solvent is evaporated in water bath under controlled conditions multi lamellar vesicles are formed [86,87].

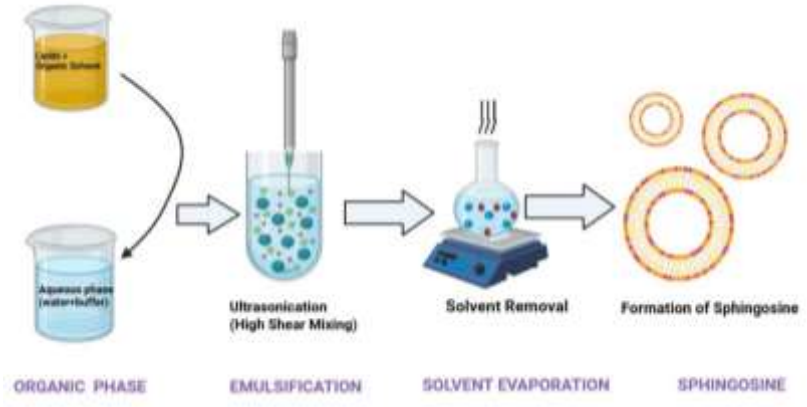


Figure 12: The image illustrates the solvent spherule method for the preparation sphingosomes using sphingolipid and cholesterol

6.4. CALCIUM INDUCED FUSION METHOD:

Multilamellar vesicles form and, when calcium is introduced is given in **Figure 13**, fuse with SUV sphingosomes. Multilamellar sphingosome vesicles can then be converted into massive unilamellar sphingosomes by adding EDTA. Macromolecules are encapsulated using this method [88].

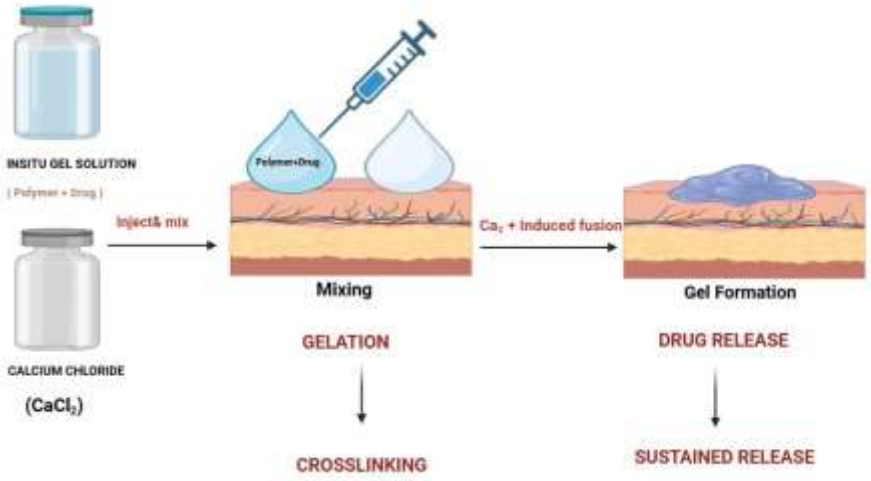


Figure 13: Sphingosome core liposomes and plain liposomes are used in the calcium-induced fusion procedure to prepare sphingosomes.

6.5. **FRENCH PRESSURE CELL METHOD**:

The French pressure cell method in **Figure 14**, yields more stable mono or oligolamellar sphingosomes than sonicated vesicles. This procedure is carried out under extremely high pressure using a French press. Here, performed sphingosomes are extruded [89].

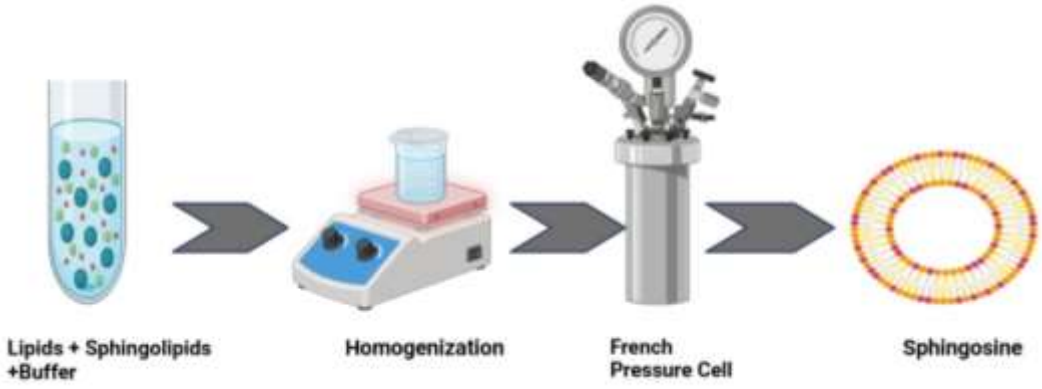


Figure 14: The image depicts the French pressure cell method for the preparation of sphingosomes using sphingosome core liposomes and plain liposomes

6.6. SOLVENT INJECTION METHODS:

The solvent injection methods involve dissolving the sphingolipid in an organic phase (ethanol or ether), followed by injecting the sphingolipid solution into aqueous medium, creating sphingosomes [90].

6.6.1. ETHER INFUSION METHOD:

The ether injection method varies from the ethanol injection method in that the ether is immiscible with the aqueous phase, which is heated to remove the solvent from the sphingosomal product. The procedure entails injecting ether-sphingolipid solutions into warmed aqueous phases above the boiling point of the ether. The ether evaporates when it comes into contact with the aqueous phase, and the dispersed shingolipid primarily forms unilamellar sphingosomes. A concentrated shingosomal product with high entrapment efficiencies is produced by the ether injection method, which has an advantage over the ethanol injection approach in that it eliminates the solvent from the product, enabling the process to run for longer periods of time [90,91,92].

6.6.2. ETHANOL INJECTION METHOD:

The main significance of the ethanol injection method is given **Figure 15** in the observation that a narrow distribution of small sphingosomes (under 100 nm) can be generated by simply injecting an ethanolic sphingolipid solution in water in one step, without extrusion or sonication [90,93].

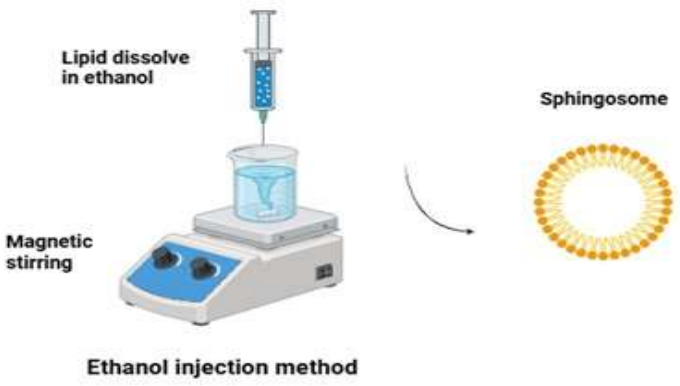


Figure 15: The image illustrates the ethanol injection method, where a syringe injects an ethanol-based sphingolipid solution into an aqueous medium contained in a flask

7. Roles of Nanomedicines with Inclusion of Combinational Therapy for Treating Psoriasis

Nanomedicines play a significant role in psoriasis management by enhancing targeted drug delivery, improving skin penetration, and reducing systemic side effects. Nanocarriers such as liposomes, ethosomes, solid lipid nanoparticles, and polymeric nanoparticles enable controlled and sustained release of antipsoriatic agents at the lesion site. These systems improve drug stability and bioavailability while minimizing irritation and toxicity. Incorporation of combinational therapy within nanomedicine platforms allows the co-delivery of anti-inflammatory, immunomodulatory, and antiproliferative agents for synergistic therapeutic effects. Such advanced strategies enhance clinical efficacy, reduce dosing frequency, and improve patient compliance in chronic psoriasis management.

7.1. Nanomedicines in Psoriasis

The epidermis and dermis are more hydrophilic than the stratum corneum. This is why it is difficult to create a formulation that can penetrate across the various skin layers. Nano-carriers like as liposomes, micelles, nanoparticles, and nano-colloidal silica can be utilized to do this, with gelling agents added for better skin retention. They improve medication availability when given topically, resulting in a higher therapeutic impact, thanks to their tiny size, which increases the surface area of exposure. Entrapping drugs in nanocarriers can alter the hydrophilic and lipophilic balance of drugs with relatively high or low partition coefficients, increasing permeability across the stratum corneum and allowing drug penetration through the thick outer barrier in psoriatic skin to reach viable areas where immune responses should be controlled. Drugs with limited stability or high molecular weight, such as immunosuppressants, biologics, or gene therapy, as well as those with low solubility or high hydrophilicity, can be encapsulated in nanocarriers to increase overall percutaneous absorption. Nanocarriers' bulk and surface properties can be changed to improve therapeutic targeting and increase drug molecule accumulation at lesion locations. All of these improved qualities brought about by the use of nanocarriers can lead to a further reduction in dose, dosing frequency, dose-dependency, and controlled drug release from such systems, resulting in better therapeutic outcomes while minimizing undesired side effects.
Several reviews have already discussed the use of drug delivery and nano-based systems to administer medications for psoriasis [94]. However, there is no emphasis on contemporary combinational therapy in nano-based delivery systems. The type of vehicle used to deliver a medicine can impact the drug's penetration on the psoriatic skin, increasing or decreasing its therapeutic effect. In the field of nanomedicine, nanocarriers are classed according to the matrix components utilized to build them, which can be organic materials such as lipids or polymers or inorganic materials that can be sourced natively or chemically produced. Lipid-based carriers are classified into vesicular or particulate systems, which include liposomes, solid lipid nanoparticles, nanostructured lipid carriers or lipospheres, and emulsion-based systems [95].

8. Case Studies

8.1. Altered Ceramide Composition and Barrier Dysfunction

Psoriatic epidermis exhibits significant alterations in ceramide subclasses, including increased very long-chain (VLC) ceramides and CER[NS], along with decreased ultra-long-chain (ULC) ceramides and phytosphingosine-containing ceramides such as Cer[NP], Cer[AP], and acylceramides. These changes impair stratum corneum integrity and increase transepidermal water loss (TEWL) [96]. Reduced expression of ceramide synthases (CERS), elongases (ELOVLs), prosaposin, and glucosylceramide-glucosidase further compromises ceramide maturation and correlates with elevated inflammatory cytokines (IL-6, IL-8) in psoriatic lesions [97].

8.2. Fatty Acid Imbalance and Lipidomic Alterations

Lipidomic profiling in psoriasis and psoriatic arthritis (PsA) reveals altered ApoB/ApoA1 ratios, increased saturated fatty acids (SFA), and reduced polyunsaturated fatty acids (PUFA), contributing to systemic inflammation [98–100]. Interferon-mediated downregulation of ELOVL1 and CERS3 promotes keratinocyte hyperproliferation [101,102]. Additionally, dysregulated PLA2G4B expression and siRNA-based targeting strategies highlight the role of lipid metabolism in Th17-mediated immune activation [101].

8.3 Dermokine Deficiency and Moisturizer-Based Interventions

Dermokine (DMKN) deficiency reduces acylceramide levels, impairing barrier formation and enhancing inflammatory susceptibility [103]. Clinical studies demonstrate that ceramide-containing moisturizers significantly reduce TEWL and improve psoriatic symptoms, reinforcing the therapeutic importance of lipid restoration [104].

8.4 Ceramide Subclass Distribution and Enzymatic Dysregulation

Studies report decreased levels of Cer 1, 3, 4, 5II, and 6I with increased Cer 2I, 2II, and 5I in psoriatic plaques, directly correlating with disease severity [105]. Reduced sphingomyelinase activity and disrupted lipid ratios further impair epidermal differentiation and barrier homeostasis [106-108].

8.5 Caveolin-1 and Sphingomyelin Cycle in Keratinocyte Regulation

Caveolin-1 (Cav1), a sphingomyelin- and cholesterol-rich membrane protein involved in endocytosis and keratinocyte differentiation, is significantly downregulated in psoriatic lesions, contributing to epidermal hyperplasia [109]. Activation of the sphingomyelin (SM) cycle by TNF and vitamin D analogs such as calcipotriol influences ceramide-mediated signaling and regulates keratinocyte proliferation [110].

8.6 Metabolic Regulators and Immune–Lipid Interactions

Key metabolic regulators including GLUT1, glucosylceramide synthase, DGAT2, and serine palmitoyltransferase (SPT) are altered in psoriasis, affecting ceramide biosynthesis and immune activation through CD1d-mediated iNKT cell pathways [111–115]. Reduced SPT levels strongly correlate with PASI scores, emphasizing the link between ceramide depletion and disease severity [116].

9. Marketed formulation/ FDA Approved drugs

S. No	Drug / Formulation	Class / Composition	Target Disease / Indication	Route	Application / Remarks	Ref
1	Vincristine (Oncovin®, Marqibo®)	Sphingosome formulation	Lymphoblastic leukemia	IV	Cancer therapy	[117]
2	Vinorelbine (Navelbine®)	Sphingosome formulation	Lung cancer	IV	Cancer therapy	
3	Topotecan (Hycamtin®)	Sphingosome formulation	Lung & ovarian cancer	IV	Cancer therapy	
4	Prostaglandins, Amphotericin B, Methotrexate, Cisplatin, Vinblastine, Doxorubicin, Ciprofloxacin, Steroids	Sphingosome-based carriers	Proliferative & immune disorders	Various	Drug delivery vehicle	
5	Beclomethasone (Sphingosome Moist®)	Sphingosome topical system	Dermal therapy	Topical	Cosmetic & skin therapy	
6	Idoxuridine	Sphingosome ocular system	Herpetic keratitis	Ocular	Enhanced ocular penetration	
7	Streptokinase, Urokinase	Enzyme-loaded sphingosomes	Enzyme deficiency conditions	Parenteral	Enzyme delivery	
8	5-Fluorouracil + Sphingomyelin; Swainsonine + Interferon	Sphingosome combination	Colon cancer, melanoma	Parenteral	Tumor therapy	
9	Sphingosine-1-phosphate	Lipid mediator system	Radiation-induced lung injury	—	Gene therapy applications	

S. No	Drug / Formulation	Class / Composition	Target Disease / Indication	Route	Application / Remarks	Ref
10	Ceramides	Bioactive sphingolipids	Radiation-induced lung injury	—	Regulation of S1P pathway	
11	Sphingosine & Sphinganine	Free sphingolipids	Infectious diseases	Topical	Antifungal therapy	
12	Sphingosine-1-phosphate & Ceramides	Immunomodulatory lipids	Immune disorders	—	Immune response regulation	
13	Deucravacitinib	TYK2 inhibitor	Psoriasis	Oral	FDA-approved therapy	[118]
14	Roflumilast	PDE-4 inhibitor	Psoriasis	Topical	FDA-approved therapy	
15	Tapinarof	AhR modulator	Psoriasis	Topical	FDA-approved therapy	
16	Risankizumab-rzaa	IL-23 antagonist	Psoriasis	Subcutaneous	FDA-approved biologic	
17	Certolizumab pegol	TNF blocker	Psoriasis	Subcutaneous	FDA-approved biologic	
18	Tildrakizumab-asmn	IL-23 antagonist	Psoriasis	Subcutaneous	FDA-approved biologic	
19	Guselkumab	IL-23 antagonist	Psoriasis	Subcutaneous	FDA-approved biologic	
20	Brodalumab	IL-17 antagonist	Psoriasis	Subcutaneous	FDA-approved biologic	
21	Ixekizumab, Secukinumab	IL-17 antagonists	Psoriasis	Subcutaneous	FDA-approved biologics	
22	Apremilast	PDE-4 inhibitor	Psoriasis	Oral	FDA-approved systemic therapy	
23	Ustekinumab	IL-12/23 antagonist	Psoriasis	Subcutaneous	FDA-approved biologic	
24	Adalimumab	TNF blocker	Psoriasis	Subcutaneous	FDA-approved biologic	
25	Infliximab	TNF blocker	Psoriasis	IV infusion	FDA-approved biologic	
26	Etanercept	TNF blocker	Psoriasis	Subcutaneous	FDA-approved biologic	

10. CONCLUSION:

Psoriasis remains a complex, immune-mediated dermatological disorder that necessitates innovative and targeted therapeutic strategies beyond conventional treatments. The integration of nanocarrier-based vesicular systems with in situ gel technology offers a promising platform for localized, sustained, and efficient drug delivery. Among these, sphingosomes have emerged as a superior vesicular drug delivery system due to their structural stability, enhanced drug encapsulation efficiency, and improved skin penetration. Their composition, based on sphingomyelin and cholesterol, closely mimics biological membranes, thereby enhancing biocompatibility and therapeutic performance. When incorporated into in situ gel formulations, sphingosomes provide prolonged residence time at psoriatic lesions and controlled drug release. This combination minimizes systemic exposure while maximizing

local drug concentration, thereby reducing adverse effects. Furthermore, sphingosomal systems can be effectively integrated with combinational therapy to simultaneously target inflammatory pathways and keratinocyte hyperproliferation. The sustained and targeted delivery achieved through sphingosome-loaded in situ gels improves bioavailability and patient compliance. Emerging research and advanced formulation strategies further support their potential in topical psoriasis management. Overall, sphingosome-based vesicular drug delivery incorporated into in situ gel systems represents a highly promising and rational approach for next-generation psoriasis therapy.

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