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ADVANCEMENTS IN NOVEL DRUG DELIVERY SYSTEMS FOR PSORIASIS MANAGEMENT: A COMPREHENSIVE REVIEW

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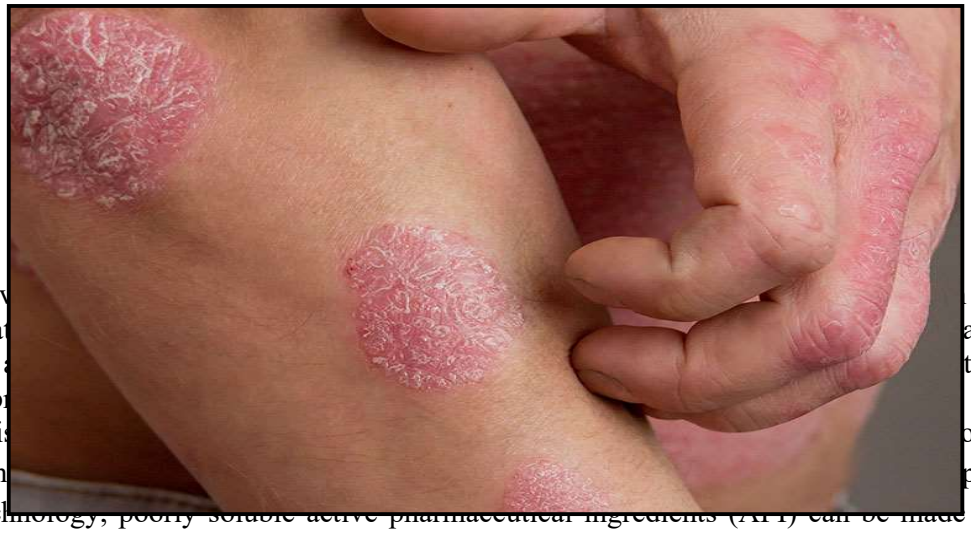
ABSTRACT

Psoriasis, a chronic autoimmune skin condition, presents significant challenges in management due to its complex pathology and persistent nature. Traditional systemic and topical treatments often result in limited efficacy and undesirable side effects. Recent advancements in novel drug delivery systems (NDDS) offer promising alternatives by enhancing drug bioavailability, targeting affected tissues, and minimizing adverse effects. This review explores cutting-edge NDDS technologies, including nanocarriers like liposomes, nanoparticles, and niosomes; transdermal systems; and microneedle-based approaches. These strategies improve therapeutic outcomes by optimizing drug release profiles and site-specific delivery. Emphasis is placed on biodegradable polymers, hydrogels, and stimuli-responsive systems that offer controlled release and reduced systemic exposure. The integration of NDDS with biologics, such as monoclonal antibodies and small-molecule inhibitors, also holds potential to revolutionize psoriasis management. Future research directions include clinical validation and addressing scalability challenges for widespread adoption. NDDS represent a paradigm shift in psoriasis therapy, addressing unmet needs and improving patient quality of life.

Keywords: Psoriasis, Novel drug delivery systems, Transdermal system, Targeted therapy, Liposomes

1. INTRODUCTION TO PSORIASIS AND CURRENT TREATMENT CHALLENGES

Systemic inflammatory disorder is another common term for psoriasis, an immune-mediated inflammatory dermatological disease. The quick accumulation of skin cells that results in erythematous (red) papules and plaques with silver scales is a sign of psoriasis (figure 1). The skin is irritated and occasionally painful due to the red, scaly plaques. Psoriasis lesions can appear on any area of the skin, including the hands, feet, scalp, neck, and face. They usually occur on joints like the elbows and knees. The abnormal connections between T cells, keratinocytes, and innate immune cells cause the inflammation. However, because psoriasis impacts both the innate and adaptive immune systems, it cannot spread. A chronic inflammatory skin condition that impacts the immune system is psoriasis. The epidermal thickening is brought on by aberrant interactions between T cells, immune cells, and inflammatory cytokines. According to international guidelines, systemic and phototherapy therapies are recommended for moderate to severe psoriasis, whereas topical drugs are recommended for mild to moderate psoriasis. Nonetheless, with the advent of many biologic medicines, treatment options for moderate to severe cases of psoriasis are now more extensive. Meanwhile, numerous unpleasant side effects have permeated through the skin as a result of the topical administration of conventional treatments (stratum corneum). Scientists have created a variety of novel drug delivery systems, including solid lipid nanoparticles, nanostructured lipid carriers, nanovesicles, and nanoemulsions, by comprehending the physiology of stratum corneum barrier activities. The capacity of these advance novel drug delivery systems to deliver the poorly soluble active pharmaceutical ingredient to the intended place is made possible by the nanosized molecules bioavailability. Because lipids are amphiphilic, they can easily encapsulate both hydrophilic and lipophilic medicines. This attribute makes nanoparticles for psoriasis therapies a paradigm for topical drug delivery[1].



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nanotechnology, poorly soluble active pharmaceutical ingredients (API) can be made more bioavailable and physicochemically stable. Low pharmacokinetic profiles, lack of stability and solubility, or restricted dosage toxicity are assumed to be characteristics of inefficient APIs. Therefore, these limitations can be addressed and the therapeutic effects enhanced by utilising advance novel drug delivery methods. Preclinical and clinical investigations have demonstrated that the use of nanoparticles can minimise the negative effects of drugs at highly regulated drug delivery with appropriate therapeutic doses. By extending the drug's half-life through the use of nanomedicine, nanoparticles help carry the active pharmaceutical ingredient (API) to the

intended action site more easily via nanocarriers. Nanosized particles, also referred to as nanocarriers or nano-based drug delivery, increase the therapeutic efficacy of APIs and lessen their side effects. Their broad surface area for carrying the API is the primary cause of this. Drug delivery methods called nanocarriers are used to control the pharmacokinetics and pharmacodynamics of the target drug. Because topical nanocarriers offer improved skin penetration and regulated release at a lower dose regimen, their usage for treating skin ailments has gained significant traction recently[3].

- **Pathophysiology of Psoriasis**

The complicated pathophysiology of psoriasis includes skin inflammation and immunologic alterations, abnormal epidermal keratinocyte differentiation, and hyperproliferation of epidermal cells. Hyperproliferation is characterised by a markedly reduced epidermal turnover rate and increased DNA synthesis (figure 2). Abnormal keratinocyte differentiation is indicated by delayed expression of certain keratins and increased expression of others that are expressed in normally differentiating skin. Inflammation is caused by T lymphocytes entering the dermis, mainly CD8+ cells, and neutrophils in the epidermis and superficial dermis [4].

As psoriatic inflammation amplifiers, keratinocytes not only participate in the start phase but also aid in the maintenance phase. High-proliferating keratinocytes can generate large quantities of chemokines (e.g., CXCL1/2/3, CXCL8, CXCL9/10/11, CCL2, and CCL20) to attract leukocytes (e.g., neutrophils, Th17 cells, dendritic cells, and macrophages), antimicrobial peptides (e.g., S100A7/8/9/12, hBD2, and LL37) to trigger innate immunity, and other inflammatory mediators to exacerbate inflammation after proinflammatory cytokines have synergistically activated them. Additionally, keratinocytes, fibroblasts, and endothelial cells aid in tissue reconfiguration through the activation and proliferation of endothelial cells as well as the deposition of extracellular matrix. Immune cells, especially Th17 cells, interact with keratinocytes to generate and sustain psoriasis. Infiltration, dilated and hyperplastic blood vessels, and keratinocyte hyperproliferation and abnormal differentiation are the results of this interaction [5].

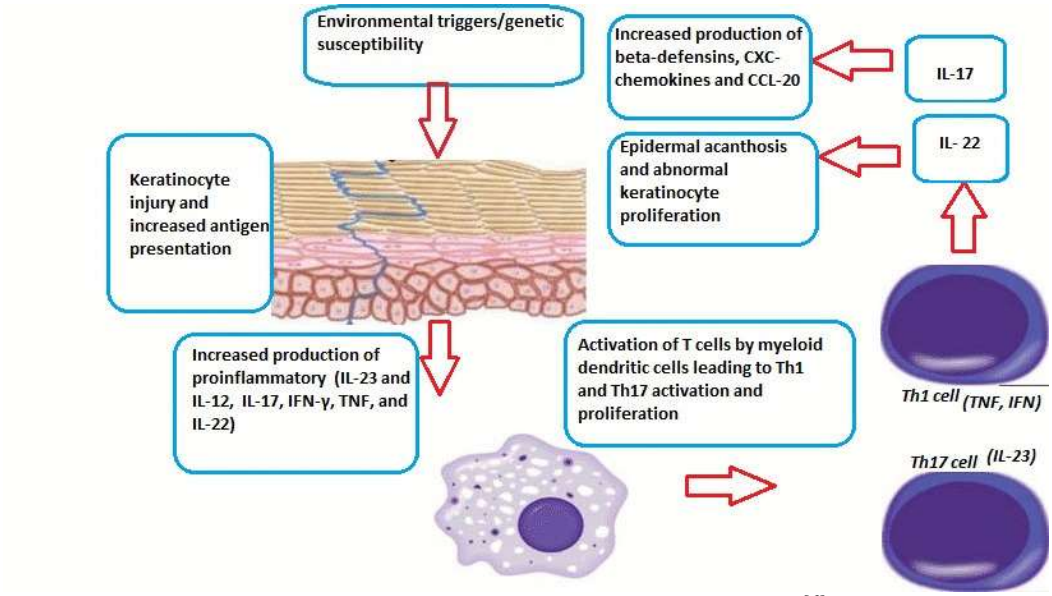


Figure 2: Pathophysiology of Psoriasis[6]

- **Current Treatment Landscape**

There are several different methods of treatment, such as topical, systemic, phototherapy, and biologics. Topical treatments are recommended for mild to moderate cases of psoriasis, and systemic medications are best for severe disease stages. Systemic therapy includes immunosuppressants, biological agents, and newly licensed phosphodiesterase-4 (PDE4) inhibitors. The current treatments have several drawbacks, and recent research on the pathophysiology of psoriasis is opening the door for more advanced treatments that address the disease at the molecular level. Numerous small molecules, biologics, PDE-4 inhibitors, and immunomodulators demonstrated efficacy; among these were novel compounds that target inhibitors of Janus kinases (JAKs), which are currently being studied. Moreover, the involvement of genetics and miRNAs in psoriasis remains incompletely understood and could potentially enhance the effectiveness of treatment. Together with the psoriasis treatments that are now licenced, this review offers insight into a number of developing medicines[7].

- **Limitations of Conventional Therapies**

The first line of treatment for moderate to severe psoriasis is phototherapy (UVB 311nm and PUVA) and traditional systemic medications (methotrexate, cyclosporine, and acitretin). But they have several drawbacks that limit their usage over an extended length of time, namely possible medication interactions and the cumulative toxicity of target organs. 47.9% of patients in a Swedish research who had traditional systemic therapy for a year stopped receiving it at that point. In another research that used a questionnaire given to patients (n=301) to assess the limits of systemic medications and UVB phototherapy in people with moderate to severe psoriasis, contraindications to conventional therapies were found in 9% to 22% of patients [8].

2. OVERVIEW OF DRUG DELIVERY SYSTEMS[9, 10]

A drug delivery system (DDS) is a formulation or a device that controls the rate, timing, and location of drug release into the body, facilitating the entry of a medicinal substance and

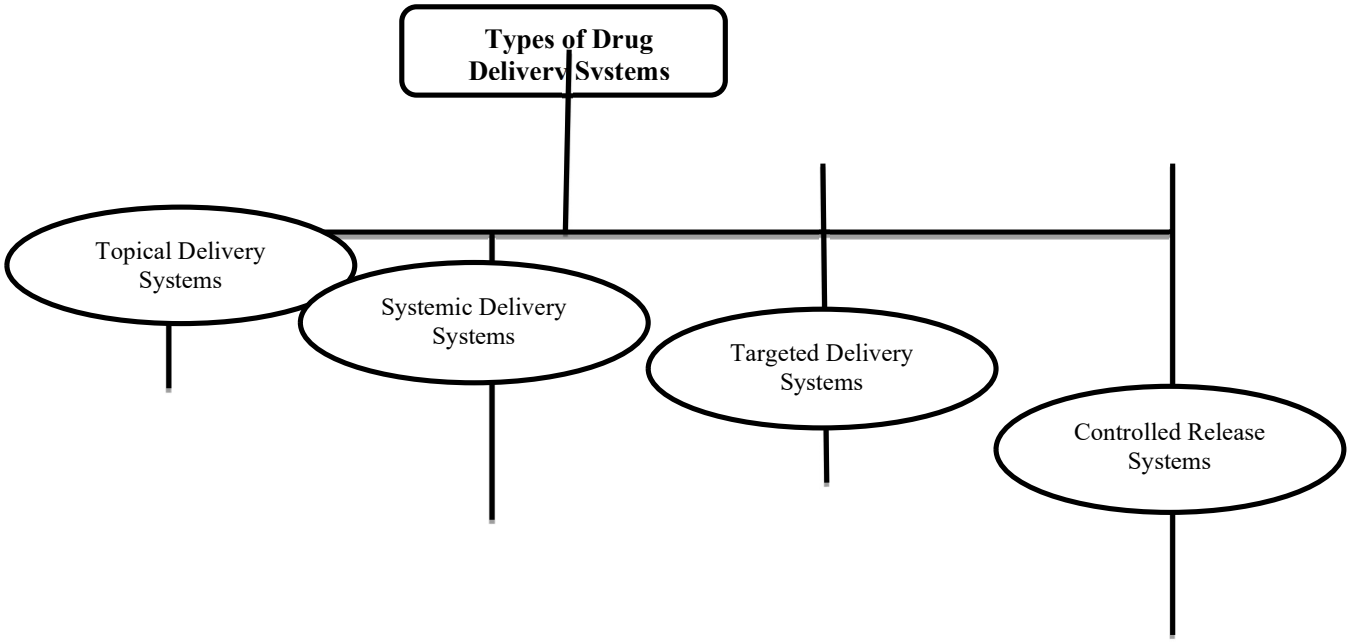
improving its safety and efficacy.

- **Introduction to Drug Delivery Systems:**

Drug Delivery Systems are a method of administering a pharmaceutical substance to humans or animals in order to achieve a therapeutic effect.

- **Types of Drug Delivery Systems**

There are mainly 4 types of Drug Delivery Systems.



2.1 Topical Drug Delivery System:
When a medicine is delivered topically, it is transferred from a topical medication to a localized area that is targeted and has dermal circulation through the human body and deeper tissues. Even yet, distribution through the layer of skin can be challenging because of the skin's barrier function.

2.2 Systemic Drug Delivery System:
A systemic drug delivery system is a way to get nutrition, medicine, or another substance into the bloodstream that has an impact on the entire body. Enteral administration, in which the medication is absorbed from the gastrointestinal tract, or parenteral administration, often through injection, infusion, or implantation, can be employed for delivery.

Drugs can be delivered systemically, which is convenient and well-liked by patients, even if it is not the most effective way to achieve significant drug concentrations within the central nervous system. Here, we will walk over the correct protocols for three commonly used systemic administration methods: oral gavage, intraperitoneal injection, and intravenous injection.

2.3 Targeted Drug Delivery System:

There are four reasons why TDD is superior to traditional DSs: inadequate medication performance with traditional delivery in terms of pharmacodynamic, pharmacokinetic, pharmaceutical, and pharmacotherapeutic aspects.

Because it can transport medications and genes to a tumour location while shielding them from the extracellular environment, targeted drug delivery, or TDD, is becoming a potent tool in the fight against cancer. Stimulus-responsive nanogels (NGs) are hydrophilic polymer networks in three dimensions that are created through covalent bonds or self-assembly processes. When external stimuli are present, NGs can alter their structural characteristics. Because of their stability, simplicity in synthesis, excellent ability to regulate particle size, and ease of functionalization, these NGs have been investigated extensively as innovative drug delivery vehicles for a range of anticancer medications as well as genes. They have control over diameters ranging from 5 to 400 nm and various polymerization conditions.

2.4 Controlled Release Drug Delivery System:

The idea behind controlled drug delivery systems is to distribute the medicine gradually and under control. Although a constant release is undesirable in some therapies, the goal is typically to release the medication over extended periods of time at a constant (zero-order) rate, restricted to the medicine's therapeutic window.

The active pharmaceutical ingredient can be released to produce the intended therapeutic effect thanks to the drug delivery mechanism. The traditional drug delivery methods (tablets, capsules, syrups, ointments, etc.) are not able to produce sustained release and have low bioavailability along with changes in plasma drug level. The therapy process may be ineffective as a whole in the absence of an effective delivery system. To attain optimal efficacy and safety, the medication must also be administered at a precise target site and at a predetermined, regulated rate. Systems for controlled drug distribution are being developed in response to issues with traditional drug delivery. Over the past 20 years, controlled drug delivery systems have undergone a remarkable transformation, moving from macro- and nano-scale to intelligent targeted delivery.

3. NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS[11,12]

Nanotechnology-based techniques are currently being used to treat psoriasis as a result of improved therapeutic efficacy and long-term effects, new drug carrier systems.

- **Nanoparticles in Psoriasis Treatment:**

The use of nanoparticles can reduce the adverse effects of medications at highly controlled drug delivery with adequate therapeutic dosages, as preclinical and clinical studies have shown.By extending the drug's half-life through the use of nanomedicine, nanoparticles help carry the active pharmaceutical ingredient (API) to the intended action site more easily via nanocarriers. Nanosized particles, also referred to as nanocarriers or nano-based drug delivery, increase the therapeutic efficacy of APIs and lessen their side effects. Their broad surface area for carrying the API is the primary cause of this. Drug delivery methods called nanocarriers are used to control the pharmacokinetics and pharmacodynamics of the target drug. Because topical nanocarriers offer improved skin penetration and regulated release at a lower dose regimen, their usage for treating skin ailments has gained significant traction recently.

- **Liposomes and Micelles:**

A lipid bilayer that divides the bulk aqueous phase from an interior aqueous compartment makes up liposomes. Micelles are closed lipid monolayers that have a polar surface and a fatty acid core, or vice versa (inverted micelle): a polar core and fatty acid surface (figure 3).

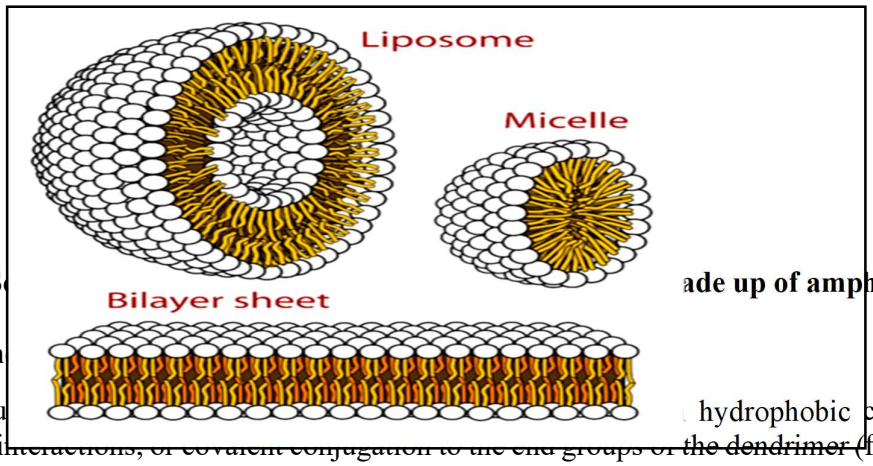


Figure 3: S ade up of amphiphilic

- **Dendrim**

Drug molecu hydrophobic coupling, electrostatic i the dendrimer (figure 4). One of the key topical medications for psoriasis treatment is dithranol.

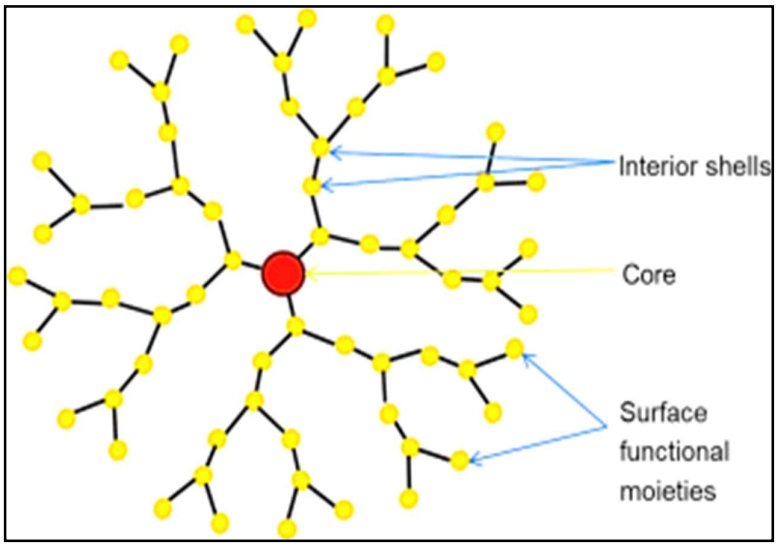


Figure 4: Schematic representation of dendrimer as nanovehicle in psoriasis therapy[14]

- **Nanoemulsions for Topical Delivery:**

Curcumin releases from the nanoemulsion according to Korsmeyer-Peppas kinetics. Hydrogel that had been integrated with a curcuminnanoemulsion displayed pseudoplasticbehaviour. The topical administration of curcuminnanoemulgel shown increased psoriasis effectiveness (fig. 5).

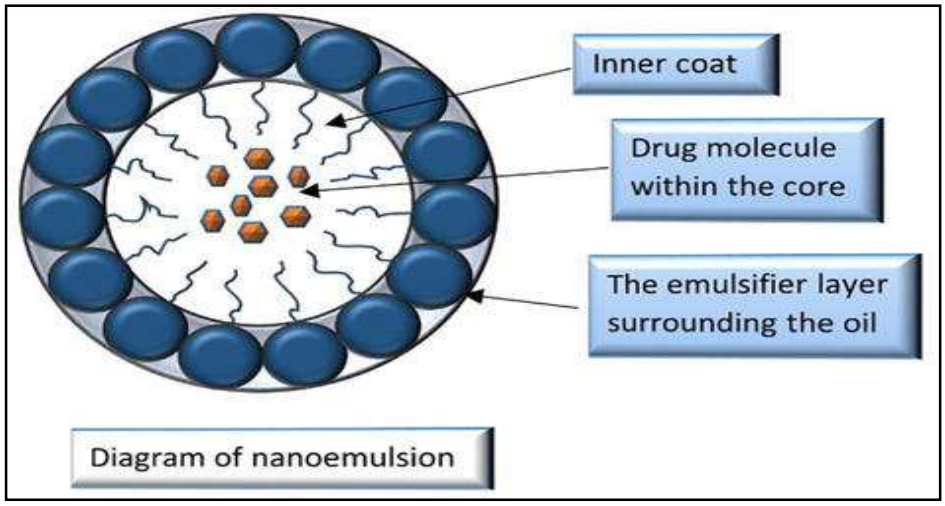


Figure 5: Schematic representation of nanoemulsions for topical delivery[15]

4. TRANSDERMAL DRUG DELIVERY SYSTEMS[16, 17]

- **Transdermal Patches**

According to in vitro research, the cannabinoid found in Cannabis sativa, cannabidiol, reverses the aetiology of psoriasis through skin receptors. Psoriasis may respond well to cannabidiol transdermal patches, despite the paucity of safety and efficacy studies (figure 6).

Figure 6: Transdermal patches as transdermal drug delivery systems[18]

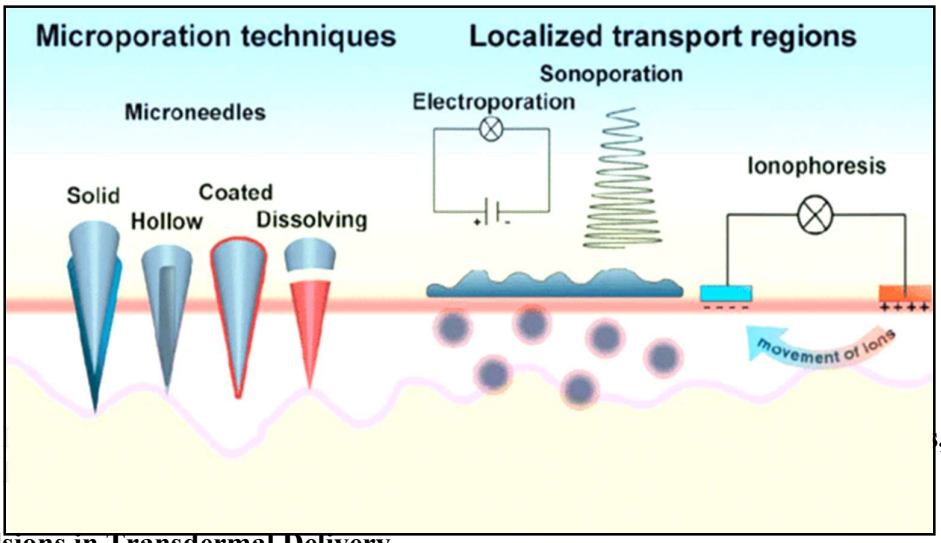
- **Iontophoresis and Electroporation**

Iontophoresis is a non-invasive method of delivering biological macromolecular medications into the skin for the treatment of psoriasis. Iontophoresis is a technique used to introduce a charged medication into skin or other tissue by applying a tiny, low voltage (usually 10 V or less) and a continuous, constant current (usually 0.5 mA/cm2 or less). On the other hand, electroporation permeabilizes the skin by applying a high voltage (usually? 100 V) pulse for a

very brief (micros-ms) time (figure 7).

- **Microneedle Technology**

By avoiding the skin barrier, a more recent delivery technology known as "microneedles" improves the transportation of the medication directly into the skin (figure 7). By varying the needle height painlessly, a single microneedle technology can deliver anti-psoriatic medications either locally (topical) or systemically (transdermally). MNPs have been developed by researchers to lessen the negative effects of microneedles and increase the effectiveness of MTX treatment for psoriasis.



- **Microemulsions in Transdermal Delivery**

Microemulsions' thermodynamic stability, simplicity of manufacturing, and appealing appearance make them useful as carriers of drugs for a range of pharmaceuticals in pharmaceutics (figure 8). Local treatment with lotions and ointments containing corticosteroids or vitamin A/D analogues is effective for mild to severe psoriasis. To improve the effectiveness of indirubin, a hydrogel-based microemulsion drug delivery system was developed for transdermal administration. Bio-Based Microemulsions for Long-Term Skin Preservation of Clobetasol Propionate: A Potential Treatment for Scalp Psoriasis

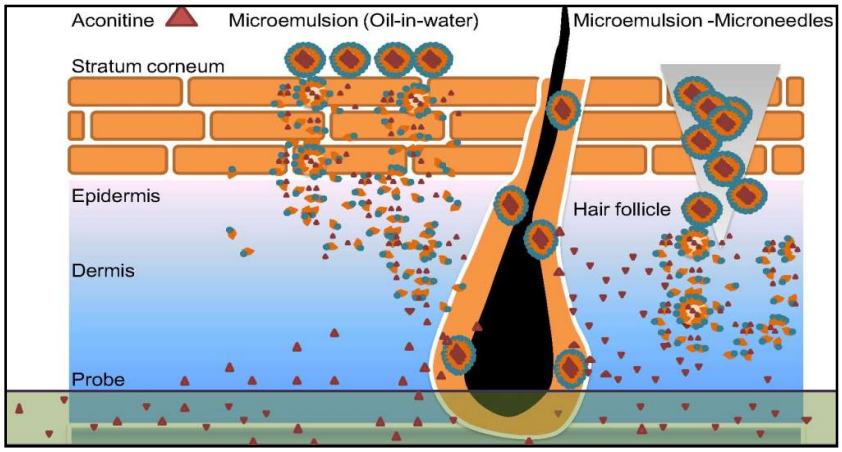


Figure 8: Schematic representation of microemulsion in Transdermal delivery [20]

5. TARGETED DRUG DELIVERY APPROACHES[21]

- **Passive Targeting Strategies**

The process of passive targeting leverages the distinct pathophysiological features of tumour vasculature to facilitate the accumulation of nanodrugs within the tumour tissue (figure 9). To achieve passive targeting, the therapeutic material is incorporated into a macromolecule or nanoparticle that passively moves to the target organ. The efficacy of the medication in passive targeting is directly correlated with its circulation time. The nanoparticle is covered in a coating to do this.

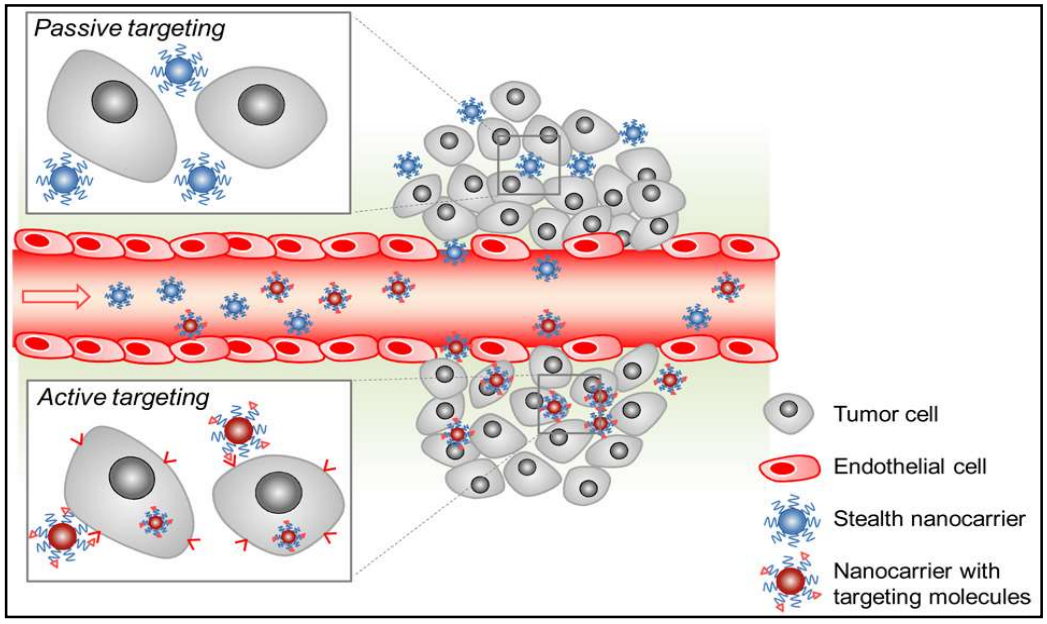


Figure 9: Passive Vs Active Targeting Strategies of drug to achieve better response of drug[22]

- **Active Targeting Strategies**

Knowing the type of receptor on the cell that the medicine will be directed towards will help you actively target only sick tissue in the body. Subsequently, scientists can employ ligands specific to particular cells, enabling the nanoparticle to attach itself to the cell that possesses the corresponding receptor (figure 9). Drug delivery using nanostructures may be an effective way to treat psoriasis. Plants with polyphenols can be used to treat psoriasis. Psoriasis can be treated more successfully with dissolved microneedles. Psoriasis treatment with treg cells is promising.

- **Antibody-Mediated Targeting**

One other T cell-targeted biologic for psoriasis treatment was efalizumab, a monoclonal antibody against the integrin CD11a. Targeted nanoparticulate delivery methods, both passive and active, have the potential to make up for the shortcomings of traditional therapy, including side effects, low medication efficiency and accumulation at the target site, poor pharmacokinetic qualities, etc. Monoclonal antibodies and their fragments are examples of physically or covalently linked ligands that are often used and researched for active targeting

to guide therapeutic agents or drug delivery systems to their target locations (figure 10). There is currently no active targeted delivery method in use in clinical settings, despite the FDA having authorised many actively targeted antibody-drug conjugates. Nevertheless, work is still being done to develop efficient actively targeted delivery systems. The use of monoclonal antibodies and their fragments as targeted ligands will be the main topic of this review.

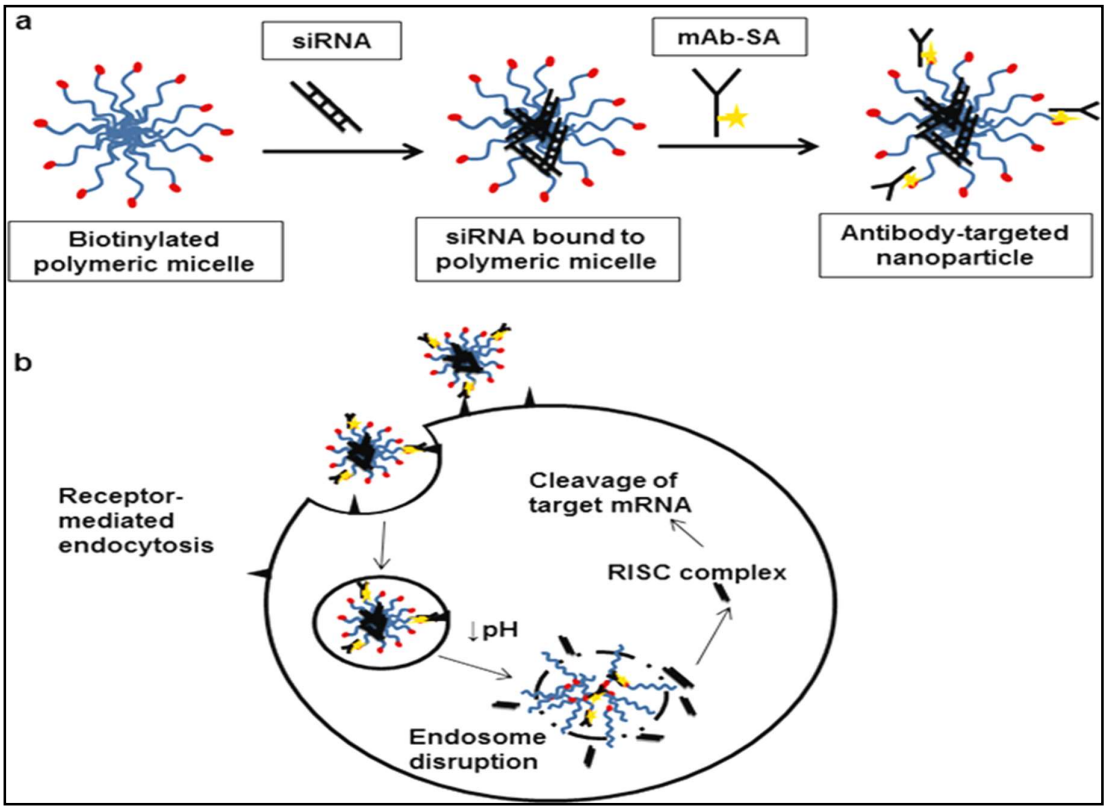


Figure 10: Antibody-Mediated Targeting drug delivery approaches[23]

- **Stimuli-Responsive Delivery Systems**

  The field of research on stimuli-responsive or smart polymeric drug delivery is a dynamic one. It involves the use of natural or synthetic polymers that are designed to treat psoriasis by exerting therapeutic effects in response to physiological and physicochemical processes as well as external stimuli.

- **Ligand-Receptor Interactions**

The analysis of ligand-receptor pair interactions is the foundation for comprehending cell behaviour and responses to neighbouring cells because receptor-ligand interactions are a major class of protein-protein interactions and play a significant role in many biological processes and the treatment of psoriasis (figure 11).

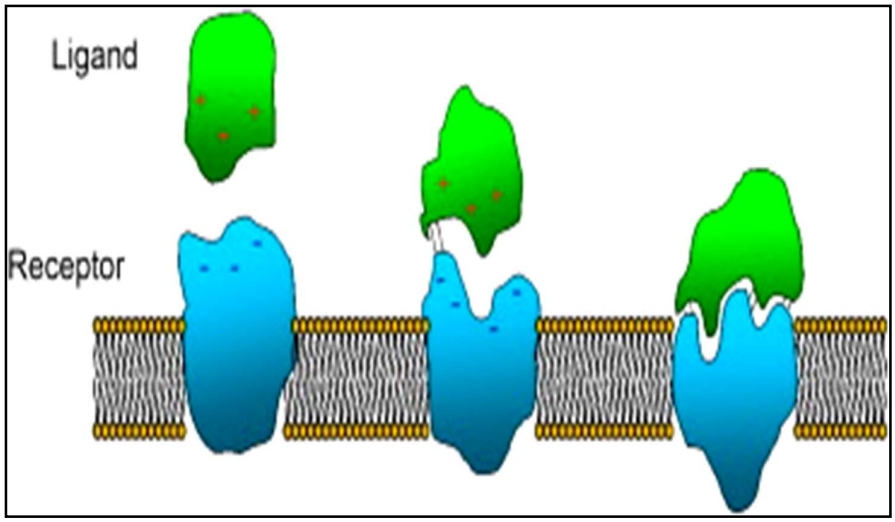


Figure 11: Ligand-Receptor Interactions of drug delivery approaches[24]

6. NOVEL TOPICAL FORMULATIONS[25, 42 45]

- **Hydrogels for Topical Delivery**

Hydrogels are three-dimensional, crosslinked polymer networks capable of holding significant water content. They release drugs primarily through diffusion and swelling-controlled mechanisms. The porous structure of hydrogels facilitates gradual release, which can be modulated by altering polymer composition or crosslinking density. Hydrogels also support localized delivery by adhering to affected skin regions, enhancing therapeutic outcomes.

- **Nanostructured Lipid Carriers (NLCs)**

Nanostructured lipid carriers (NLCs) are novel medicinal formulations composed of physiological and biocompatible lipids, surfactants, and co-surfactants. NLCs have a lot of promise in the pharmaceutical and cosmetics sectors because of their numerous beneficial qualities, which include enhanced bioavailability, skin targeting to cure psoriasis, occlusion, and skin hydration.

- **Transferosomes and Ethosomes**

Scientists developed elastic vesicles in an attempt to replicate the transdermal route's effectiveness with liposomes in treating a variety of carcinomas and systemic viral illnesses. Etosomes and transfersomes were created in this direction with the goal of creating vesicles that could penetrate skin. According to the study, the ethosomes and transferosomes enhance the drug's skin permeability and make treating psoriasis easier.

Lipid-based carriers release drugs through diffusion across the lipid bilayer or through the degradation of the carrier itself. These systems enhance skin penetration and improve the bioavailability of poorly soluble drugs. Their biocompatibility and capacity for controlled release make them particularly suitable for topical applications in psoriasis.

- **Solid Lipid Nanoparticles (SLNs)**

The first generation of lipid-based nanocarriers for the treatment of psoriasis, known as solid lipid nanoparticles (SLNs), are made of lipids, which are solid at body temperature. They offer many benefits, including the capacity to protect drugs from severe environments, the convenience of producing large quantities of drugs utilising the high pressure homogenization technique, biocompatibility, and biodegradability.

Nanoparticles leverage their large surface area and nanoscale dimensions to encapsulate active pharmaceutical ingredients (APIs). These carriers enable controlled drug release through diffusion, degradation, swelling, or erosion of the nanoparticle matrix. By adjusting particle composition and surface modifications, the release profile can be fine-tuned to ensure a prolonged therapeutic effect while minimizing systemic exposure.

- **Controlled-Release Systems**: Advanced delivery technologies, such as transdermal patches and microneedles, employ stimuli-responsive mechanisms (e.g., temperature, pH) to trigger drug release. These systems ensure a steady therapeutic effect while reducing dosing frequency, improving patient compliance.

7. BIOLOGICS DELIVERY SYSTEMS[26]

- **Introduction to Biologics in Psoriasis Treatment**

Biologics are more recent and potent medications. A biologic can only quiet or target the portion of the immune system that psoriasis has caused to become hyperactive. This indicates that compared to other potent psoriasis medications, biologics carry a lower chance of creating issues with the liver, kidneys, and other organs. Biologics function by preventing the bodily processes that lead to psoriasis and its associated symptoms. The most efficacious medications are risankizumab, infliximab, bimekizumab, and ixekizumab.

- **Challenges in Biologics Delivery**

Owing to the intrinsic difficulties that biologics encounter following oral delivery such as;

i. An acidic pH of the stomach,
ii. The presence of digestive enzyme
iii. Poor intestinal absorption
iv. Restricted gastrointestinal tract permeation

A number of substitute delivery methods have been studied in order to facilitate adequate drug absorption into the systemic circulation.

- **Stability Issues**

Compared to its parenteral counterpart, a medical product designed for oral delivery of a biomacromolecule may include a more complex formulation. The recognised constituents of parenteral formulations—the active pharmaceutical substance, an appropriate buffer (such as

phosphate, citrate, histidine, or succinate), a surfactant (including polysorbates or pluronics), and a stabiliser (such sucrose or trehalose)—are often included in formulations for oral protein and peptide administration.

- **Immunogenicity Concerns**

Compared to other delivery methods, the subcutaneous route of administration for biologics has particular immunogenicity problems. Immunogenicity risk assessment must be carried out during the developmental stages; yet, many existing techniques lack mechanistic insight and predictive capacity. Certain biologics designed for splenic distribution have shown improved immunogenicity when administered using this method.

- **Advances in Biologics Delivery Platforms**

i. Polymer-based delivery methods: Certain techniques, such the use of micro- and nanoparticles, can prevent the breakdown of biologics in the gastrointestinal system. These delivery techniques might be designed to release the biologic in the small intestine, which is the best place for absorption. Polymer-based delivery systems can be advantageous for biologics administered orally because they can improve bioavailability, target specific body regions for distribution, and inhibit degradation in the stomach and intestines.

ii. Peptide-based carriers: Biologics can be more easily administered orally by using peptides, which are short sequences of amino acids. These carriers can be tailored to attach to receptors in the gastrointestinal tract or other target tissues in order to optimise the biologic's efficacy.

iii. Enzyme inhibitors: It is possible to stop the breakdown of biologics in the digestive system by using protease inhibitors and other enzyme inhibitors. By raising the biologic's bioavailability, this may improve its therapeutic efficacy.

iv. Oral formulations of monoclonal antibodies: Because of the complexity of their structures, monoclonal antibodies (mAbs) are a type of biologic that have proven particularly challenging to deliver orally. On the other hand, novel approaches to formulation and distribution have led to the development of oral formulatiomabs, which exhibit potential for the management of certain illnesses.

8. GENE DELIVERY SYSTEMS FOR PSORIASIS THERAPY[27]

- **Gene Therapy Approaches in Psoriasis**

Although there is not a treatment for gene therapy at the moment, research on the genetic reasons of psoriasis is growing. Among the numerous exciting findings was the identification of a rare gene mutation connected to psoriasis. As a result, cutting-edge gene therapy-based therapeutic approaches like antibody-based therapy, stem cell therapy, silencing RNA complex, and antisensing nucleotide are being considered.

- **Viral Vectors for Gene Delivery**

The most significant and recent advancements in viral vector siRNA delivery methods for local

administration are in response to the growing body of research suggesting novel and ideal delivery strategies for the effective silencing of gene-related disorders by local administration of siRNAs. Furthermore, in order to treat psoriaris, the primary illness targets for the local distribution of siRNA to particular tissues or organs, such as the skin, the eye, and the vagina, were investigated.

- **Non-viral Gene Delivery Systems**

On the other hand, nonviral vectors have drawn a lot of interest because of their many benefits, which include improved payload capacity, a better safety profile, and stealth capabilities. Nonviral vectors face various intra- and extracellular hurdles that hinder the passage of genetic payload into the nucleus of the target cell. A direct approach does away with the need for a particular carrier for gene delivery by using physical techniques like electroporation, sonoporation, and gene guns. On the other hand, chemical gene transfer techniques use artificial or natural substances as carriers to improve cellular targeting and the efficacy of gene therapy.

- **Lipid-Based Vectors**

The first class of lipid-based vectors used to transport plasmid DNA in vitro were liposome vectors based on DOTMA. However, due of their cationic charge, DOTMA-based formulations also produced cellular damage in addition to immune system activation. Therefore, different in vivo investigations cannot be conducted using DOTMA-based formulations. In an effort to produce a smaller particle size and tolerable levels of lipid, this further led to the investigation of helper lipids and lipids other than phospholipids. Lipid nanoparticles (LNPs) are distinct from liposomes in that they lack an aqueous core and use ionizable lipids to encapsulate nucleic acids. Because lipids are amphiphilic, they can easily encapsulate both hydrophilic and lipophilic medicines. This attribute makes lipid-based nanoparticles for psoriasis therapies a paradigm for topical drug delivery.

- **Polymer-Based Vectors**

An further advantage of carrier systems utilising polymer-based vectors is the creation of smaller, uniform particle sizes, which enhances transfection efficiency. Nucleic acids, which possess a negative charge, prefer to condense and aggregate with cationic polymers. The initial cationic polymer investigated for DNA transfection was poly-L-lysine (PLL). Because of its charged amino group, poly-ethylenimine (PEI) is a highly branched network that can be protonated. PEI has a better transfection effectiveness because of its numerous amino group buffering capacity, which can quench protons pumped by the endosome-present vesicular ATPase proton pump. PEI's "proton-sponge effect" causes an influx of water and chloride ions into the endosome, which ultimately causes endosomal disruption and osmotic swelling.

9. COMBINATION THERAPY DELIVERY SYSTEMS[28]

- **Rationale for Combination Therapy in Psoriasis**

Remission in people with moderate-to-severe psoriasis can be hard to attain and maintain. Agents with both long-term maintenance and acute action are required. The safety of currently existing monotherapies is generally adversely correlated with their speed and efficiency.

Compared to single-agent therapy, combination, rotational, and sequential techniques are frequently safer and more successful. It is desirable to combine medicines with comparable adverse effect profiles. The majority of paired combinations involving the four main therapies—acitretin, phototherapy (ultraviolet B/psoralen with ultraviolet A), cyclosporine, and methotrexate show apparent synergistic enhancement. Out of all of those, the combination of cyclosporine, psoralen, and ultraviolet A is contraindicated due to an elevated risk of cancer. With differing degrees of success and safety, combinations of each of those main treatments with topical drugs (retinoids, steroids, vitamin D derivatives, and others) have been employed. Additionally, hydroxyurea and thioguanine, two immunomodulators, have demonstrated some efficacy in combined therapy. The recently developed biologic medicines may prove to be valuable adjuncts in combination, rotational, or sequential methods due to their unique mechanisms of action and side effect profiles.

- **Challenges and Opportunities**

Monotherapy, whether utilising systemic medications or phototherapy, can occasionally manage moderate-to-severe conditions efficiently. The advantages of a single-agent regimen encompass decreased expenses and more patient compliance. Nevertheless, a singular modality will be inadequate for several reasons, including diminished effectiveness, adverse effects, cumulative or acute toxicity, and notably the inability to eliminate resistant lesions. For most people with moderate-to-severe psoriasis, the use of two or more medicines is customary rather than atypical. Nevertheless, selecting a combination that effectively balances safety and efficacy necessitates meticulous deliberation, especially in the absence of evidence-based therapy recommendations.Combining therapies for psoriasis is not always beneficial or even safe. Using salicylic acid topically on your skin in conjunction with UVB phototherapy is not advised as it reduces the effectiveness of the UVB light. Additionally, cyclosporine, psoralen, and ultraviolet A together may increase your risk of developing cancer.

- **Advances in Combination Drug Delivery Platforms**

i. Topical medications: You apply these creams and ointments to your skin. Corticosteroids are the most widely used. Additional substances include coal tar, salicylic acid, calcineurin inhibitors, topical retinoids, vitamin D compounds, and anthralin.

ii. Photomedicine: Another name for it is UV radiation therapy. It makes use of a variety of light sources, such as sunlight, ultraviolet B (UVB), and photochemotherapy (PUVA), which employs ultraviolet A photons that penetrate deeper than usual.

10. IMMUNOMODULATORY DRUG DELIVERY SYSTEMS[29]

- **Modulating the Immune Response in Psoriasis**

- In clinical practice, regulation of the immune system to selectively inhibit immune cell activation, cytokine production, proliferation, and differentiation is essential for managing psoriasis. Psoriasis vulgaris, the most recognised and readily curable form of human

psoriasis, is induced by T lymphocytes and dendritic cells. Th1 cells, Th22 cells, and IL-17-producing T cells generate substantial amounts of the psoriatic cytokines IL-17, IFN-γ, TNF, and IL-22 in response to the production of IL-23 and IL-12 by inflammatory myeloid dendritic cells. These cytokines exacerbate psoriatic inflammation by influencing keratinocytes. Therapeutic trials utilising anticytokine antibodies have established the significance of the key cytokines IL-23, TNF, and IL-17 in this process.

- **Targeting Cytokines and Signalling Pathways**

Another important inflammatory cytokine that is significantly expressed in psoriatic lesions is tumour necrosis factor (TNF)-α. The pathophysiology of psoriasis is significantly influenced by this cytokine, as evidenced by the effectiveness of therapy targeting TNF-α. Numerous cells linked to the development of psoriasis, including keratinocytes, DCs, neutrophils, mast cells, NKT, Th1, Th17, and Th22 cells, release TNF-α. It primarily affects the targeted cells through TNFRI (p55) and TNF-RII (p75), two different forms of TNF receptors. It has been documented that TNF-α binds to the p55 TNF-R.78 in order to biologically affect epidermal cells.One the one hand, TNF-α dramatically reduces plasmacytoid dendritic cells' (pDCs') ability to secrete IFN-α.
It is the primary cause of newly developed paradoxical psoriasis or exacerbated psoriasis that occurs when using TNF-α inhibitors.80 However, in order to create IL-2381, TNF-α promotes the maturation of pDCs into more traditional dendritic cell phenotypes. Additionally, TNF-α can stimulate the production of IL-12 and IL-18, two cytokines that are strong inducers of IFN-γ, in order to contribute to the control of the Th1 immune response.82 Moreover, TNF-α and IL-17A work together to coregulate genes associated to keratinocytes and psoriasis-related cytokines, which impacts keratinocyte function.

- **Biomimetic Delivery Systems (37, 38)**

Biomimetic delivery systems draw inspiration from natural biological processes and substances to improve drug delivery efficacy and biocompatibility. These systems mimic the structural, functional, or biochemical properties of endogenous materials to enhance therapeutic outcomes. A common example is the use of cell membrane-coated nanoparticles. These nanoparticles are cloaked in cell membranes derived from red blood cells, platelets, or cancer cells. Such coatings provide immune evasion, prolonged circulation times, and targeted delivery by leveraging natural ligand-receptor interactions. For instance, platelet-mimicking nanoparticles can bind to inflamed vascular sites, making them particularly effective in inflammatory conditions like psoriasis. Another example is exosomes, naturally occurring lipid vesicles secreted by cells, which can be engineered to carry drugs or genetic material. Exosomes have inherent targeting capabilities, as they interact with specific cell types via surface proteins. Hyaluronic acid, an endogenous polysaccharide, is frequently incorporated into biomimetic systems for its biocompatibility and ability to bind CD44 receptors overexpressed in many inflammatory conditions. Similarly, collagen and gelatin, derived from extracellular matrix components, are used to create hydrogels and scaffolds that mimic tissue environments, promoting local drug retention and sustained release.

- **Immunosuppressive Nano carriers**

These nanocarriers are currently gaining popularity as delivery systems for anti-psoriasis medications due to their excellent biocompatibility, natural degradation, non-toxicity, and

biodegradability; they also easily exit the body and do not trigger any negative inflammatory reactions. Cyclosporin was first used as an immunosuppressant to prevent organ rejection following transplant, but it quickly showed promise as an antipsoriatic medication. Its action stems from calcineurin inhibition, which prevents the release of pro-inflammatory cytokines and suppresses T cell activation.

11. BIOMATERIAL-BASED DELIVERY SYSTEMS[30]

- **Introduction to Biomaterials**

To build devices and systems composed of therapeutically responsive biomaterials, a range of chemical, physical, mechanical, and biomimetic properties are absorbed into biomolecules through solution processing, modification, or merging with some other natural or artificial elements. Using biocompatible and biodegradable drug carriers can help prevent or reduce adverse effects that may result in drug delivery to cells with improved efficiency and performance during the health rehabilitation process. Fundamentally, these are metallic, ceramic, or polymeric biomaterials. These materials have to have biological origins throughout their whole life cycle.

- **Hydrogel-Based Delivery Systems**

Hydrogel system injections intraperitoneally are thought to be an effective way to administer a variety of medicinal medicines. For the purpose of treating psoriasis, the injected hydrogel compounds have the ability to effectively transport medication while displaying anti-adhesive qualities on the peritoneum.

- **Polymeric Nanoparticles**

Polymeric nanoparticles are among the most successful ways for improving medication bioavailability or tailored distribution to the site of action. Due to their versatility, polymers may be the optimal selection for fulfilling the requirements of any specific drug-delivery system. Research on employing polymeric nanoparticles as drug delivery methods has primarily focused on applications where the associated disease has a significant morbidity, a marked decline in the patients' quality of life, or even a high death rate. A review of the application of polymeric nanoparticles for nutraceutical administration, psoriasis diagnosis and treatment, and ocular medication delivery was conducted, along with a brief assessment of these systems' potential in the future.

- **Scaffold-Based Approaches**

Three-dimensional tissue engineering (TE) scaffolds with improved characteristics can be created by combining several technologies and materials into a single operational process. Scaffold-free TE was developed as an alternative approach, offering a number of benefits over traditional scaffold-based techniques. It is based on the assembly of building blocks such cell sheets and spheroids. Important elements for tissue engineering are scaffolds. But when choosing scaffolds for tissue creation, researchers frequently face a dizzying array of options.

12. CHALLENGES IN CLINICAL TRANSLATION[31]

- **Preclinical Studies and Animal Models**

Being able to forecast a drug candidate's safety and efficacy in humans with accuracy is a major goal of preclinical drug development. However, the fundamental disparities between human and animal models make achieving high predictive validity difficult. Since many novel chemical entities (NCEs) with promising preclinical characteristics have failed clinical trials, animal models have come under growing criticism for their poor capacity to predict the safety, toxicity, and efficacy of NCEs in humans across all therapeutic areas. In order to evaluate target engagement and NCE efficacy, it is necessary to evaluate pharmacokinetic/pharmacodynamic (PK/PD) correlations and create validated disease-associated biomarkers prior to testing disease hypotheses and NCEs in multiple disease models.

- **Regulatory Hurdles**

Moving nanoparticulatenanomedicines (NNMs) from the bench to the bedside will require addressing a number of experimental hurdles. The present trends and difficulties with regulatory barriers in the clinical translation of NNMs, along with possible avenues for translational development and commercialisation, will be covered in this study. Important topics pertaining to the clinical development of NNMs will be discussed, such as the costs associated with developing NNMs overall compared to existing treatments, biological difficulties, large-scale production, biocompatibility and safety, intellectual property (IP), and government regulations. Whether or not NNMs are useful for treatment, these issues can create substantial obstacles that prevent them from entering the market.

- **Clinical Trial Design and Patient Selection**

The most reliable method for assessing the efficacy and safety of medical interventions is randomised clinical trials, or RCTs. The most significant obstacles were those pertaining to patient recruiting, managing ethical and regulatory frameworks, and the shortage of funding and qualified personnel for carrying out clinical studies. The most significant recommendation in these research was training to raise the calibre of randomised clinical trial studies at various stages and levels.

- **Safety and Long-Term Efficacy Assessment**

Almost every day, there are reports of new medication formulations for nanomedicine and innovative uses for nanomedicine. Industrial acceptability and clinical translation are coming under closer scrutiny, even as scholarly advancement and societal potential keep reaching new heights. When trying to further the clinical translation of nanomedicines, there are some obstacles that must be taken into account. The development of successful nanomedicines will be aided by critical analysis and strategic planning of the translation process for nanomedicine. The absence of an established gold standard for evidence, the restricted statistical power of randomised controlled trials leading to type 2 error, the inadequate reporting of adverse events, and the restricted applicability of trials that do not involve high-risk patients are some of these problems.

13. PATIENT PERSPECTIVES AND ACCEPTANCE[32]

- **Patient Preferences in Psoriasis Therapy**

Between October 4 and October 8, 2021, data were gathered. The risk of major infections necessitating hospitalisation was found to be the second most favoured attribute for selecting

biologics, after administration route and visits, based on data from 357 psoriasis patients. A few variations were noted between particular groupings. The findings indicate that psoriasis patients choose biologics that need less frequent administration and visit schedules, together with a reduced risk of severe infections necessitating hospitalisation, diverging from previous studies that prioritised medication efficacy.

Adherence and Compliance Issues

The findings showed that adherence rates in psoriasis patients were typically low and impacted by a number of variables, including patient motivation, physician-patient relationships, treatment efficacy, and patient characteristics. Regarding the factors that predict adherence, the results were not in agreement. The findings show that while patients getting topical medicines were the least satisfied, those receiving biologic treatment consistently reported higher levels of satisfaction than patients receiving traditional systemic therapies. Furthermore, the positive correlation shown between clinical treatment success and satisfaction raised the possibility that better satisfaction rates could be attained by the use of efficient medications that result in a larger reduction in illness severity (PASI score).

When it comes to chronic skin disorders, compliance behaviour and disease management are crucial concerns. Patients with psoriasis are "experts by experience" due to years of therapy. As such, patient data regarding the real-world application of antipsoriatic medicines is crucial.

- **Impact of Drug Delivery Systems on Quality of Life**

  Novel drug delivery strategies have been shown to enhance treatment results by increasing patient compliance, reducing toxicity, improving therapeutic efficacy, and facilitating the development of new medical therapies.

- **Patient-Centric Considerations in Drug Delivery Systems (39-41)**

  The practicality and user-friendliness of drug delivery systems play a crucial role in patient compliance and overall therapeutic success. Incorporating patient-centric perspectives ensures that advanced systems are not only efficacious but also tailored to meet the needs of diverse populations.

- **Ease of Application**: Hydrogels and topical systems, such as creams and patches, are generally straightforward for patients to use. Hydrogels, with their moisturizing and cooling properties, are particularly beneficial for psoriasis patients with thick plaque formations, providing comfort alongside medication delivery. However, issues such as poor adhesion in mobile areas (e.g., elbows, knees) may reduce their effectiveness and convenience.
- **Patient Compliance**: Transdermal patches and microneedles offer long-lasting drug release, reducing the frequency of application. These features are especially advantageous for patients who find it challenging to adhere to frequent dosing schedules. However, patient education is vital to ensure correct application and consistent use.
- **Tailored Delivery for Specific Populations**: Pediatric psoriasis patients may benefit from non-invasive, pain-free systems like patches and hydrogels, which minimize discomfort. In contrast, adults with severe psoriasis might require more robust options like microneedles or systemic delivery systems, which could necessitate additional education on use and side effects.

- **Patient Education**: Clear instructions and support from healthcare providers are essential for integrating these advanced systems into daily routines. Patient-friendly designs, such as pre-filled applicators or single-use patches, can enhance usability and adherence.

14. FUTURE DIRECTIONS AND EMERGING TRENDS[33]

- **Personalized Medicine Approaches**

Primary or secondary lack of efficacy is still conceivable, despite the fact that new targeted medicines have favourablyrevolutionised the treatment of psoriasis by moving the treatment goals to total or almost complete skin clearing. Therefore, finding reliable biomarkers that represent the different clinical psoriasis phenotypes would enable patients to be categorised into endotypes or subgroups and have their therapies customised based on their unique characteristics (precision medicine). Psoriasis treatment that is tailored to the patient's needs would minimise negative effects while producing good results. Despite the fact that a number of candidates have been put forth and evaluated thus far, the limited quantity and variability of the findings preclude the determination of the gold-standard biomarker for every treatment.

- **Advances in Imaging Techniques for Drug Delivery Monitoring**

i. Dermoscopy and videodermoscopy as non-invasive methods for diagnosing psoriasis vulgaris: A horizontal view or slice can be achieved using dermoscopy, revealing tissues with a superficial vascular pattern. Dermoscopy study of psoriatic lesions reveals distinctive vascular characteristics, with a bright red hue accompanied by diffuse white scales, with capillaries appearing as "dotted," "pinpoint," and coiled (or glomerular). Terms like "red globules" or "red dots" (measuring up to 0.1 mm) might be employed to characterise the same dermoscopic event.

ii. High frequency ultrasonography in monitoring therapeutic response in plaques psoriasis: A non-invasive technique for morpho-functional assessment of the subcutaneous fat, skin appendages, and epidermal and dermal tissues is called HFUS. It is a valuable imaging tool for in vivo examinations of psoriatic lesions. It can be used for a variety of purposes, including the assessment of inflammatory disorders including scleroderma, psoriasis, and contact dermatitis or acne. It enables direct measurements of the acoustic density and thickness of the subcutaneous fat, dermis, and epidermis as well as high-resolution images. Typically, it makes use of transducers with varied frequencies (5–20 MHz) that can target various tissue layers.

- **Integration of Digital Health Technologies**

Three primary categories of digital technologies are available to enhance psoriasis diagnosis and treatment: teledermatology, artificial intelligence (AI), and mobile phone applications (Apps).

- **Novel Biomarkers for Treatment Response Prediction**

Serum levels of interleukin (IL)-12 and polymorphisms in the IL-12B gene exhibit potential

as indicators of PsV therapy response. Higher baseline C-reactive protein (CRP) levels were linked, but not always, to improved clinical responses to treatment in PsA patients. Ten papers looked into the possible use of particular human leukocyte antigen (HLA) alleles and genetic polymorphisms as indicators of treatment response. Associations between response and the HLA-C*06 haplotype were found in three of these investigations.

- **Critical Evaluation of Challenges in Advanced Drug Delivery Systems(34-36)**

  While advanced drug delivery systems like nanoparticles and hydrogels offer promising solutions for psoriasis treatment, they are not without challenges. A balanced discussion of these limitations is essential to understand their translational potential.

  - Nanoparticles: These systems boast targeted delivery and enhanced bioavailability, but their potential for toxicity and immunogenicity raises significant concerns. For instance, prolonged accumulation of nanoparticles in organs like the liver or spleen can cause adverse effects. Immunogenic responses may also arise, particularly when non-biocompatible materials are used. Additionally, scaling up nanoparticle production for commercial use presents hurdles due to the complexity of manufacturing processes and ensuring batch-to-batch consistency.
  - Hydrogels: Despite their biocompatibility and controlled release properties, hydrogels can suffer from stability issues, particularly in harsh environments. Their low mechanical strength and potential for microbial contamination during prolonged use must be addressed.
  - Regulatory Hurdles: Translating these systems from bench to bedside involves stringent regulatory requirements. Demonstrating safety, efficacy, and stability through preclinical and clinical trials can be time-intensive and expensive. Nanoparticles, for instance, often require extensive testing to address concerns about long-term toxicity and environmental impact.
  - Patient-Specific Factors: Advanced systems may demand specialized application techniques, which could affect adherence. For instance, while microneedles and transdermal patches minimize systemic side effects, their acceptability varies among patient demographics. Cultural preferences, ease of use, and cost also play pivotal roles in patient compliance.

15. CONCLUSIONS AND RECOMMENDATIONS[34]

CONCLUSIONS:-

Advanced drug delivery systems, such as nanoparticles, hydrogels, and biomimetic carriers, hold immense promise for revolutionizing psoriasis treatment. These technologies provide targeted delivery, improved bioavailability, and controlled drug release, addressing limitations of conventional therapies. However, translating these innovations into clinical practice requires overcoming significant challenges. Future research must focus on optimizing delivery mechanisms for skin-specific penetration. Enhancements such as stimuli-responsive materials or surfactants could improve the ability of these systems to bypass the skin barrier without causing irritation. Long-term safety and toxicity also remain key concerns. Comprehensive preclinical studies evaluating systemic absorption, immunogenicity, and organ accumulation are crucial to ensuring these systems are safe for

widespread use. Scalability and cost-effectiveness present additional barriers to clinical adoption. Standardized manufacturing processes and quality control protocols are essential for large-scale production. Patient-centric designs should also be prioritized, with systems tailored to specific populations, such as pediatric or elderly patients, to enhance compliance and ease of use. Clinical trials should focus on comparing novel delivery systems to existing therapies, assessing real-world usability, and exploring emerging technologies such as CRISPR-based gene therapies

- **Summary of Key Findings**

As a result of improved therapeutic efficacy and long-term effects, new drug carrier systems and nanotechnology-based techniques are currently being used to treat psoriasis. By applying nanotechnology, poorly soluble active pharmaceutical ingredients (API) can be made more bioavailable and physicochemically stable. Low pharmacokinetic profiles, lack of stability and solubility, or restricted dosage toxicity are assumed to be characteristics of inefficient APIs.

- **Future Directions for Research and Development**

With the advent of innovative biologic drugs that target specific pathways, such RORγt inhibitors and IL-23 inhibitors like mirikizumab, the therapy of psoriasis appears to have a bright future. There is a chance that these agents will improve disease control and efficacy. Improvements in topical therapies, especially in the areas of microneedles and nanoparticle-based carriers, have the potential to enhance psoriatic plaque therapy efficacy and medication delivery. By reducing side effects and enhancing patient adherence, these cutting-edge techniques might offer more effective and focused treatments.

- **Recommendations for Clinical Practice**

The standard course of treatment for plaque psoriasis that does not involve intertriginous areas is topical corticosteroids. When used under a doctor's close supervision, topical corticosteroids can be used for more than 12 weeks. Oral PUVA is a suggested treatment for adult psoriasis. Bath PUVA is a suggested treatment for persons with moderate-to-severe psoriasis.

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