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An Overview of Potential Nanotechnological Methods for Psoriasis Treatment

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KEYWORDS

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ABSTRACT:

Introduction: Psoriasis is a chronic, immune-mediated skin disorder characterized by hyperproliferation of keratinocytes, inflammation, and the formation of red, scaly plaques. Conventional therapies, including topical treatments, phototherapy, and systemic drugs, often have limitations such as side effects, low skin permeability, and reduced patient compliance. Nanotechnology offers a promising approach to overcome these challenges by enabling targeted drug delivery, enhanced therapeutic efficacy, and reduced systemic toxicity. This review explores the potential of nanotechnological methods for the effective treatment of psoriasis.
Objectives: The objective of this study is to provide an overview of emerging nanotechnological strategies for psoriasis treatment, focusing on their mechanisms, efficacy, and potential to address current therapeutic limitations.

Methods: A comprehensive literature review was conducted, analyzing studies on various nanocarriers such as liposomes, niosomes, solid lipid nanoparticles, dendrimers, and polymeric nanoparticles for the delivery of antipsoriatic drugs. Key parameters, including drug encapsulation efficiency, skin penetration, and therapeutic outcomes, were evaluated to assess the effectiveness of these nanotechnological methods.

Results: Nanocarriers demonstrated enhanced drug stability, controlled release profiles, and improved skin penetration compared to conventional formulations. Liposomes and niosomes facilitated the localized delivery of drugs with minimal systemic absorption, reducing side effects. Solid lipid nanoparticles and polymeric nanoparticles showed significant improvement in anti-inflammatory and antiproliferative effects in preclinical models of psoriasis.

Conclusions: Nanotechnology-based approaches hold immense potential for revolutionizing psoriasis treatment by addressing limitations of conventional therapies. Further clinical studies are needed to establish their safety, efficacy, and scalability for routine clinical applications.

1. Introduction

Psoriasis is chronic inflammatory skin disease caused by the immune system that is characterized by scaly plaques, red. Though any part of the skin may be impacted, they usually show up on the scalp, knees, elbows, and lower back. It may appear at any age but is commonly observed in an age group 50-69. The cause is not well understood the disease is known to have factors that are genetic [1]. Different nations have varying rates of psoriasis prevalence from 0.09% to 11.4% meaning that psoriasis is an important global problem. In India, the prevalence of psoriasis falls in the range of 0.44–2.8%; it mostly affects patients between 30 to 40 years of age and most often the sufferers are males twice as vulnerable to the disease than females. Psoriasis affects over 125 million people worldwide. Prevalence of psoriasis by regions: Almost negligible in some Asian locations, such as at 0.5%, up to 8% in Norway. Psoriasis was more frequent among adults than among children, and the highest reported number of affected adults is in the US with 3.4 million, with an uncertainty interval at 95% between 1.5 and 7.7 million cases. The other countries ranked sequentially are India with 2.9 million, at 0.8 to 10.0 million cases; China, with 2.3 million, from 0.9 to 6.1 million; Germany, with 1.5 million, ranging from 0.8 to 2.9 million; Brazil, at 1.2 million, from 0.3 to 4.8 million; France, with 1.0 million, with an uncertainty interval at 95% between 0.5 and 2.1 million; and the UK, with 1.0 million, uncertainty interval at 95%, between 0.5 and 1.9 million. An estimated 29.5 million adults worldwide had psoriasis in 2017, and the physician-diagnosed lifetime prevalence within the global adult population was around 0.59% (95% uncertainty interval of 0.19% to 1.66%) [2-3]. The pathology of psoriasis is somewhat complex and poorly described, but the key role has been assigned to some adaptive immune pathways activated. Most of these cells such as plasmacytoid dendritic cells, keratinocytes, natural killer T cells, and macrophages release cytokines for the activation of myeloid dendritic cells in early phases of development of psoriasis. For example, DNA-LL37 complexes activate plasmacytoid dendritic cells to secrete interferon alpha that further activates myeloid dendritic cells.

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These activated myeloid dendritic cells release IL-12 and IL-23. The former stimulates differentiation of naive T cells to TH1 cells, and the latter sustains survival and proliferation of TH17 and TH22 cells. TH1 cells induce interferon gamma (IFN-γ) and TNF-α; TH22 cells produce IL-22; and TH17 cells induce production of IL-17, IL-22, and TNF-α. Of these, it has been hypothesized that IL-23 has a dominant role in the activation of the TH17 pathway. It signaling via Tyk2-Jak2 and STAT3 pathways leads to events such as proliferation of keratinocytes, increased angiogenic mediators, up-regulation of endothelial adhesion molecules, and finally infiltration of immune cells within the skin lesions of psoriasis [4-5]. Overall goal of psoriasis treatment is to regulate the disease and symptoms which will thereby enhance patients' quality of life, instead of complete remission where relapses are possible. These therapies are generally categorized into: Topical therapies, Biologic, Ultraviolet light therapy and Conventional systemic medication. First-line treatments include topical medications such corticosteroids or vitamin D analogs (calcipotriol). Combination of vitamin D and steroids are common nowadays but these should not be used for too long because side effects from prolonged usage include steroid-induced atrophy and irritation caused by the vitamin D to the skin. Secondary treatments include phototherapy, such as narrowband ultraviolet B (NB-UVB) and psoralen mixed with ultraviolet A (PUVA), as well as standard systemic medications including acitretin, ciclosporin, and methotrexate. Systemic PUVA previously was used to sensitize the skin to UVA radiation by combining with the drug psoralen. But prolonged use of this therapy is associated with an increased risk for both squamous cell carcinoma and melanoma of skin [6-7]. The use of plant-derived compounds for transformation into pharmaceutical formulations remains of high value for the treatment of diseases such as psoriasis. "Green approach" is the latest trend includes formulating biocompatible systems with herbal extracts incorporated within a lipid matrix. Patient safety is ensured because they will have minimal or no side effects when applied on the skin. The inclusion of natural molecules within a nanocarrier system has been found to provide an eco-friendly, non-toxic method. Plants and their secondary metabolites have played a very vital role in discovering new and effective anti-psoriatic treatments formulations (Fig 1). Despite considerable advances in its treatment, some patients still there are many difficulties to effective topical treatments for psoriasis, such as differences in patient profiles because various populations react differently to medicines, problems with the skin barrier, and worries about patient satisfaction or adherence to the recommended course of treatment [8-9]. Nanocarriers of less than 100 nm in size are novel approaches for the treatment of diseases in skin. Nanotechnology has received significant attention in this field, due to its advantages over the traditional formulation. Among the most important advantages provided by such nano-based systems are the decrease in side effects resulting from traditional treatments, enhanced penetration of drugs, and controlled release profiles of drugs that may efficiently help reach therapeutic targets. Several drug delivery systems based on nano particles facilitate the delivery of adequate amounts while ensuring the buildup and retention of drugs within the layers of the skin. Generally, these lipid nanoparticles are categorized on the basis of lipid structures, which include; ethosomes, lipid nanoparticles, niosomes, nanostructured Containing lipid carriers, liposomes transferosomes and nanoemulsions.

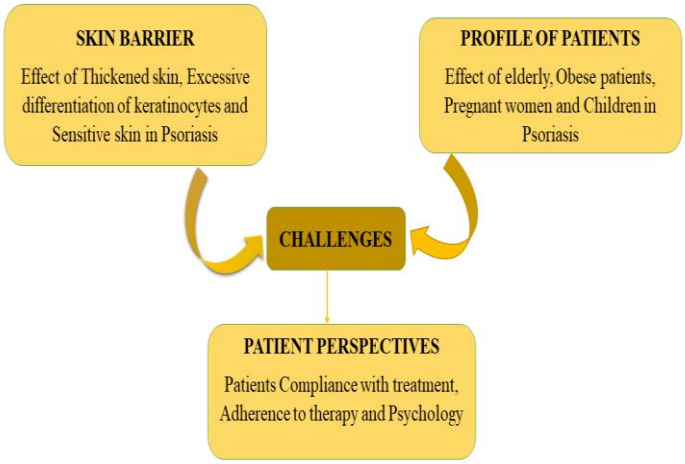

Fig 1: Tackling the Challenges of Managing Psoriasis

Pathophysiology of Psoriasis

Psoriasis's pathophysiology is intricate and not entirely understood. The pathogenesis of psoriasis is primarily ascribed to the overactivation of certain components of the adaptive immune system. Numerous Cell involved include macrophages, T cells, keratinocytes and plasmacytoid dendritic cells release cytokines that stimulate myeloid dendritic cells during the early stages of psoriasis pathogenesis. Myeloid dendritic cells are activated by DNA-LL37 complexes, for instance, which cause plasmacytoid dendritic cells to release interferon alfa (IFN-α). Myeloid dendritic cells are activated by DNA-LL37 complexes, for instance, which cause plasmacytoid dendritic cells to release interferon alfa (IFN-α). Myeloid dendritic cells release IL-12 and IL-23 when they are activated. Naive T cells differentiate into TH1 cells in response to IL-12. For TH17 and TH22 cells to survive and proliferate, IL-23 is essential. Interferon gamma (IFN-γ) and TNF-α are secreted by TH1 cells, IL-22 by TH22 cells, and IL-17, IL-22, and TNF-α by TH17 cells.11. The activation of the TH17 pathway by IL-23 is believed to be the most common of these routes. Important inflammatory mediators are transcriptionally triggered by IL-23 signaling, which is intracellularly mediated by Tyk2-Jak2 and STAT3. These cytokines cause immune cells to infiltrate the lesional skin, downstream keratinocyte proliferation, and elevated production of angiogenic mediators and endothelial adhesion molecules basically the adaptive immune system is excessively feed-forward activated in the pathogenesis of psoriasis. Excess IL-12 and IL-23 are secreted by activated myeloid dendritic cells. Naive T cells are differentiated into T-helper cells type 1 (TH1) by IL-12. For TH17 and TH22 cells to survive and proliferate, IL-23 is essential. Tumor necrosis factor (TNF -α) is secreted by TH1 cells. TH22 cells release IL-22; and TH17 cells (as well as numerous other inflammatory cells) release IL-17 (Fig 2). The cytokines that are released

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cause keratinocytes to undergo intracellular signal transduction, which in turn triggers the transcription of cytokine and chemokine genes. This starts a chain reaction of inflammation that eventually leads to psoriatic disease symptoms [10-16].

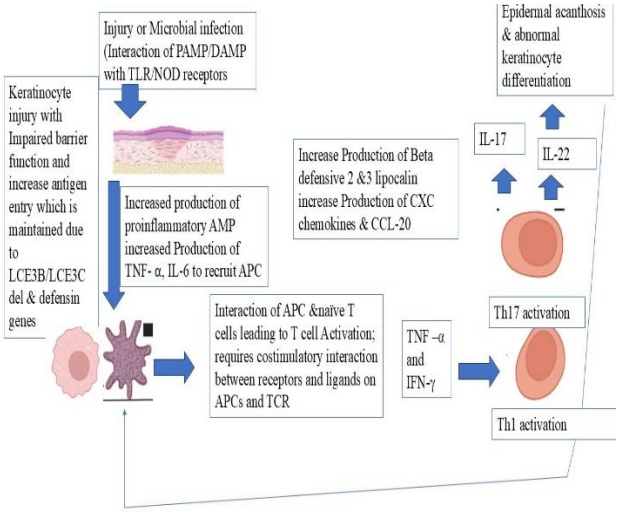

Fig 2: Pathophysiology of Psoriasis [17].

Solid lipid nanoparticles (SLNs)

This method was first used in the 1990s, SLNs represent the initial Development of Lipid-based nanocarriers system. The submicron particles (40–1000 nm) in this cutting-edge drug delivery vehicle are made of lipids and they are distributed in aqueous solution in which the surfactant acts as an emulsifier for SLN the lipids which include glycerides, steroids and fatty acids are solid at the body temperature and in the environment warmth. SLNs are frequently created by hot or chilly homogenization technique, Depending on thermal stability. High pressure can also be used to formulate SLNs. techniques for homogenization and ultrasonography. Site-specific liposome nanoparticles (SLNs) were created to Problems with the polymeric nanoparticles and the liposomes includes permeation of drugs, phospholipid degradation, polymer degradation and cytotoxicity. Comparison with liposomes, there the dynamic system permits the incorporation of parts. For instance, co-surfactant is typically used with the surfactant to reduce the size of particles can be either ionic or non-ionic. However, well-established research indicates that certain lipid and surfactant components in SLN formulation, such as stearic acid (lipid) and sodium dodecyl sulphate (surfactant), may have contributed to their high cytotoxicity level and, consequently, their reduced biocompatibility feature [18-20].

Nanostructured lipid carriers (NLCs)

Within the NLC system, the medication is Contains within it in a blend of liquid (oils) and solid (lipids that are unsaturated, amorphous, or mixed together. The design of the NLCs were also refined to produce solid core with the minimal to non-existent crystalline matrix. Similar preparation techniques used for SLNs and NLCs include hot homogenization, cold homogenization, and hot emulsification-ultrasonication. Lipid defects in their matrix systems also increase drug incorporation. NLCs can thereby produce a regulated release profile and increased drug solubility. NLCs are thought to be a better drug carrier than SLNs because of their greater biocompatibility and formulation. Additionally, NLCs are site-specific, and when applied topically, they enhance skin occlusive qualities, skin penetration, and skin retention [21-22].

Liposomes

The water compartment of the liposomes, which range in diameter from 50 to 1000 nm, is surrounded by Either through lipid bilayers. Liposomes are nano and microsized colloidal multilayer vesicles. Liposomes exhibit osmotically sensitive behaviour and water permeability. Liposomes can take on the forms of multivesicular, tiny, big, or multilamellar structures. Nevertheless, the size and homogeneity of liposomes rather than their lamellar numbers are more crucial for drug encapsulation. Conventional methods for preparing liposomes include solvent injection, thin-film hydration, detergent dialysis and reverse phase evaporation. To produce smaller unilamellar vesicles, further creation steps like sonication, high-pressure homogenization, or extrusion technique are needed [21-22]. Certain features that are important for anti-psoriatic activity are changed to enhance liposomal formulations for gene delivery applications. The inclusion of Positively charged lipids is attached to the outer surface of liposomes which Form strong complexes led to a recent move towards cationic liposomes and has sparked a lot of interest in the delivery of specific nucleic acids. In this sense, the genes are somewhat shielded from degrading reactions by liposomes. Most crucially, the cationic liposomal structures have the ability to target particular cells or tissues and will entrap themselves in the big negatively charged DNA segments, maybe around chromosomal size [23-24].

Niosomes

It has been shown that niosomes are a better option than liposomes. They were developed to overcome the problems of poor physical stability associated with the low manufacturing cost of liposomes. Because they contain non-ionic surfactants and does not carry a charge, niosomes are less harmful to human health, which is how they got their name. They have biocompatible qualities because they contain non-ionic, surfactants, which cause them to be less haemolytic and to disrupt cellular surfaces. Cholesterol is typically present throughout the development of niosomes, providing the membrane with stability and rigidity because of its charge [25-26]. Numerous methods for niosomes preparations have been documented, including as reverse phase evaporation, thin-film hydration, micro-Fluidization and ether injection, all of which have the potential to produce vesicles with varying sizes [27-31].

Transferosomes and Ethosomes

Transferosomes were created in 1992 by Cevc and Blume; they are sometimes referred Ultra deform liposomes or also

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commonly referred to as elastic liposomes. Phospholipids, which resemble edge activators (EA), liposomes and a single-chain surfactant and membrane-sorbening agent (e.g. sodium cholate and Tween 80), are the major ingredients of transferosomes. Improved deformability has been achieved by the introduction of novel techniques; yet, the formulation of these vesicles lacks a universal recipe, as the specific payload and drug type require customization of the medium suspending composition. In addition, vesicle stability and high bilayer flexibility are the two key components in the formation of transferosomes [32-34]. Touitou et al. created etherosomes in 1996 as an additional improved means of delivering active drugs. Like liposomes, phospholipids and ethanol make up etherosomes, and ethanol is crucial for effective topical medication administration. Because ethers have a higher ethanolic content (20–50%), they penetrate the skin more quickly. Ethosomal systems have the ability to distribute therapeutics trans dermally, much like transferosomes do. Because of their capacity to squeeze themselves through skin pores, the vesicles have been shown in multiple investigations to these are more effective as therapeutic agents than liposomes as they enhance the permeability of drugs. The standard cold approach, hot method, the ethanol injection: sonication, the TFM and reverse phase evaporation procedures are some of the commonly used ethosomal formulations [35-36]. Propylene glycol could be added to the ethosomal formulations to change how long the vesicles travel and collect in the skin. Furthermore, compared with ethosomes and transferosomes, transethosomes demonstrated the highest efficiency of medication incorporation consequently, transethosomes are more deformable compared to the others because of the components of ethanolic and surfactant. [37-40].

Nanoemulsions

Dispersions in nano-emulsions ensure that drugs are effectively dispersed at nano meter-sized droplets is achieved by two immiscible liquids in an isotropic, heterogeneous system called a nanoemulsion. Depending on the phase media, amphiphilic surfactants stabilize the two liquids, which are typically water-in-oil (W/O), oil-in-water (O/W), or double emulsions. The mean droplet sizes of these liquids are of less than 200 nm. In addition, the last recent studies and literature review has revealed that nanoemulsions are proven highly efficient encapsulating natural bioactive compounds and essential oils. Due to their great versatility, the emulsion approach can be produced in spray, gel, cream, and aerosol forms. These have been more extensively researched for the reason that they offer an advantage of practicality, non-invasive nature, and low cost, especially in high metabolic applications active drugs [41]. There are two types of preparation methods for nanoemulsions which include: high energy techniques and low-energy methods. A reliable High energy method is a preparative method used for the making of nanoemulsions such as Techniques as high-pressure homogenization break up large droplets to nanosized particles by using mechanical devices or over shear. Creates a reliable method for creating nanoemulsions by breaking up Mechanical devices or intense shear forces are applied to break large droplets into nanosized particles [42-48].

Mechanical dispersion technique

Using the mechanical dispersion method, phospholipids containing ethanol are mixed with terpene or a combination of terpenes and active drugs/biomolecules. To produce a straightforward solution, the liquid should be well mixed before being vortexed for five minutes and then sonicated for five minutes. Next, using a syringe and continuous vortexing for five minutes, phosphate buffer (pH 7.4), phosphate buffer saline (PBS), and an appropriate solvent were added to the solution to hydrate the vesicles (fig 3). Eventually, the mixture was sieved in order to extrude multilamellar vesicles using polycarbonate membranes with pore sizes ranging from 400 nm to 50 nm [49-51].

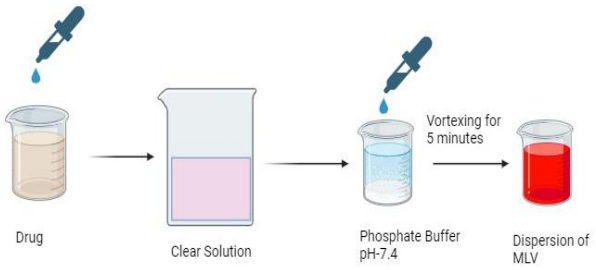

Fig 3: Mechanical Dispersion Method

Film hydration technique

2:1 v/v combination of methanol and chloroform, the phospholipid and ethanol mixture was dissolved in the film hydration process. This mixture was dried for two hours at 50°C using a rotary flash evaporator with a pressure drop from 500 to 1 mbar. Following that, a nitrogen flush was applied and the film was stored for two hours at a pressure of one millibar. For the 30-minute hydration of the deposited film, PBS (pH 7.4) or a combination of terpenes, ethanol, and PBS can be used. The Invasomes vesicles can then be created by adding the terpene or combination of terpenes and ethanol after the mixture has cooled. The prepared Invasomes were extruded via polycarbonate in membranes of the different pore sizes, then vortexed, ultrasonicated, and seized [52-54].

Preparation of Oleogel

In hot homogenization, the oil phase is mixed with the oleogelator, a material that will be responsible for the gel network, by heating it above the melting point of the oleogelator. This ensures the oleogelator molecules or particles distribute evenly in the oil phase. The mixture then undergoes intense shear forces caused by homogenization in either a high-speed blender or a homogenizer (fig 4). These forces will break apart any clusters and ensure uniform dispersion of oleogelator within the oil phase in a stable, homogenous network of a gel. With cooling, the solidification or consolidation of the gel network will take place as the temperature decreases [55-58].

Solvent Evaporation

Solvent evaporation requires preparing an appropriate solvent with the oleogelator and then mixing it with the oil phase. The

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final result of carefully managed evaporation of the solvent means that the oleogelator remains uniformly distributed within the oil phase while the solvent molecules evaporate out. Several methods may be used for such evaporation: vacuum drying, rotary evaporation, or simple air drying (fig 5). The method is especially appropriate for oleogelators with limited oil solubility or when particular control over the gel network structure is desired [59-61].

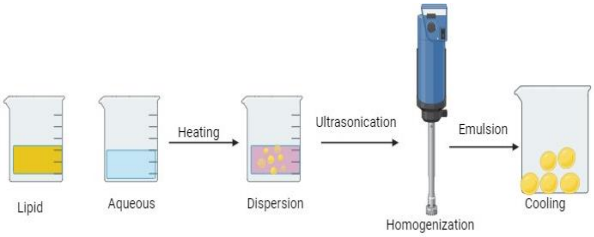

Fig 5: Solvent Evaporation

Melt Blending

Melt blending is quickly combining the oil phase and oleogelator at temperature greater than melting point of the oleogelator. Till the oleogelator is distributed uniformly throughout the oil phase, the combination is agitated or mixed in a similar way. This easy-to-use melt blending technique doesn't require any specialist tools, such as homogenizers or solvents. That might not be appropriate for all oleogelator, particularly those that are prone to structural deterioration or modifications at elevated temperatures. The necessary amounts of oil and gelator are meticulously weighed in accordance with the specified formulation. After that, these ingredients are combined in a dry, clean container. To encourage dissolution and uniformity, the mixture is then heated. This can be achieved by using an appropriate heating method, such a water bath or heating mantle [62-65].

Preparation of Aquasomes

The first stage is to fabricate a ceramic core; the process varies depending on the materials chosen. Diamond and calcium phosphate ceramic cores are the two types most frequently utilized. Among other techniques, sonication, inverted magnetron and colloidal precipitation, plasma condensation and sputtering can be used to create them. The most Common material utilized for core manufacture is ceramic due to its extremely uniform structure [66-68].

A carbohydrate (polyhydroxyl oligomer) coating the composition is applied to the ceramic cores. The aqueous dispersion of the cores is mixed with glucose, while it is being sonicated, the coating is applied. After that, lyophilization is applied to them in order to encourage the Permanent bonding of carbohydrates to a ceramic surface. Centrifugation is used to extract the unadsorbed carbohydrate (fig 6).

Adsorption is the last step in loading the medication onto the coated particles [69-74].

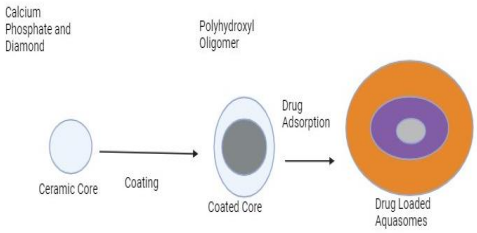

Fig 6: Preparation of Aquasomes

Ultrasonication

Ultrasonication is more effective than other high energy methods in terms of cleaning and operation**.** Ultrasonic waves create cavitation forces during ultrasonic emulsifications, which split the macroemulsion into nanoemulsions. This technique makes use of ultrasonicators, which are probes that produce ultrasonic waves. The nanoemulsion can be stabilized by varying the duration and ultrasonic energy input (table 1). Acoustic cavitation is the primary mechanism that provides physical shear in ultrasonic emulsification. The process of microbubble production, development, and collapse known as cavitation is brought on by variations in the sonic wave's pressure. The collapse of microbubbles creates high turbulence that leads to the emergence of nanoscale droplets [82-86] (fig 7-fig 9).

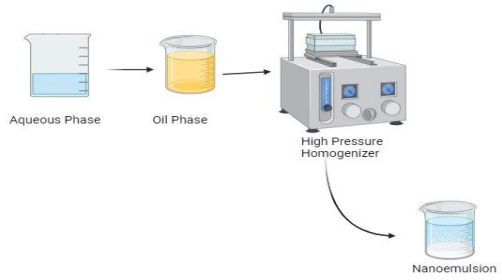

Fig 7: Homogenizer at High Pressure Method

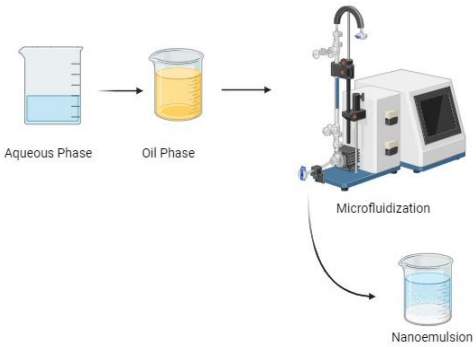

Fig 8: microfluidizer

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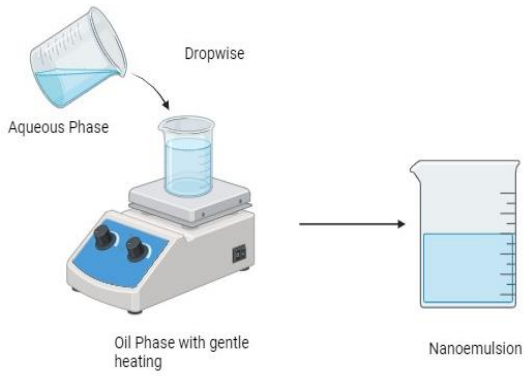

Fig 9: Nanoemulsion techniques

Phase Inversion

Emulsification process in this method a phase changes due to the spontaneous curving of the surfactant. Variations in temperature, composition, and other factors can cause variations in the surfactant's spontaneous curvature [87-97].

Table 1: Latest nano formulation work

S. No	Study Name	Drug	Formulation	Technique	Reference
1	M El-Kayal et al	luteolin	Invasomes	film hydration technique	[90]
2	Y Tomar et al	Curcumin	liquid crystalline nanoparticles	high-speed mixing technique	[91]
3	LC Pünnel et al	Beta - methasone dipropionate and calcipotriole	oleogel		[92]
4	ME Franco-Gil et al	(Neossance hemisqualane	Cream		[93]
5	AG Yurtsever et al	fluvastatin	transethosomes	thin film hydration method	[94]
6	P Kakade et al	tacrolimus	nanostructured lipid carrier	microemulsion	[95]
7	S Kulkarni et al	berberine hydrochloride	aquasomes	adsorption method	[74]
8	GS Gomes et al	tacrolimus	Pectin-based hydrogel loaded with polymeric nanocapsules	solvent displacement method	[96]
9	S Devadiga et al	clobetasol-17-propionate	nanoemulgel	water titration method	[97]

Conclusion

The integration of nanotechnology into psoriasis treatment has emerged as a promising frontier, offering innovative and targeted therapeutic approaches to overcome the limitations of conventional therapies. Psoriasis, a chronic inflammatory skin disease, remains challenging to manage due to the complexities of its pathophysiology, poor drug penetration through the skin barrier, systemic side effects, and lack of targeted delivery. Nanotechnology-based methods, including liposomes, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, dendrimers, micelles, and metal-based nanoparticles, have demonstrated significant potential in enhancing the efficacy and safety of anti-psoriatic therapies. These nanocarriers facilitate the controlled and site-specific delivery of therapeutic agents such as methotrexate, cyclosporine, calcipotriol, corticosteroids, and emerging biologics to psoriatic lesions, reducing systemic toxicity while improving drug bioavailability and skin permeability. Additionally, surface modification and functionalization of nanoparticles with ligands, peptides, or antibodies enable active targeting of inflammatory pathways, immune cells, and cytokines involved in psoriasis progression. Advances in stimuli-responsive nanocarriers, such as pH-sensitive, temperature-sensitive, and enzyme-responsive nanoparticles, have further allowed precise drug release at psoriatic sites. The incorporation of phytochemicals and natural anti-inflammatory agents like curcumin, quercetin, and ursolic acid into nanocarriers has also shown promising results, offering biocompatible, cost-effective, and sustainable alternatives for psoriasis treatment. Furthermore, the utilization of nanotechnology in gene therapy and RNA interference holds potential to downregulate psoriasis-related genes and inflammatory mediators, providing long-term therapeutic effects. However, despite the immense promise, the translation of these nanotechnological approaches into clinical practice faces several challenges, including scalability, reproducibility, safety, cost, and regulatory approvals. Long-term toxicological evaluations and clinical studies are imperative to ensure the safety and efficacy of nanocarrier-based formulations. Future research must focus on optimizing nanocarrier designs, improving skin-targeting efficiency, and exploring combination therapies for synergistic effects in managing psoriasis. Collaborative efforts between pharmaceutical

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scientists, dermatologists, and regulatory authorities are essential to overcome these challenges and accelerate the clinical adoption of nanotechnology for psoriasis treatment. As technological advancements continue to evolve, nanotechnology has the potential to revolutionize psoriasis management, offering patients more effective, targeted, and personalized therapeutic solutions with reduced side effects, ultimately improving their quality of life. The journey from bench to bedside may still be ongoing, but the integration of nanotechnology holds great promise for addressing the unmet clinical needs in psoriasis treatment, marking a significant step towards precision medicine and sustainable healthcare solutions.

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Ethics declarations

NA

Competing interest

The authors declare no known conflict of interest.

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Data availability

All data obtained during this study are included in this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The work described has not been submitted elsewhere for publication, in whole or in part, and all authors participated in the work and have agreed to the content of the manuscript.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this study.

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