DERMIS

Review Article

Volume and Issue: 05, 01

Skin Based Delivery Systems for Therapeutic Molecules: Advancing Dermatological Treatments through Innovative Drug Delivery Technologies

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Received : February 09, 2025
Published : February 21, 2025

ABSTRACT

The skin, recognized as the body's largest organ, plays a dual role as both a protective barrier and a vital conduit for transdermal therapeutic interventions. Recent decades have witnessed significant progress in the realm of skin based drug delivery systems, fundamentally transforming the administration of dermatological treatments. Traditional delivery methods, including oral medications and injectable therapies, frequently confront challenges such as diminished bioavailability, delayed therapeutic onset, and systemic side effects. In contrast, skin based delivery systems present a compelling alternative by facilitating the direct application of therapeutic agents at the targeted site of action, thereby minimizing systemic exposure and optimizing localized effects. Beyond their applications in dermatology, skin based delivery systems hold promise for the management of systemic conditions that manifest with cutaneous symptoms. Diseases such as rheumatoid arthritis, diabetes, and certain malignancies often present with dermatological manifestations, and localized delivery of systemic treatments via the skin could provide a more efficient and less invasive approach to managing these conditions. This review aims to explore the burgeoning field of skin based delivery systems for therapeutic molecules, with a particular emphasis on the utilization of nanotechnology, microneedles, and other innovative delivery methodologies in dermatology.

Citation: Owsley A, et al. (2025). Skin Based Delivery Systems for Therapeutic Molecules: Advancing Dermatological Treatments through Innovative Drug Delivery Technologies. Dermis. 5(1):30.

DOI: https://doi.org/10.35702/Derm.10030

Keywords: Transdermal Drug Delivery, Skin-Based Therapies, Nanotechnology, Cutaneous Manifestations, Drug Administration, Medical Applications, Therapeutic Agents

INTRODUCTION

The stratum corneum, the outermost layer of the skin, presents a formidable barrier that restricts the transdermal absorption of therapeutics at effective concentrations, posing significant challenges in treating various dermatologic conditions. For diseases such as psoriasis, eczema, and acne, achieving adequate drug levels in the systemic circulation is crucial for effective management. Researchers have explored the use of chemical enhancers to improve absorption; however, their application has been linked to adverse reactions and reduced patient compliance [1]. These issues highlight the necessity for more refined, patient-friendly methods to improve drug delivery through the skin, particularly for those with chronic skin conditions requiring long-term treatment. Moreover, the structural composition of the epidermis, characterized by protein-rich cellular structures alongside lipid-dense extracellular matrices, complicates the emulsification of highly lipid-soluble drugs. This challenge is especially relevant in treating conditions like atopic dermatitis, where the skin barrier is inherently compromised [2]. Understanding the interactions between drug properties and skin composition is essential for optimizing transdermal formulations capable of delivering therapeutics for dermatologic applications.

Lipids in the stratum corneum play a crucial role in preventing transepidermal water loss, which hinders the penetration of hydrophilic drugs into the epidermal layers [2]. This dual function not only preserves skin integrity but also complicates the delivery of therapeutic agents needed for the effective management of conditions like psoriasis and acne. Overcoming these intricate physiological barriers is essential for advancing the efficacy and reliability of transdermal therapeutic delivery systems targeting dermatologic disorders. Ongoing research and innovation in formulation technologies and penetration enhancement strategies will be vital in unlocking the full potential of this drug delivery route in dermatology. Nanotechnologies are one of the most crucial developments for precise intracellular pharmacological delivery, particularly for dermatologic conditions that require targeted intervention. Nanotechnology is the science of engineering and producing materials at the molecular and anatomic levels, allowing for the development of structures roughly in the 1–100 nm size regime in at least one dimension [3]. Creating technology of this scale has opened the door to countless new medical treatments previously thought not possible. The first FDA-approved generation of nanoparticles included lipid systems like liposomes and micelles, which can contain inorganic nanoparticles such as gold [4]. Liposomes, as the name implies, are composed of lipids (mainly phospholipids), which provide a unique advantage for drug delivery as their composition is analogous to the cell membrane, thus facilitating targeted treatment for various skin conditions while minimizing systemic exposure.

NANOTECHNOLOGY IN SKIN-BASED DRUG DELIVERY

Nanotechnology plays a pivotal role in enhancing the efficacy of skin-based drug delivery systems in dermatology. There are currently four main types of liposomes utilized for dermatological applications: conventional liposomes, PEGylated liposomes, ligand-targeted liposomes, and theranostic liposomes [3]. Conventional liposomes feature a lipid bilayer composed of anionic, cationic, or neutral lipids, primarily cholesterol and phospholipids, which encase an aqueous core. Both the lipid bilayer and the aqueous core can be filled with hydrophobic or hydrophilic substances, respectively [3,5]. For dermatological applications, these liposomes can encapsulate therapeutic agents such as anti-inflammatory drugs, corticosteroids, or antibiotics, allowing for localized treatment of skin conditions like eczema, psoriasis, or acne. PEGylated liposomes, which have polyethylene glycol (PEG) attached to their surface, enhance steric stability and reduce the likelihood of immune system recognition [3]. This property is particularly beneficial in dermatological therapies, as it extends the drug's residence time on the skin surface, permitting prolonged therapeutic effects while minimizing systemic exposure.

Ligand-targeted liposomes can be engineered with specific ligands—such as antibodies, carbohydrates, or peptides—that can bind to skin-specific receptors [3]. This targeted delivery approach is advantageous for conditions like psoriasis, where specific skin cells are involved. By delivering therapeutics precisely to these target cells, the efficacy of treatments can be significantly improved while reducing off-target effects. Theranostic liposomes combine characteristics of the previous three types by incorporating nanoparticles along with components for targeting, imaging, and therapy [3,4]. Such liposomes can be invaluable in dermatology for both

DOI: https://doi.org/10.35702/Derm.10030

diagnostic and therapeutic purposes, such as providing real-time imaging of skin lesions while simultaneously delivering therapeutic agents directly to the site.

Nanoparticles facilitate two primary methods of drug delivery: self-delivery and passive delivery. Passive delivery involves incorporating drugs into the nanoparticle's inner cavity via hydrophobic interactions [3,5]. In the context of dermatology, this method ensures targeted drug release at the site of application, which is vital for treating localized skin conditions effectively. Self-delivery, whereby drugs are conjugated to a carrier, allows for larger quantities of drugs to be loaded onto the nanoparticle [3]. However, when addressing dermatological issues, precise control of drug release is critical to prevent adverse effects associated with systemic absorption. Microemulsions have shown significant potential in transdermal drug delivery [5]. By emulsifying liposomes prior to topical application, the permeation of therapeutic agents through the stratum corneum is enhanced, which is crucial for disorders requiring topical treatment.

Incorporating therapeutic agents into nanoparticles or liposomes has demonstrated several advantages for dermatological applications. One notable benefit is enhanced stability, particularly for nucleic acid therapeutic agents, which can be fragile and susceptible to degradation [3,6]. This protection is essential for delivering gene therapies or mRNA vaccines aimed at treating skin lesions or disorders effectively. Moreover, liposomes are effective carriers for nucleic acids like siRNA or mRNA, which can improve gene therapy efficacy for skin conditions through better cellular uptake [3]. This feature is crucial for conditions like skin cancer, where precise gene delivery can alter disease outcomes. Additionally, the use of nanoparticles or liposomes can improve patient tolerance. Avoiding metabolism from the gastrointestinal tract can alleviate nausea and gastrointestinal upset related to oral medications, common adverse drug reactions (ADRs) when treating skin conditions. This improvement can lead to better patient adherence and treatment outcomes. Furthermore, encapsulating biologics in nanoparticles or liposomes may help reduce immunogenicity, enhancing their acceptance in the body and minimizing adverse reactions [3-5]. This reduction in immunogenic responses is especially beneficial in managing chronic dermatological diseases, promoting better overall patient health and quality of life. By focusing on skin-specific applications and the unique properties of various nanocarriers, there's a significant opportunity to revolutionize dermatological treatments through improved drug delivery systems.

CHALLENGES IN NANOTECHNOLOGIES IN DERMATOLOGY

Despite considerable advancements in medical technology, the application of nanoparticles in dermatological settings remains significantly underutilized, revealing a notable gap between research and practical implementation. Nanoparticles offer promising solutions for treating a variety of complex skin conditions, due to their unique properties, such as increased surface area and enhanced interaction with biological systems [6]. For instance, their ability to penetrate deeper layers of the skin can potentially improve the efficacy of topical treatments for conditions such as psoriasis, eczema, and acne. One of the foremost challenges in dermatology is discovering effective, reliable, and safe methods for drug delivery that not only improve therapeutic outcomes for skin conditions but also minimize potential side effects. The delicate nature of the skin microbiome and the risk of irritation or allergic reactions are critical factors to consider when developing nanoparticle-based treatments. Tailoring the size and surface characteristics of nanoparticles could enhance their compatibility with skin tissues, thereby improving patient acceptance and adherence to treatment regimens.

The primary obstacles to the widespread clinical application of nanoparticles in dermatology include technical issues such as stability, which affects the shelf life and effectiveness of nanoparticle formulations, especially in topical products. Additionally, the drug release profiles must be fine-tuned to ensure that therapeutic agents are released at the optimal rate and concentration for skin absorption. Regulatory challenges pose significant hurdles for bringing these innovative treatments to market, as dermatological applications often require rigorous testing to confirm safety and efficacy on human skin [6]. Despite these obstacles, it is crucial to explore the potential of nanotechnologies in addressing complex dermatological conditions. Innovative approaches, such as incorporating nanoparticles into cosmetic formulations or using them to enhance the delivery of biologics for conditions like atopic dermatitis and skin cancer, could revolutionize treatment paradigms. Finally, ongoing collaboration between researchers, dermatologists, and regulatory bodies is essential to navigate the challenges and unlock the full potential of nanotechnologies in dermatology.

Microneedle Technology

The skin serves as a dynamic interface for drug delivery, offering a non-invasive yet highly effective route for both localized and systemic therapies. However, its natural function as a protective barrier limits the passive diffusion of most therapeutic molecules, particularly large, hydrophilic, or unstable compounds. Traditional transdermal drug delivery methods, such as topical creams, patches, and iontophoresis, often suffer from low bioavailability, inconsistent absorption, and limited penetration beyond the epidermis, restricting their utility to superficial conditions [7]. To address these limitations, researchers have been exploring innovative solutions. Microneedle technology has emerged as a revolutionary approach, enabling precise intradermal or transdermal drug administration while preserving the skin's integrity [8,9]. Microneedles function by mechanically disrupting the stratum corneum, forming transient microchannels that allow for controlled diffusion of therapeutic agents without causing significant pain or discomfort. Unlike traditional needle-based injections, which result in systemic drug distribution, microneedles localize drug delivery to targeted skin layers, optimizing therapeutic effects while minimizing systemic exposure and associated side effects.

Microneedles are categorized based on their composition and drug delivery mechanism, with each type offering distinct advantages for dermatological and systemic applications. Solid microneedles, commonly fabricated from silicon, metal, or polymers, are primarily used for pre-treating the skin to enhance passive drug absorption [10]. In addition to their varying structures and materials, each type of microneedle serves a unique therapeutic purpose. Hollow microneedles feature microscale lumens that actively deliver liquid formulations into the dermis, allowing for precise dosage control in conditions requiring localized action, such as psoriasis or melanoma [11]. This innovative approach contrasts with other techniques in microneedle technology, such as dissolvable microneedles. Dissolvable microneedles, composed of biocompatible materials such as hyaluronic acid, chitosan, or polylactic acid, encapsulate drugs within their matrix, offering a controlled-release profile that extends therapeutic efficacy over time [12]. This approach contrasts with coated microneedles which are much faster in drug delivery. Coated microneedles utilize a thin film deposition technique, ensuring rapid drug diffusion upon skin penetration, particularly beneficial for hormonal therapies, biologics, and pain management applications [13]. The diversity of microneedle designs has expanded their potential beyond dermatology, with applications in autoimmune disorders, metabolic diseases, and oncology, where transdermal drug delivery enhances treatment adherence and reduces systemic toxicity. Beyond simply facilitating drug absorption, microneedles exploit the immunological properties of the skin to enhance vaccine efficacy and therapeutic response in inflammatory diseases. The dermis and epidermis are rich in antigen-presenting cells, including Langerhans and dendritic cells, which play a crucial role in initiating immune responses. Microneedle-based vaccine delivery, by directly targeting cutaneous immune networks, has demonstrated superior immunogenicity compared to conventional intramuscular injections, leading to dose-sparing effects and enhanced protection [14]. This mechanism has been explored for transdermal immunotherapy in atopic dermatitis, psoriasis, and allergic conditions. In these cases, localized immune modulation could mitigate disease severity while reducing reliance on systemic immunosuppressants [15,16]. This approach not only offers targeted treatment but also minimizes systemic side effects. Additionally, microneedles have shown potential in oncology, where transdermal administration of immune checkpoint inhibitors and oncolytic agents could localize therapy to cutaneous tumors or metastatic lesions while bypassing systemic adverse effects commonly associated with chemotherapy and biologics [17]. These innovations position microneedle technology as a versatile and patient-centric solution in dermatology and beyond, with the potential to redefine how systemic and localized conditions are managed through skin-based delivery.

Microneedle Applications

Microneedles have expanded the therapeutic landscape for both localized dermatological conditions and systemic diseases with cutaneous involvement. One of their primary advantages lies in their ability to efficiently deliver both hydrophilic and lipophilic drugs, overcoming the solubility and permeability challenges that often limit conventional transdermal formulations [18]. This innovative approach allows for a more versatile application of various drug types. Hydrophilic molecules, which struggle to diffuse through the lipophilic stratum corneum, benefit from microneedle-induced micropores, which create direct access points for enhanced absorption [19]. As a result, this method can significantly increase the effectiveness of the treatment.

Conversely, lipophilic drugs which are prone to hepatic first-pass metabolism when taken orally exhibit improved systemic bioavailability when administered via microneedles [20]. These properties have facilitated their use in anti-inflammatory agents for psoriasis, corticosteroids for eczema, and retinoids for acne, conditions where localized therapy with minimal systemic absorption is preferable.

Beyond traditional dermatological drugs, microneedles are reshaping the landscape of transdermal biological therapies, particularly for vaccines, peptides, and hormone replacement therapies. Vaccine delivery via microneedle patches has demonstrated enhanced antigen uptake and immune response activation, making them particularly suitable for influenza, COVID-19, and HPV vaccinations [21-23]. This innovative approach not only provides effective immunization but also improves patient compliance. The room-temperature stability of microneedle vaccines eliminates the need for cold-chain storage, significantly expanding vaccine accessibility in low-resource settings [24]. This accessibility is crucial, especially in regions where traditional vaccine storage is a challenge. In endocrine applications, microneedle technology has been successfully investigated for transdermal insulin delivery [25], offering an alternative to daily injections for diabetic patients seeking a pain-free and user-friendly solution. This method not only enhances comfort but also promotes better adherence to treatment regimens. Similarly, microneedle patches for testosterone, estrogen, and progesterone therapies allow for sustained hormone release, avoiding the peaks and troughs associated with oral or injectable formulations [26]. These applications align with the growing demand for patient-centered, minimally invasive drug delivery systems, particularly for chronic conditions requiring long-term adherence.

SKIN-BASED DRUG DELIVERY IN DERMATOLOGY

Chronic dermatological disorders such as psoriasis, eczema, and acne present unique challenges for effective management, primarily due to the intricate structural properties of human skin. The stratum corneum, being the outermost layer, acts as a protective barrier, significantly limiting the penetration of therapeutic agents required to alleviate these conditions. Traditional topical therapies, including creams, ointments, and gels, often fall short in achieving consistent clinical outcomes due to their inability to effectively deliver drugs to the deeper layers of the skin where they are most needed [27]. However, the advent of advanced drug delivery systems such as nanoemulsions, liposomes, and microneedles is transforming dermatological treatment by overcoming these barriers.

Nanoemulsions have emerged as a groundbreaking solution for enhancing drug delivery in dermatology, particularly in the context of psoriasis. By virtue of their small droplet size and increased solubility, nanoemulsions facilitate improved drug deposition directly in psoriatic lesions and thickened plaques [28]. This targeted approach not only enhances the therapeutic outcomes but also reduces potential systemic side effects, a significant advantage in the treatment of chronic skin conditions. These nano-sized carriers can effectively penetrate the lipid matrix of the stratum corneum, achieving localized delivery while minimizing systemic absorption [28]. The improved efficacy derives from the nanoemulsion's role in breaking down the lipid matrix of the stratum corneum in specific and targeted areas. The larger surface area provided by the nanoemulsion droplets allows for greater interaction with skin cells, thereby increasing the overall absorption of the therapeutic agents. Compared to traditional therapy, these attributes deliver higher drug concentrations directly to psoriatic lesions while reducing systemic exposure.

For conditions like acne, nanoparticles play a crucial role by targeting the sebaceous glands directly to deliver antimicrobials and retinoids. This localized delivery minimizes irritation to surrounding healthy skin and addresses underlying issues such as inflammation and bacterial proliferation more effectively than traditional therapies [29]. The utilization of nanotechnology not only improves the efficacy of treatments but also enhances patient compliance by providing less irritating and more effective options.

Furthermore, one innovative drug delivery approach to treat chronic dermatological disorders is microneedling. Through microneedling, the action of the therapeutic agents becomes more effective via microchannels which facilitate the delivery of drugs into deeper layers by bypassing the skin's natural barrier. Research by Alquam et al., published in Skin Health and Disease, demonstrated the safety and efficacy of microneedling as a treatment for acne vulgaris. The study revealed a notable reduction in acne lesions while reporting minimal post-treatment complications, thus reinforcing the potential of microneedling as a viable intervention for

DOI: https://doi.org/10.35702/Derm.10030

chronic skin conditions [30]. This not only improves treatment outcomes, but also improves patient satisfaction. Moreover, a comparative study by Lima et al. investigated the effectiveness of microneedling combined with topical agents versus topical agents alone in the treatment of chronic melasma. The findings indicated that the combination treatment yielded marked clinical and histologic improvements, suggesting that microneedling significantly enhances the effectiveness of traditional topical therapies [31]. These studies suggest a greater potential for its application as a versatile and effective adjuvant therapy in the field of chronic dermatological disorders. While research into its uses continues, microneedling holds promise for innovation in the developing area of skin-based drug delivery.

ENHANCED PATIENT OUTCOMES

Traditional therapies are limited in their effectiveness in dermatological conditions and currently come at a cost of frequent applications, subpar results, and unpleasant or even uncomfortable sensations. This has become a growing concern, however, with advanced skin-based drug delivery systems, innovative technology has continuously and progressively improved to enhance therapeutic efficacy, minimize side effects, and increase patient adherence.

Therapeutic drugs now more than ever have higher remedial effectiveness and can maintain consistent and prolonged activity due to advanced drug delivery devices. For example, to reduce flare-ups and provide consistent symptom control, hydrogels for eczema offer a prolonged release of corticosteroids [32]. Hydrogel has a unique mechanism of forming a moist protective barrier over the skin which restores hydration to the area and enhances drug penetration. This dual benefit enhances drug penetration and leads to reduced flare-ups, resulting in longer periods of remission. Beyond simply managing symptoms, such innovations markedly improve the quality of life for patients by offering effective, user-friendly solutions tailored for chronic conditions.

Skin-based drug delivery systems have also focused on lessening the side effects of therapeutic agents. Traditional treatments often result in systemic absorption of drugs leading to unwanted side effects. New technology such as liposomal formulations, encapsulate corticosteroids and reduce their potential for systemic absorption while maintaining anti-inflammatory efficacy [33]. Similarly, in acne treatments, solid lipid nanoparticles (SLN) reduced the irritation typically associated with traditional formulations. By reducing the quick release of active compounds, SLNs provide a steady and localized delivery of therapeutic agents to sebaceous glands, minimizing skin dryness, redness, and peeling [34]. These delivery methods significantly improve patient comfort and also strengthen adherence to treatment regimens making patients more likely to continue therapy when having fewer side effects.

Patient adherence is another crucial and key component of advanced skin-based drug delivery systems. Limitations of traditional therapies such as the sensory attributes of topical formulations, texture, and ease of application, greatly influence patient satisfaction and adherence [35]. Modern systems are gearing towards a more patient-friendly experience. Innovations such as nanoemulsions and microneedle patches significantly reduce application frequency by enabling sustained drug release. These advanced systems make treatment regimens more manageable, encouraging consistent use among patients. Studies published to *Nano Coverage* show that patients are more likely to adhere to treatments that are more convenient, comfortable, and result in fewer side effects [36]. With this, addressing challenges that involve patient adherence will lead to better clinical outcomes and overall patient satisfaction.

Advanced skin-based drug delivery systems represent a significant leap forward in the treatment of chronic dermatological conditions. By addressing the limitations of traditional therapies, leading-edge technology offers more targeted, sustained, and effective drug delivery. Innovations like hydrogels, liposomal formulations, and solid lipid nanoparticles provide localized treatment with fewer side effects, improving patient outcomes and quality of life. As research continues to refine these systems, their potential to further revolutionize dermatology remains immense, paving the way for more personalized, efficient, and patient centric approaches to managing skin disorders.

REGULATORY AND SAFETY CHALLENGES

While skin-based drug delivery systems hold immense potential to enhance therapeutic delivery, reduce side effects, and improve adherence for patients with chronic conditions, it remains a novel approach for which regulation is still evolving. The Food & Drug Administration (FDA)'s Center for Devices and Radiological Health (CDRH) is responsible for regulating companies who manufacture, repackage, relabel, and/or import

medical devices in the United States. CDRH is responsible for classifying every device into one of three regulatory classes: exempt (Class I), 510(k) (Class II) or Pre-market approval (PMA) (Class III) [37]. These classifications are based on the devices' intended use and indications and are essential in determining the level of regulation required to ensure patient safety. Class I includes microneedle based products intended for general dermabrasion including tattoo removal, blemish removal, and acne/minor injury related scar revision. A key FDA regulation for this class mandates that products must have a needle length of 0.3 mm or less as they should not affect the structure/function of deeper skin layers [37]. Innovative advancements in microneedling for therapeutic uses has created a need for greater regulation. In November 2020 a pivotal milestone was achieved when the FDA released guidance titled "Regulatory Considerations for Microneedling Products" which explained when microneedling devices would be classified as medical devices and thus subjected to premarket notifications (510(k)). According to this guideline, if a product "treats scars", "treats wrinkles and deep facial lines", "treats acne", "treats alopecia", "stimulates angiogenesis", "stimulates collagen production", or "promotes wound healing" it can be classified as a device under class II devices under 21 CFR 878.4430 [38]. As innovation in skin-based therapies continues to advance, regulatory frameworks will likely need to expand accordingly. Nevertheless, this FDA guideline provides a crucial foundation for manufacturers and plays a key role in ensuring patient safety.

Along with regulations governing skin-based therapies, safety remains a significant concern, requiring careful consideration of potential risks and patient well-being. A systematic review investigating the safety of microneedling highlighted that most patients experience the expected procedural side effects including transient erythema/edema, pain, pruritus, and bruising [39]. These side effects are generally mild and resolve quickly, underlining the non-invasive nature of the procedure. Infection is also a potential risk with microneedling and can result in increased redness, warmth, swelling, and/or pus formation [40]. However, this risk can be mitigated by prioritizing proper hygiene. As a result, microneedling indications have expanded and proven effective in improving varicella scars in dark-skinned teenagers, treating vitiligo as a monotherapy or as a combination therapy, in addressing alopecia/alopecia areata, and more [41]. This wide spectrum of microneedling use is reflective of the value of skin-based delivery systems and highlights patients' tolerance of the therapy. Research is however limited in assessing the long term safety of nanotechnological devices, therefore more longitudinal research is recommended.

STABILITY AND OPTIMIZATION

Oral delivery systems are the most preferred method for administering pharmaceuticals due to their painless self-administration, safety, patient compliance, and flexibility with dosage. However, their disadvantages include poor stability when exposed to acidic environments in the gastrointestinal tract [42]. Given that drugs administered orally often have low bioavailability, an alternative pathway was developed, intravenous injection delivery. Unlike orally administered drugs, IV injections are 100% bioavailable and avoid hepatic metabolism. However, it is an invasive and painful delivery that is not always well tolerated by patients [43]. Skin-based delivery therapies present a promising alternative by being less invasive, bypassing metabolic processes, and reducing patient burden through less frequent administration. Nanocarriers including liposomes and transfersomes serve as innovative solutions that can help deliver hydrophilic and hydrophobic compounds but they too have limitations. Liposomes function as medication localizers by operating on the skin's outer layer; however, their larger size, stiffness, and lower stability often limit their ability to penetrate deeper into the skin. Meanwhile, transfersomes offer enhanced permeability, but since their permeation relies on the water gradient, they pose challenges when used under occlusive conditions and are also difficult to load with hydrophobic drugs [44]. As research continues to refine skin-based drug delivery systems, optimizing nanocarriers will be key to overcoming these limitations and enhancing therapeutic outcomes.

MANUFACTURING CHALLENGES

Though the use of nanotechnology has promising benefits for the management of dermatologic disorders, there are currently multiple challenges in bringing this drug delivery system to the mass market. One of the major issues facing nanotechnology is ensuring production can offer consistent quality on a large-scale. Many of the carriers currently used, such as liposomes, have unstable physical and chemical structures [45]. Biosynthesis of nanoparticles is difficult to reproduce when moving from a small-scale laboratory to industrial production as even with highly specific techniques and materials, there is still often non-reproducible, batch-to-batch variability. Slight environmental changes can impact the nanoparticles' fragile chemical structures, which can alter vital characteristics such as particle size and solubility, decreasing drug efficacy [46]. These challenges highlight the need for improved stabilization techniques to enhance the durability

DOI: https://doi.org/10.35702/Derm.10030

of nanoparticles. With such unstable structures, nanoparticles are also difficult to store, which causes a lack of sufficient inventory for mass distribution [47]. These issues in production and storage will require both high levels of standardization at the manufacturing level and constant monitoring to produce a sustainable amount of nanotechnology that is safe and effective for patients.

The scalability of the drug delivery mechanisms for nanotechnologies has their own set of challenges as well. Just as the nanotechnologies themselves, delivery systems such as microneedle arrays face issues with large-scale production due to unstable chemical and physical structures as well as the complexities of producing these systems [48]. With such complexities on a production level, national and international standards should be created for both the production process itself and for standardizing quality control metrics. There are also high costs associated with producing drug delivery devices for nanotechnologies, which can be partially alleviated via mass production, but are also due to bureaucratic complexities in the current patent processes for these devices [49]. Additionally, advancements in materials and technology are needed to improve the design and functionality of these devices. Scalability issues continue past production into the clinic, as there are no clinical guidelines to evaluate toxicity and efficacy in humans of these products [48]. These challenges imply that more must be done in the fronts of production and clinical research to decrease costs and confirm efficacy when these drug delivery systems are used on a larger scale.

FUTURE DIRECTIONS

The promising results of nanotechnology and their associated delivery systems within the field of dermatology can bring new targeted treatments to the forefront of medicine. There are many promising novel nanomaterials that are in development such as silver nanoparticles for wound care. Silver nanoparticles have emerged as a particularly exciting development for wound care due to their potent anti-inflammatory and antibacterial properties, making them highly effective in treating a variety of wounds such as burns and diabetic ulcers. The anti-inflammatory and antibacterial properties of silver nanoparticles make it promising for use in wounds from burns to diabetic ulcers [50]. Reducing infection rates and accelerating healing times is critical for patients with compromised wound healing abilities. There is also a trend towards creating new nanomaterials with environmental sustainability in mind. Oligosaccharide-based nanotechnologies, such as nanocellulose and chitin nanofibrils, are being studied in the field of cosmetic dermatology as these natural materials are more easily biodegradable [51]. The interest in cosmetic application of these nanomaterials is partially due to the fact that they are biodegradable, but they also offer skin friendly properties that could enchanted the efficacy of topical cosmetics applications without being too harsh on the skin.

Furthermore, innovative nanoparticle delivery platforms, such as nanoemulsions, are on the horizon. These formulations, which involve suspending nanoparticles in two immiscible liquids, have shown remarkable potential in improving drug bioavailability. For instance, clinical trials have demonstrated that mixing cyclosporine with coconut oil and nutmeg in a nanoemulsion significantly enhances absorption in psoriasis patients, leading to more effective treatment outcomes [52]. The ongoing development of nanotechnology-based drug delivery systems spans various dermatologic fields, from cancer therapy to the treatment of inflammatory diseases and cosmetic applications. Continuous research is vital to refine these technologies, as they promise to improve drug bioavailability for targeted skin conditions while simultaneously minimizing systemic side effects, which can enhance patient compliance with prescribed therapies.

BROADER IMPACT OF SKIN BASED DELIVERY

Skin-based drug delivery systems have the potential to revolutionize both dermatology and the pharmaceutical industry as a whole. The innovation of less invasive and more efficient drug administration methods offers an opportunity to provide a more targeted approach to the treatment of a wide variety of both acute and chronic conditions. The non-invasive and convenient nature of these systems increases the chance of patient compliance, markedly improving drug administration for chronic diseases [53]. Skin-based drug delivery systems provide the unique opportunity for targeted drug delivery in dermatologic conditions such as eczema, psoriasis, and acne, with the treatment of interest being delivered directly and locally to the targeted skin region. This localized delivery not only ensures that the medication reaches the precise site of action but also facilitates enhanced drug absorption. Furthermore, these skin-based systems allow for enhanced drug absorption through slow and controlled release of the drugs over long periods of time, and enhanced

ability to overcome the skin barrier by way of micro-needles or nanoparticles [54]. The non-invasive nature and local delivery of these revolutionary drug systems helps to reduce the likelihood of systemic side effects and minimize adverse effects compared to traditional oral drug administration. This makes microneedling a safer alternative for patients who cannot afford the risk of side effects that come with oral medications, such as pregnant patients.

Looking beyond dermatology, these skin-based drug delivery systems have the potential to positively impact systemic drug administration, creating the opportunity to treat a wider range of diseases. Many chronic conditions have the potential to be managed medicinally via the skin-based delivery of medications such as insulin, anti-hypertensives, testosterone, estrogen, vaccines, and pain medications. Administration of these medications through the skin offers a new pathway for symptom management. Targeted delivery to specific areas, like inflamed joints in rheumatoid arthritis, enables precise intervention while reducing the burden of systemic administration. Treatments can be delivered directly to locations of interest, such as inflamed joints in rheumatoid arthritis or other sites of chronic pain, thus lowering the dosage of medication needed to reach the affected area. Transdermal patches or gels are an easily accessible and well-tolerated method of both hormone replacement therapies and chronic pain management, with greatly increased patient compliance compared to needle-based or oral alternatives [55]. These methods also minimize the risk of injection-related complications, making them a safer choice for many patients. Additionally, their ability to provide long-acting drug release can be particularly beneficial for managing conditions like diabetes and hypertension, where medication dosages frequently fluctuate [56]. Through controlled release mechanisms, these systems can provide therapeutic effects through localized therapy while simultaneously reducing adverse systemic effects compared to other drug administration methods.

POTENTIAL FOR PERSONALIZED MEDICINE

The ability of these skin-based drug delivery systems to be tailored to the unique needs of individual patients highlights the potential for these models to greatly impact the field of personalized medicine. Multiple variables in drug administration could be controlled through these systems, such as drug absorption rates, drug release duration, and patient compliance [57]. In particular, these systems enable customized dosing regimens that can adapt to a patient's specific metabolic rate, providing a more personalized approach to treatment. Furthermore, the timing of drug administration can be aligned with the patient's activities or specific needs, ensuring maximum effectiveness during critical periods, an example of such would be arthritis being managed before activists or movements that are known to cause pain.

One exciting aspect of these wearable drug delivery systems is their integration with real-time health monitoring technologies. Through the use of wearable smart devices, valuable health data—such as vital signs, skin conditions, electrolyte levels, and drug concentrations—can be wirelessly collected and transmitted to external monitoring systems. This continuous flow of data not only aids in maintaining an accurate dosing regimen but also facilitates immediate adjustments based on current patient conditions. This creates the unique opportunity to provide closed-loop drug administration on-demand [58]. The concept of closed-loop drug administration stands out as a particularly transformative innovation. With the integration of real-time data, these systems can automatically adjust drug delivery in response to fluctuations in patient health metrics. For example, if a wearable device detects a rise in blood glucose levels in a diabetic patient, the drug delivery system could immediately release a pre-set dose of insulin. This on-demand capability could significantly enhance patient safety and treatment outcomes by ensuring that medications are delivered when needed and in the precise amounts required.

CONCLUSION

Dermatological conditions have faced challenges in management of various conditions due to transdermal absorption barriers preventing adequate treatment. The skin's role as a defensive membrane hinders the effortless uptake of most therapeutic molecules. A primary challenge in treatment is the difficulty of delivering medications to the deeper skin layers, resulting in only superficial treatment of dermatological issues. Certain conditions such as psoriasis, eczema, and acne require systemic uptake to achieve significant improvement. These challenges emphasize the need for innovative modalities that overcome existing treatment barriers. Novel approaches should emphasize the interactions between the skin and drug properties as a means to optimize treatment. Emerging interventions, such as nanotechnologies and microneedling, are promising ways to effectively address these obstacles.

Microneedling and nanotechnologies are significant ways to deliver skin based treatment in chronic conditions. Nanoparticles display promising potential due to their ability to provide patient-friendly solutions for skin conditions. Nanoparticles have illustrated several advantages such as increased stability for more efficient gene therapy delivery, enhanced uptake of nucleic acids, and improved patient tolerance by gastrointestinal tract metabolism bypass. Additionally, encapsulating biologics in nanoparticles or liposomes can reduce immune reactions, improving their acceptance in the body and minimizing adverse effects. These benefits contribute to better management of chronic dermatological conditions and overall patient health. Microneedling has displayed its impressive ability in treating chronic skin conditions due to its capability of creating microchannels that bypass the skin's protective layers, enabling deeper delivery of treatments. This approach facilitates efficient delivery of both hydrophilic and lipophilic drugs, offering a minimally invasive solution especially beneficial for chronic conditions that require long-term adherence. Furthermore, microneedling leverages the skin's immune properties, enhancing vaccine efficacy and improving therapeutic responses in inflammatory diseases.

Despite innovative advances in skin based delivery systems, their clinical implementation remains limited. Continued research and collaboration are crucial to addressing the gaps and challenges that hinder the translation of these innovations into clinical practice. Steady development in nanotechnology, microneedles, and other advanced delivery systems holds the potential to greatly improve patient outcomes in dermatology. To maximize on the full capabilities of these technologies, further innovation in formulation strategies and penetration enhancement methods is pivotal. Collaboration between researchers, dermatologists, and regulatory bodies will be essential to overcoming challenges and ensuring the effective integration of nanotechnologies into dermatology practice. Ultimately, advancing these systems will pave the way for more personalized, efficient, and patient-centered approaches to managing skin disorders.

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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