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A Literature Review on Spicule-Assisted Transdermal Delivery Systems (S-TDS) : Penetration Mechanistic and Translational Perspectives

Siti Maimunah[1], Alifia Putri Febriyanti[1*], Begum Fauziyah[1], Adhe Septa Ryant Agus[2]

[1]UIN Maulana Malik Ibrahim, Malang, East Java, Indonesia
[2]Airlangga University, Surabaya, East Java, Country

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Corresponding author e-mail: alifia.putri@farmasi.uin-malang.ac.id

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ABSTRACT

Introdiction*: Spicules are microscopic needle-shaped structures derived from marine sponges or synthetic biomimetic materials that have recently attracted attention as an innovation in enhancing transdermal penetration in cosmetic dermatology. This structure is capable of temporarily disrupting the protective layer of the stratum corneum and forming high-density microchannels that facilitate the delivery of bioactive compounds such as peptides, hyaluronic acid, growth factors, and nucleotides to deeper skin layers.* ***Aims****: The purpose of this review article is to provide comprehensive information on penetration mechanistic and translational perspectives aspects of spicule-assisted transdermal delivery systems (S-TDS) as well as to describe the mechanisms of skin absorption, local distribution, and the resulting biological effects.* ***Methods:*** *This review was conducted through a literature study using databases including Scopus, PubMed, and ScienceDirect, focusing on publications from 2016 to 2025 with the keywords "spicule," "transdermal delivery," "pharmacokinetic," "pharmacodynamic," and "cosmetic dermatology."* ***Result:*** *Based on the literature, S-TDS have been shown to enhance skin permeability and prolong the retention time of active ingredients in the epidermis and dermis, leading to improve bioavailability and sustained biological response. Pharmacokinetic parameters based on literature include flux metrics, percentage penetration, tissue deposition, and duration of spicule. Pharmacodynamic parameters, spicules induce controlled micro-injuries that stimulates fibroblast proliferation, collagen synthesis, and skin remodelling, resulting in anti-aging and skin rejuvenation effects.*
Conclusion: *The preclinical and clinical studies suggest that spicules can enhance the penetration of various bioactive molecules, with potential applications in therapeutic dermatology, anti-aging and whitening cosmetics, transdermal vaccination and immunotherapy and systemic delivery for chronic therapy.*

KEYWORDS*: microneedle; skin delivery; spicule; sponge spicule; transdermal*

INTRODUCTION

Advances in cosmetic dermatology demand the development of skin delivery systems that are not only effective in penetrating the stratum corneum layer but also safe, biocompatible, and capable of precisely regulating the release profile of active ingredients. Human skin is the primary physiological barrier to the absorption of topical compounds, with a dense lipid layer

that limits the diffusion of large and highly polar molecules (Zhang et al., 2017). This barrier poses a significant obstacle to the effectiveness of modern cosmetic active ingredients such as peptides, hyaluronic acid, and growth factors, which generally have molecular weights above 500 Da. Conventional approaches to enhancing skin penetration have included the use of chemical enhancers, lipid emulsions, microneedles, and nanoparticle technology, but these methods often present limitations such as potential irritation, high production costs, and difficulty in controlling penetration depth (Kim et al., 2022).

In this context, spicule-assisted transdermal delivery systems (S-TDS) emerge as a biomimetic innovation offering an alternative solution. S-TDS utilises the natural needle-shaped microscopic structure of sea sponges to create temporary microchannels on the skin's surface, thereby enhancing skin permeability to cosmetic active ingredients (Zhang et al., 2019a). Conventional microneedles that require special tools, rather spicules can be applied simply through light rubbing in the form of powder, cream, or patches, making them more commercially acceptable and more comfortable for consumers to use This innovative S-TDS approach not only improves the delivery of active ingredients but also minimizes discomfort compared to traditional methods (Chen, n.d.; Tandon et al., 2025).

In Indonesia, the rich potential of marine resources opens up significant opportunities for the development of active ingredients and cosmetic biomaterials based on sea sponges. Some local studies have highlighted this potential. Putra et al. (2024) reported the identification of Haliclona and Clathrina species in the Spermonde Islands, South Sulawesi, which have spicule morphologies similar to the Haliclona oculata species used in cosmetic research in China and Korea (Putra et al., 2024). Another study by Rahmanisa et al (2025), found that Indonesian sea sponge extract contains natural silica spicules that have the potential to be used as a topical penetration enhancer without causing toxicity to keratinocyte cells (Rahmanisa et al., 2025)

The industry is currently starting to develop micro-needle formulation technology for drug delivery, which investigate micro-needle raw materials from natural ingredients that are safe and can dissolve to skin such as spicules. This review article aims to provide a comprehensive overview of the mechanism of penetration in spicule-assisted trandermal delivery systems, focussing on the relationship between the morphological and compositional characteristics of spicules and their mechanism through pharmacokinetic and pharmacodynamic effects. This approach is expected to serve as a reference for researchers, lecturers, and pharmacy practitioners in designing innovative cosmetic formulations that are based on scientific evidence, safe, and adhere to the principles of sustainability.

METHODS

This review article was developed by systematically collecting and analysing peer-reviewed literature relevant to mechanism and tanslational perspectives of spicule (Spicule-Assisted Transdermal Delivery Systems (S-TDS). A literature search was conducted through the PubMed, ScienceDirect, Scopus, and Google Scholar databases using journal articles published in the last ten years (2015–2025); peer-reviewed original research, review articles, and meta-analyses; search terms included the following keyword combinations: "spicules", "sponge spicule", "transdermal delivery", "skin delivery" and "skin penetration". The selection and evaluation stages followed the PRISMA recommendations adapted for narrative reviews, including qualitative thematic analysis to identify convergent evidence between physical morphology, and penetration data correlations. All data was extracted manually by cross-referencing databases and validated using the citation tracking tool in Mendeley Reference Manager. The synthesis was completed after peer cross-verification to ensure the accuracy and replicability of the included studies (Figure 1).

RESULT

An Overview of Spicule

In the transdermal delivery systems, spicules refer to needle-like structures obtained from marine sponges and used as mechanical agents to enhance skin permeation. The most studied of spicules from the genus Haliclona which is a silicic oxeas, sharp and rod-shaped with a length of about 120 μm and a diameter of about 7 μm, and can disrupt the integrity of the stratum corneum in a dose-dependent manner and persist in the skin for at least 72 hours, thus allowing continuous penetration for hydrophilic biomacromolecule (Zhang et al., 2017). The main function of spicules in drug delivery is to create a physical pathway of microchannels in the stratum corneum layer so that large vesicles, particles, or molecules can pass through the skin barrier; this method has been used alone or in combination with nanocarriers such as flexible liposomes to deliver macromolecules to the dermis and deeper tissues (Kim et al., 2022; Zhang et al., 2021).

The use of spicules in transdermal applications is due to their capacity to increase the amount and depth of penetration of active substances without the need for complex invasive equipment, as well as preclinical data showing a large increase in the absorption of model molecules (Jin et al., 2025). Fluorescein isothiocyanate-dextran (FD-10) was used to evaluate penetration of sponge Haliclona sp. spicules increased by 33.09 ± 7.16 times and cross-dermal accumulation by 62.32 ± 13.48 times in in vitro studies, and in vivo results also reported increased absorption compared to controls and compared to conventional microneedling. In addition, toxicology studies and measurements of transepidermal water loss showed that spicule-induced skin damage

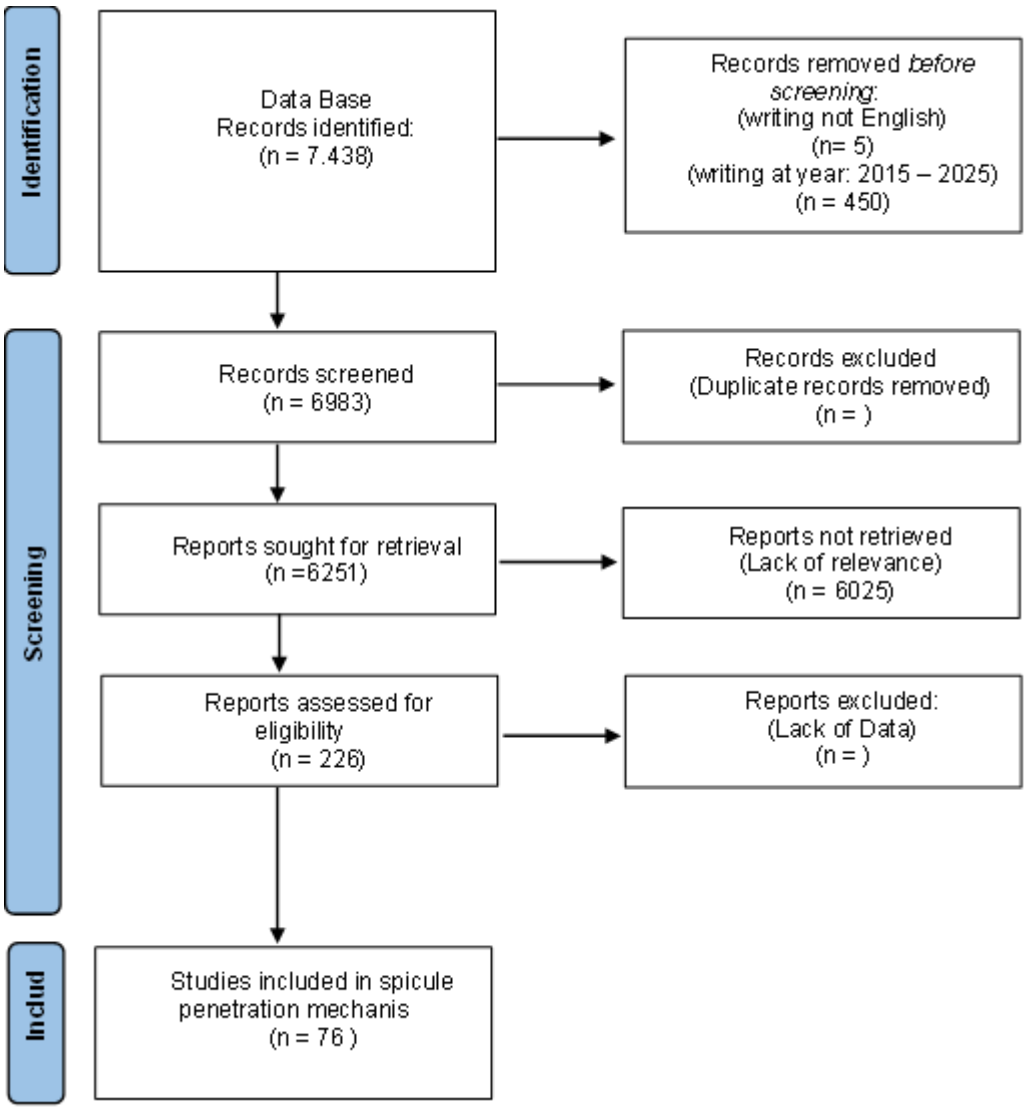

Figure 1. Identification of studies via PRISMA 2020

was limited and the skin could recover within a relatively short time in the tested animal models (Kumar et al., 2022). This spicule-based technology offers a promising alternative for non-invasive drug delivery, especially for large molecules such as peptides, proteins, and vaccines that have difficulty penetrating the skin barrier conventionally.

Spicules used in transdermal delivery systems are primarily derived from marine organisms, particularly marine sponges (Porifera) (Kim et al., 2022; Lukowiak, 2020). The genus Haliclona are the most common source studied in the scientific literature for transdermal drug delivery applications. Marine sponges produce spicules as part of their structural framework, and these structures can be isolated and processed for biomedical applications. In addition Haliclona, several other marine sponge species have also been explored as sources of spicules, including *Suberites domuncula* and *Monorhaphis chuni*, although with a more limited level of research for transdermal applications (Alves et al., 2020; Zhang et al., 2017).

Based on their mineral composition, spicules can be classified into two main types: siliceous spicules and calcareous spicules (Pisera et al., 2021). Siliceous spicules, which are composed of biosilica, are the most widely used type in transdermal applications due to their superior mechanical properties and good biocompatibility. Calcareous spicules, which are composed of calcium carbonate, are found in some mollusks and other organisms, but their use in transdermal delivery systems is still limited (Werner et al., 2015). In terms of morphology, spicules can be oxea (rod-shaped with both pointed ends), monaxon (one axis), or other more complex forms depending on the species of origin and their biological function in the organism (Putra et al., 2024; Schröder et al., 2016).

Structure and Morphology of Spicule

Discussion of the physical structure of spicules is relevant to understanding how morphological parameters determine the penetration and effectiveness. Morphologically, sponge spicules (e.g. from Haliclona) are usually described as sharp rods (oxea) with a pointed surface that penetrate the stratum corneum (Kim et al., 2022; Ogundele & Okafor, 2017) . The typical size of spicules reported is approximately 120 μm × 7 μm, while variants of microspicules from other sources or preparations may exhibit different dimensions. For example, processed microspicules have a width of approximately 11.89 μm and a length of approximately 176.77 μm before further processing. Sharpness, aspect ratio (length/diameter), and structural integrity influence the ability of spicules to form microchannels: spicule treatment can produce continuous microchannels with an average depth of approximately 48.6 ± 13.5 μm and a high density (e.g., approximately 850 ± 125 microchannels per mm^2), parameters that determine the extent to which vesicles or assembled molecules can penetrate deeper layers of the skin (Kumar et al., 2022; Zhang et al., 2017).

The nanostructural spicules exhibit a complex hierarchical organization. The evaluation used transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM) which revealed that spicules consist of nanofibrils ~10 nm in diameter that form bundles and then become axial filaments. These axial filaments serve as scaffolds or templates for concentric silica deposition. This hierarchical structure begins with silica nanoparticles that combine to form annuli (concentric rings), which then form a macroscopic needle-like structure (Görlich et al., 2020; Putra et al., 2024; Werner et al., 2015). The silica layers are arranged concentrically in a lamellar pattern that provides mechanical strength while allowing gradual degradation in biological environments (Samanci et al., 2021; Schröder et al., 2016).

The biosilica in sponge spicules has a different chemical structure from synthetic

silica because it is formed through a biomineralization process involving specific proteins and enzymes such as silicatein. Silicatein is a key enzyme that catalyzes the polycondensation of silica from a soluble silica precursor (silicic acid) to solid biosilica (Ehrlich et al., 2024; Pozzolini et al., 2022; Rahmanisa et al., 2025). The chemical composition of silicic spicules is mainly composed of hydrated silicon dioxide (SiO_2) with the general formula $SiO_2 \cdot nH_2O$, where n varies depending on the degree of hydration (Pisera et al., 2021). In addition to the main silica component, spicules also contain structural proteins and an organic matrix that play a role in the biomineralization process and provide better biocompatibility properties compared to pure synthetic silica. The main proteins involved in spicule formation include: (1) Silicatein - the main enzyme that catalyzes silica deposition and forms axial filaments; (2) Silintaphin-1 - a scaffold protein that interacts with silicatein to form the axial filament structure; (3) Galectin - a protein involved in the regulation of silica deposition; and (4) Collagen - a component of the organic matrix that provides structural flexibility (Ehrlich et al., 2024; Schröder et al., 2016)

In formulation practice, biosilica spicules are often used as is or after their surfaces have been modified. Several studies have reported surface modification (e.g., making it more hydrophobic) for specific purposes such as modulating the interaction of spicules with cargo/vesicles or for transdermal vaccine applications, making the surface chemistry and post-isolation treatment factors that can be modified to optimize performance (Chen et al., 2020; Jin et al., 2025; Zeng et al., 2025). Spectroscopic analysis using Fourier-transform infrared spectroscopy (FTIR) and solid-state nuclear magnetic resonance (NMR) showed that biosilica spicules have an amorphous structure with varying degrees of condensation and water content between layers (Pisera et al., 2021; Werner et al., 2015).

The term "spicule" encompasses the diversity of biominerals in invertebrate phyla. In addition to the silicic spicules in many marine sponges, there are also calcaric spicules found in some mollusks and other organisms, where the nanoscale organic matrix acts as a template for the formation of calcium carbonate or silica phases depending on the taxonomy and biomineralization pathway (Putra et al., 2024). The chemical composition of spicules is not uniform across organisms and must be determined according to the biological source used in a particular transdermal application. Calcareous spicules are composed primarily (Görlich et al., 2020; Putra et al., 2024)

Morphological variability also has formulation and safety implications because physical processing (e.g., grinding or blending) can shorten or break the spicules into short fragments or fine powders, thereby altering the dermabrasion effect and potential irritation (Luo et al., 2024; Waghule et al., 2019; Zhang et al., 2017). Comparative studies

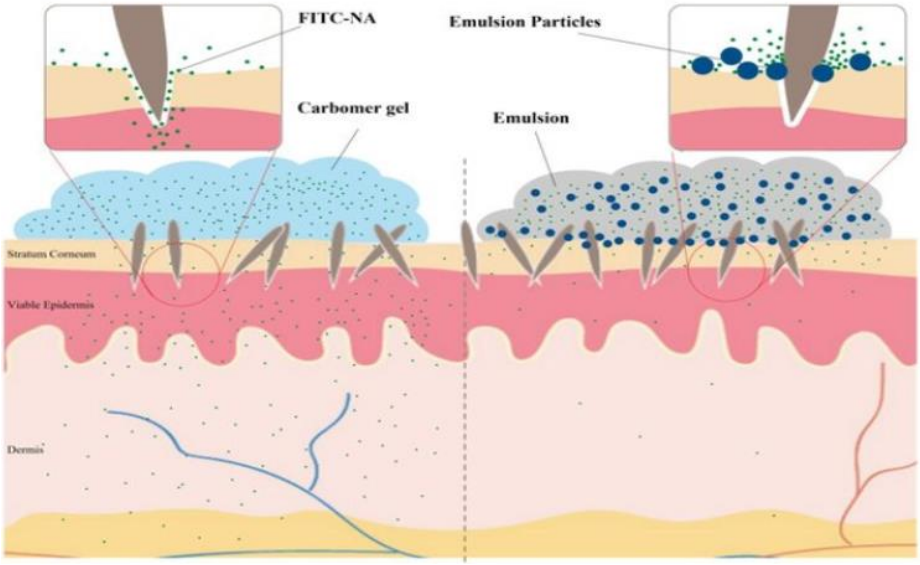

Figure 2. Schematic illustration microchannels wound to enhance drug permeation at the stratum corneum of S-TDS with different formulation (produced from Zhang et al., 2025 under the terms of CC-BY 4.0 License)

on spicules from several sponge species have shown a correlation between the L/D (length/diameter) aspect ratio and increased skin permeability, making the choice of spicule type and preparation process critical parameters in the design of spicule-based delivery systems. These structural characteristics enable spicules to function not only as microchannel generators but also as scaffolds that can persist long enough to facilitate sustained drug delivery (Jin et al., 2025; Zeng et al., 2025).

Mechanism of Action of Spicules in Transdermal Delivery Systems

Spicules are skeletal structures of sea sponges composed of silica or calcium carbonate with sharp and rigid geometries These unique morphological characteristics enable spicules to act as microneedles that can physically penetrate the stratum corneum, creating microchannels to enhance drug permeation (Figure 2) (Ehrlich et al., 2024; Li et al., 2022; Liang et al., 2020; Zhang et al., 2017). The mechanism of action of spicules in transdermal systems can be divided into four main interrelated stages: (1) physical penetration and microchannel formation; (2) temporary disruption of the skin's lipid and protein barriers; (3) enhanced diffusion and transport of active ingredients; and (4) controlled drug retention and release in the target tissue (Kim et al., 2022; Liang et al., 2020; Zhang et al., 2017).

1. *Physical Penetration and Microchannel Formation*

The initial stage of the system *Spicule-Assisted Transdermal Delivery System* (S-TDS) is characterized by direct physical interaction between spicule particles and the skin surface, especially *the* stratum corneum (SC). The sharp tips of the spicules allow penetration into the skin's "brick-and-mortar"

structure—corneocytes as the "bricks" and intercellular lipids as the "cement"—without damaging the underlying epidermis (Kim et al., 2022; Liang et al., 2020). The spicules penetrate the lamellar lipid layer and partially break the protein bonds between corneocytes, forming microscopic channels 30–60 μm deep that are evenly distributed throughout the application area (Ali et al., 2022; Zhang et al., 2019). This mechanism is known as micro-mechanical poration, which is the elastic deformation of the stratum corneum that does not cause permanent damage to the epidermis (Zhang et al., 2017)

Chemically, the spicule surface is composed of amorphous biosilica with hydrophilic silanol (–Si–OH) groups that can form weak hydrogen bonds with skin lipids, allowing for transient adhesion to the SC surface (Engqvist & Engqvist, 2025; Liang et al., 2020; Luo et al., 2024). This interaction stabilizes the spicule position during penetration, while facilitating the formation of more regular channels compared to inert metal needles. Because spicules are biocompatible and immunologically nonreactive, they do not induce acute inflammatory reactions or granuloma formation in the tissue (Fung-A-Jou et al., 2023; Ma et al., 2022; Silva et al., 2018). Therefore, the physical penetration and microchannel formation steps of the spicule-transdermal delivery system (S-TDS) can be viewed as a combined process of microscopic material mechanics and surface chemical interactions that result in a transient but effective diffusion pathway (Abdoh et al., 2024; Kim et al., 2022; Uchida et al., 2021; Vaseem, et al., 2024)

Microchannel formation by topical application of spicules has been reported to result in a very high canal density and sufficient depth to reach the living epidermis and superficial dermal zones. Studies combining spicules with flexible liposomes recorded continuous microchannels with an average depth of 48.6 ± 13.5 μm and a density of approximately 850 ± 125 microchannels per mm^2, expressing the ability of spicules to create thousands of permeation pathways in a small area of skin (Zhang et al., 2017). This high microchannel density is crucial which increases the surface area reached to drug diffusion, significantly enhancing transdermal flux compared to a smaller number of microchannels (Aswar et al., 2024; Tandon et al., 2025).

The formation of channels is dose-dependent on the number of spicules applied and can be maintained for periods of hours to several days. Studies have shown that spicules can be retained in the skin for at least 72 hours after application providing a sustained penetration effect (Liang et al., 2020; Milewski et al., 2010). The timing of channel closure has also been systematically measured, with gradual closure reported to last up to approximately 120 hours after application in porcine skin models under both in vitro and in vivo conditions. This relative slow closure timeline provides a sufficient time window for

optimal drug penetration, while still allowing for complete restoration of the skin barrier to prevent excessive transepidermal water loss or the risk of infection (Donnelly, 2017).

2. *Temporary Disruption of The Skin's Lipid and Protein Barriers*

The temporary disruption of the lamellar lipid structure and protein matrix of corneocytes, which naturally act as the primary barrier to skin permeation. The stratum corneum is composed of corneocytes held together by lipid lamellae (ceramides, cholesterol, free fatty acids) and proteins such as filaggrin, loricrin, and involucrin. Mechanical penetration by spicules causes disorganization of the lipid lamellae, an increase in the inter-bilayer distance from ~6 to 9–10 nm, and a decrease in the compactness of desmosomes (Liang et al., 2020; Zhang et al., 2021). Mechanical and localized disruption confined to the area surrounding the formed microchannels, minimizing overall barrier damage while still providing an effective penetration pathway.

The specific protein or lipid components disrupted are not explicitly described in the available corpus, data on microchannel closure and spicule retention suggest that barrier disruption occurs over a controlled timeframe. Microchannels formed remain open and functional for approximately 120 hours post-application. The skin barrier recovery process involves keratinocyte proliferation, new lipid synthesis, and structural reorganization of the stratum corneum, with microchannels closed and skin barrier function gradually returns to normal (Hajleh et al., 2025; Kim et al., 2022; Lee et al., 2025; Lim & Kim, 2022). The reversibility of this disruption is an important aspect, as the increased permeability is temporary and minimizes the risk of excessive transepidermal water loss or pathogen penetration. Safety studies have shown that spicule application does not cause significant skin irritation or prolonged inflammatory reactions, supporting a good safety profile for clinical application (Kim et al., 2022; Liang et al., 2020; McAlister et al., 2017; Sim et al., 2022; Vaseem, et al., 2024; Załęska & Smuda, 2023a).

The safety aspects of spicule-induced barrier disruption have been evaluated in various preclinical studies. Histopathological evaluations showed that spicule penetration caused minimal tissue trauma with a mild and transient inflammatory response. There was no evidence of tissue necrosis, significant bleeding, or permanent structural damage to the dermis or epidermis. Furthermore, functional parameters such as trans-epidermal water loss (TEWL) showed a transient increase after spicule application, which returned to baseline values within a few days, confirming complete barrier restoration (Lim & Kim, 2022; Zeng et al., 2025; Zhang et al., 2021). Tolerability in animal models indicates that repeated application of spicules does not cause cumulative skin damage or sensitization. Mechanical disruption results in an increase 10–20% transepidermal water loss (TEWL)

within the first 12 hours, indicating increased skin permeability and effects are reversible (Kim et al., 2022; Lee et al., 2025; Liang et al., 2020; Zhang et al., 2019). Subsequently, skin compensatory mechanisms are immediately activated: lamellar bodies in the granular layer secrete new lipids that repair the barrier structure within 48–72. Spicule system is categorized as a reversible barrier modulation system—it utilizes microtransient disruptions to increase diffusion without causing chronic damage and induce structural protein differentiation. Immunohistochemical analysis shows a transient decrease in filaggrin and loricrin expression, indicating relaxation of intercorneocyte bonds. This deformation creates microfissures that expand the diffusion area and facilitate the penetration of carriers such as flexible liposomes. After the channels close, skin protein expression returns to normal, demonstrating the skin's natural recovery properties following spicule application (Kim et al., 2022; Lee et al., 2025; Załęska & Smuda, 2023b; Zhang et al., 2019; Zhang et al., 2017; Zhang et al., 2025)

3. *Enhanced Diffusion and Transport of Active Ingredients*

The primary mechanism for enhancing diffusion and transport of active ingredients through the spicule system is the formation of a direct permeation pathway that bypasses the stratum corneum barrier. Microchannels created by spicules provide a diffusion route with significantly lower resistance compared to passive diffusion through the intact stratum corneum (Abdoh et al.,2024). Thus only molecules with low molecular weight (<500 Da) and moderate lipophilic properties can effectively penetrate at the normal skin. Microchannels form allowed large hydrophilic molecules, peptides, proteins, and even nanoparticles to penetrate deeper skin layers (Kim et al., 2022; Liang et al., 2020; Lim & Kim, 2022; Neubert, 2024; Tansathien et al., 2019). In addition to the direct physical pathway, spicules can also function as carriers or reservoirs for drugs, especially when modified with mesoporous layers or polymer coatings. Spicules coated with mesoporous silica (mSHS) can contain drugs within their pores and release them gradually as they become embedded in the skin (Luo et al., 2024; Sanjay et al., 2018; Tandon et al., 2025). This high loading capacity and controlled release adds an additional dimension to the transport mechanism, where the drug not only diffuses through the microchannels but is also released locally from the embedded spicules, creating a favorable concentration gradient for deeper penetration (Kim et al., 2022; J. Li et al., 2022; Luo et al., 2024).

Diffusion becomes much more efficient when spicules are combined with flexible carrier systems such as ethosomes, transfersomes, or flexible liposomes. These carriers stabilize active ingredients during their passage through narrow channels and adapt their shape (ultraformability) to the channel diameter. The combination of spicules with flexible carriers has been shown to enhance the

penetration of large molecules such as siRNA (Liang et al., 2020), peptides (Zhang et al., 2021), and hyaluronic acid (Zhang et al., 2019a). Positively charged liposomal carriers also strengthen electrostatic interactions with negatively charged skin, accelerating transport into tissues (Ibaraki & Kanazawa, 2022). In various animal models, the spicule system has been shown to enhance the penetration of anti-inflammatory drugs, insulin, and anti-aging molecules without increasing toxicity. A combination with stem cell exosomes (MSC-exosomes) enhances skin regeneration through exosome accumulation in the dermis (Kim et al., 2022; Lee et al., 2025; Liang et al., 2020). Diffusion enhancement process is not merely passive, but rather a synergistic interaction between microchannels, carriers, and the biological dynamics of skin tissue (Abdoh et al., 2024).

A quantitative comparison between spicule-based delivery and passive diffusion revealed a dramatic increase in transdermal flux. Larger hydrophilic molecules such as hyaluronic acid (250 kDa), the spicule-flexible liposomes system increased penetration by up to 19.4-fold compared to a control group (Kim et al., 2022). An even greater increase was observed for siRNA, with a factor of up to 72.95-fold, indicating that highly hydrophilic and negatively charged nucleic acid molecules, which are barely able to penetrate the skin passively, can be delivered effectively via the spicule route. Model molecules around 10 kDa dextran increase penetration 33.09-fold has been reported (Kim et al., 2022; Liang et al., 2020). Smaller molecule- spicule is more permeable and significant improvements in delivery of active ingredient lidocaine increased total skin absorption to 78.45 ± 6.96% compared to only 8.20 ± 1.60% in a control group (Zhang et al., 2025).

The photosensitizer protoporphyrin IX (PpIX) loaded for quantitative data on mSHS permeation rates, deposition in the epidermis reached 5.1 ± 0.4 μg/cm² and in the dermis 0.5 ± 0.2 μg/cm², indicating substantial penetration into the target layers for photodynamic therapy. Hyaluronic acid permeation rates up to 86.8 ± 4.1% of the total absorbed HA accumulated in the deep skin layers (epidermis and dermis), asignificant dose of the drug that penetrated the stratum corneum barrier successfully reached the target tissue and was not simply retained in the stratum corneum (Liang et al., 2020; Zhang et al., 2025).

4. Controlled Drug Retention and Release in The Target Tissue

Initial access to skin tissue by spicule, contributes to drug retention in the target tissue and gradual release, which can result in a longer therapeutic effect (Tandon et al., 2025). The presence of fragment spicules retained in skin tissue for at least 72 hours provides a physical reservoir that supports continued penetration and accumulation of the payload in the dermis over a longer period than with conventional topical application. Embedded spicules act as local depots that continuously

release the loaded drug or facilitate drug diffusion from the topical formulation applied to the skin surface (Kim et al., 2022; Liang et al., 2020; Zhang et al., 2019a).

Microchannels gradually close over approximately 120 hours, creating a controlled therapeutic window during which particles and vesicles can continue to enter before epidermal integrity is restored, allowing for sustained distribution into the early dermis (Lio et al., 2020; Tandon et al., 2025). During this period, the drug can diffuse deeper into the dermis and even reach the subcutaneous tissue, depending on the characteristics of the molecule and formulation. Higher retention in the dermis compared to the stratum corneum indicates that the drug successfully crosses the barrier and reaches its intended site of action, such as hair follicles, sebaceous glands, or dermal blood vessels for systemic absorption (Fong et al., 2023; Li et al., 2018).

Release kinetics indicated by pharmacodynamic results and deposition measurements support the concept of slower and more sustained release when using spicules. The use of SHS for insulin delivery resulted in a slow and sustained glucose-lowering profile: SHS treatment reduced blood glucose levels to 13.1 ± 6.3% of baseline within 8 hours, while subcutaneous injection reduced levels to 15.9 ± 1.4% within 4 hours, followed by a rebound at 8 hours. These data demonstrate a more distributed and sustained transmucosal effect of the spicule route compared to the direct subcutaneous injection route, which results in higher peak concentrations but a shorter duration of action (Zhang et al., 2017).

The sustained release profile achieved by the spicule system is highly advantageous for applications requiring stable drug concentrations over a long period, such as local anesthesia, anti-inflammatory therapy, or hormone delivery. For lidocaine, the spicule-gel system showed significantly higher accumulation in the deep skin layer (97.51 ± 0.17%) compared to the passive control (35.99 ± 4.80%), indicating that the drug not only penetrates better but is also retained in the target tissue for a longer duration (Hasanpour et al., 2024; Zhang et al., 2025)

Translational Perspectives in Therapeutic Applications

1. *Dermatology and Treatment of Skin Diseases*

S-TDS shows significant potential for the treatment of various dermatological conditions that require drug delivery to deeper layers of the skin. The combination of spicules with nanoparticles containing anti-inflammatory or immunomodulatory agents may increase the effectiveness of therapy while reducing systemic side effects for atopic dermatitis. Recent studies have shown that nanoparticle delivery of Cutibacterium acnes using spicules can modulate the skin microbiome and immune response for the treatment of atopic dermatitis (R et al., 2024; Yang et al., 2025).

In psoriasis, a layered spicule system that releases phospholipid complex nanoparticles has been developed to remodel skin immune homeostasis. This approach combines mechanical penetration with controlled release of immunomodulatory agents to address the complex pathophysiology of psoriasis. Preclinical results a showed significant reduction of inflammatory markers and improvement of psoriatic lesions in animal models (Li et al., 2025; Wang et al., 2022)

The application of S-TDS for the therapy of non-melanoma skin cancer and early melanoma offers a non-invasive alternative to surgical excision Photodynamic therapy using mSHS@PpIX has demonstrated complete tumor eradication in preclinical models of metastatic melanoma. Combination with topical immunotherapy or targeted therapy can further increase the effectiveness of therapy. Therapy of mSHS@PpIX has shown promising results, indicating that advanced drug delivery systems can significantly enhance treatment outcomes for various skin cancers (Liang et al., 2024; Qu et al., 2022).

This innovative approach not only targets the tumor effectively but also minimizes systemic toxicity associated with conventional therapies. These findings highlight the potential of S-TDS in revolutionizing dermatological treatments by providing targeted, efficient, and safer alternatives to traditional methods.

2. Cosmetic and Anti-Aging Application

The cosmetics industry has shown great interest in S-TDS for the delivery of anti-aging and skin rejuvenation active ingredients. Hyaluronic acid delivery using a combination of spicules and flexible liposomes results in superior skin hydration and wrinkle improvement compared to conventional topical formulations. The accumulation of HA in the deep layers of the skin contributes to a long-lasting plumping effect and increased skin elasticity(Kim et al., 2022; Nam et al., 2023; Nguyen & Nguyen, 2023; Zhang et al., 2021)

Delivery of growth factors, peptides, and MSC exosomes using S-TDS for skin rejuvenation applications has shown promising clinical results. The nano-encapsulated spicule system containing the MSC secretome resulted in significant improvements in skin biometric parameters including elasticity, hydration, and wrinkle reduction. Mechanism involves stimulation of collagen synthesis, modulation of matrix metalloproteinases, and anti-oxidant effects (Cho, 2023; Zhang et al., 2020). The application of S-TDS for hyperpigmentation reduction and skin brightening has also been explored. Delivery of depigmenting agents such as vitamin C, niacinamide, or plant extracts using spicules can enhance penetration to melanocytes in the basal layer of the epidermis for better effectiveness (Avcil et al., 2021; Kim et al., 2022; Zhang et al., 2024)

Deer antler velvet (DAV) extract-loaded microspicules (MS) serum significantly increases macromolecular protein permeation through the skin, with deposition into the deepest skin layer enhancing hair elongation and melanin content, with increasing skin hydration and decreasing the erythema index, thereby promoting hair growth without skin irritation (Tansathien et al., 2021).

This multifaceted strategy not only improves the efficacy of active ingredients but also addresses the underlying mechanisms of skin conditions, paving the way for innovative therapeutic solutions.

3. Vaccine and Immunotherapy Delivery

As mentioned previously, S-TDS offers an attractive platform for transdermal vaccination with the advantage of directly targeting skin APCs.. The development of influenza, hepatitis B, and COVID-19 vaccines using S-TDS is currently under active research. The ability to induce robust mucosal and systemic immune responses with lower antigen doses than intramuscular injection is a significant advantage (Liang et al., 2024; Nguyen & Nguyen, 2023; Pielenhofer et al., 2020; Zeng et al., 2025)

For cancer immunotherapy, delivery of tumor-associated antigens or immune checkpoint inhibitors using S-TDS can activate local and systemic anti-tumor immune responses. Combination with appropriate adjuvants can increase the magnitude and duration of the immune response. This approach is particularly promising for melanoma and other skin cancers where direct access to the tumor allows for efficient local delivery (Liang et al., 2024; Zeng et al., 2025)

This novel approach a promising alternative for future immunization strategies by enhancing vaccine and allergen-specific immunotherapy efficacy, safety, and a more effective alternative to traditional methods.

4. Systemic Delivery for Chronic Therapy

Although most S-TDS applications focus on local skin effects, the development of systems for systemic delivery of drugs for chronic therapy is also of interest. Transdermal delivery of LMWH for anticoagulant therapy using cSoSp has demonstrated adequate bioavailability for therapeutic effect. Other potential applications include insulin delivery for diabetes, hormones for hormone replacement therapy, and analgesics for chronic pain management (Nguyen & Nguyen, 2023; Zhai et al., 2021). Development of S-TDS systems with feedback control or on-demand drug release could further enhance the utility for systemic applications. Integration with biosensors that monitor specific biomarkers (e.g., glucose for insulin delivery) could enable closed-loop drug delivery systems.(Nguyen & Nguyen, 2023; Zhang et al., 2021).

The advantages of systemic transdermal delivery include avoidance of hepatic first-pass metabolism, more stable and controlled drug release, and increased patient compliance. However, challenges include inter-individual variability in absorption,

limitations in the deliverable dose, and the need for formulation optimization to achieve therapeutic plasma concentrations (Vaseem et al., 2024).

This innovative approach offers a promising method for improving patient adherence to chronic therapies while enhancing the overall efficacy of the drug delivery system while minimizing adverse effects.

LIMITATION

The pharmacokinetic data : Cmax (maximum concentration), Tmax (time to reach maximum concentration), AUC (area under the curve), or fully measured systemic bioavailability for many spicule-formulation combinations have not been reported. The presentation of these pharmacokinetic parameters based on literature includes flux metrics, percentage penetration, tissue deposition, duration of spicule retention in situ, and substitutive pharmacodynamic effects (e.g., blood glucose lowering or tumor eradication). Comprehensive pharmacokinetic studies are needed to fully characterize the plasma concentration-time profile, absolute and relative bioavailability, and inter-individual variability. Thus, although clinical and experimental indicators suggest a sustained release profile and enhanced retention in the skin, the need for comprehensive pharmacokinetic studies remains to fully quantify the systemic and local kinetics of spicule-based therapies. Advances in formulation technology with spicules assisted the penetration of active ingredients into the skin, which is it can be developed for pharmaceutical preparations to avoid the effects of first-pass metabolism in the liver and improve bioavailability.

CONCLUSION

Spicule-Assisted Transdermal Delivery Systems (S-TDS) represent an innovative platform that combines the advantages of mechanical penetration with the flexibility of modern pharmaceutical formulations to overcome the limitations of conventional transdermal delivery. The mechanism of action of spicules in transdermal delivery systems is a complex and interrelated multi-step process : (1) the physical penetration of spicules into the stratum corneum and the formation of microchannels; (2) a temporary disruption of the lipid and protein barrier of the stratum corneum, creating a paracellular pathway that allows hydrophilic molecules and macromolecules to penetrate; (3) diffusion and transport of active ingredients; (4) controlled drug retention and release in the target tissue, with embedded spicules acting as local depots supporting sustained release. Although comprehensive pharmacokinetic data are limited, pharmacodynamic and tissue deposition evidence consistently demonstrates the superiority of spicule systems in achieving sufficient and sustained therapeutic concentrations in target tissues. Preclinical and clinical studies suggest that spicules can

enhance the penetration of various bioactive molecules, with potential applications in therapeutic dermatology, anti-aging and whitening cosmetics, transdermal vaccination and immunotherapy and systemic delivery for chronic therapy.

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