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Nanospanlastics For Transdermal and Topical Drug Delivery: Formulation, Characterization, and Therapeutic Applications

(*Nanospanlastik untuk Penghantaran Obat Transdermal dan Topikal: Formulasi, Karakterisasi, dan Aplikasi Terapeutik*)

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ABSTRACT

Nanospanlastic is an elastic nanovesicular drug delivery system developed to enhance skin penetration, retention, and therapeutic efficacy in topical and transdermal applications. However, variations in formulation methods, characterization parameters, and evaluation approaches across studies have limited the standardization of its performance. This review was conducted systematically in accordance with the PRISMA guidelines. A comprehensive literature search was performed using international electronic databases, including ScienceDirect, Springer, PubMed, SAGE, and Taylor & Francis online, covering publications from 2015 to 2025. The keywords used were "nanospanlastic," "spanlastic," "nanovesicles," "transdermal," "topical," "characterization," and "application." Articles were screened based on predefined inclusion and exclusion criteria, and 32 eligible studies were selected for qualitative meta-synthesis analysis. This article presents a cross-study comparative analysis focusing on formulation factors, physicochemical characteristics, deformability, stability, and dermatological applications. The synthesis results indicate that surfactant–edge activator composition, manufacturing methods, and component ratios significantly influence particle size, polydispersity index (PDI), entrapment efficiency, and deformability index, which, in turn, determine skin penetration and retention performance. Although nanospanlastic demonstrates improved permeation and promising pharmacological effects, challenges remain regarding long-term stability, chronic safety, and scalability for GMP-based industrial production. This review highlights critical research gaps and proposes future development directions, including formulation optimization, harmonization of characterization methods, and broader clinical validation. Therefore, nanospanlastic represents a promising innovative platform for dermatological drug delivery but requires further systematic and translational development.

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INTRODUCTION

Drug delivery via topical and transdermal routes has gained increasing attention due to its non-invasive nature, safety, and potential to improve patient compliance. However, the effectiveness of these routes is largely determined by the drug's ability to penetrate the skin barrier. The stratum corneum, the outermost layer of the skin, is rich in lipids and possesses a densely packed structure that significantly restricts molecular diffusion (Elsherif et al., 2017). Consequently, it allows only a small portion of a drug to penetrate the skin passively. Additionally, physiological factors such as hydration, age, and skin disorders exert a greater influence on drug permeation variability. These limitations highlight the need for advanced drug delivery systems that not only enhance penetration but also adapt to the dynamic biophysical properties of the skin (Kakkar et al., 2018).

Nanotechnology offers an opportunity to overcome the obstacle to penetration by developing vesicular-based nonionic surfactant systems, such as niosomes, ethosomes, and transferosomes. These systems offers greater stability compared to conventional phospholipid vesicles and can facilitate improved drug penetration through a mechanism involving membrane elasticity (Marianecci et al., 2014). However, many of these conventional vesicular systems still rely on alcohol-based penetration enhancers or phospholipid components, which may cause skin irritation or formulation instability (Morrow et al., 2007). These challenges necessitate the development of more advanced vesicular systems with improved stability, elasticity, and skin compatibility.

To address these limitations, researchers have developed Nanospanlastic, specifically elastic vesicles based on surfactant-modified nonionic materials, utilizing an edge activator to enhance membrane deformability, thereby allowing them to pass through skin lipid channels more efficiently (Sharma et al., 2020). Although numerous studies have reported the potential effects of nanoscale vesicles in enhancing drug penetration, the available review articles remain limited in scope. Previous studies mainly focused on formulation composition, manufacturing methods, and permeation testing, while the mechanism of vesicle deformability in relation to the skin's biological barrier structure has not been widely discussed (Annisa et al., 2025). Therefore, existing reviews have not yet provided a comprehensive explanation of the relationship between vesicle characteristics and skin responses.

Similar limitations are also observed in the international reviews. Yusuf et al. (2023) and Sharma et al. (2020**)** highlight improvements in drug permeation through nanospanlastic and the optimization of surfactants, but no connection to technology using natural biomaterials or the modern filmogen system matrix. Furthermore, the existing literature largely focuses on formulation optimization rather than system integration within innovative topical delivery platforms. Consequently, current knowledge of nanospanlastic remains fragmented and lacks systematic integration.

Moreover, studies on nanospanlastic systems remain limited in scope and focus only on one type of drug or one formulation, making it difficult to draw general conclusions and identify an ideal formulation. Only limited research has examined the long-term stability, despite its crucial importance for the commercialization process, particularly in preventing drug leakage or changes in vesicle size during storage (Pandey et al., 2020). Likewise, studies on the toxicity of chronic surfactants and *edge activator*s are still very limited, so there is no long-term safety data for dermatological or transdermal applications.

Another important yet underexplored challenge is industrial translation. Most studies have been conducted at the laboratory scale using relatively simple methods such as thin-film hydration and sonication. In contrast, large-scale production requires more robust and reproducible techniques, such as microfluidization, along with strict control of manufacturing parameters in accordance with Good Manufacturing Practice (GMP) standards (Lopes et al., 2019; Mehta et al., 2021). Additionally, standard characterization of deformability, vesicle stability indices, and skin penetration between studies is not yet harmonized, which limits reproducibility.

Given the limitations mentioned, a scientific review is needed that not only exposes the formulation nanospanlastic but also provides a comprehensive cross-research analysis, evaluating factors that influence the formulation's success and identifying challenges to be addressed for commercial clinical application. This review was designed to fill the gap by providing more comprehensive and critical assessments of formulation, characterization, mechanism of action, therapeutic applications, and aspects of stability and translation in the industry, with a focus on the nanosystem nanospanlastic as a topical and transdermal delivery drug for the future.

MATERIAL AND METHODS

Materials

This study was conducted systematically using several databases, including computer-based electronic searches. The inclusion criteria included the years 2015–2025, articles published in English or Indonesian, and research journals. Others included literature related to nanospanlastic formulation and its applications. Exclusion criteria included articles that were not fully accessible. Furthermore, the literature was retrieved from electronic databases, including various easily accessible databases. The databases included ScienceDirect, Springer, PubMed, Sage, and Taylor & Francis online. The keywords used included nanospanlastic, spanlastic, nanovesicles, transdermal, topical, characterization, and applications. A qualitative meta-synthesis approach was used for data analysis because the objects representing data in the literature were heterogeneous. The PRISMA guideline diagram was used to collect relevant studies, and 13 were selected for a more detailed review. The strategy used in the review is shown in Figure 1.

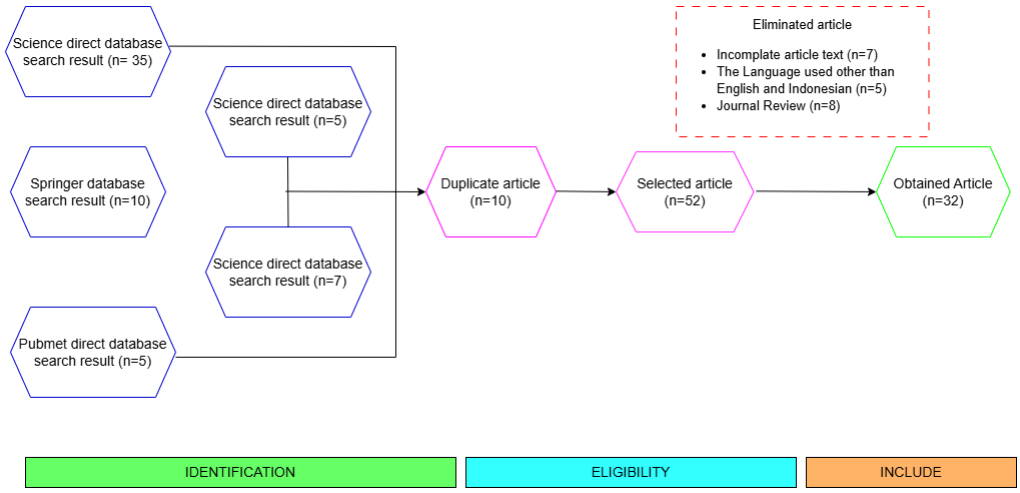

Figure 1. Systematic review workflow based on PRISMA guidelines, including identification, screening, eligibility assessment, and qualitative synthesis of selected studies

RESULTS AND DISCUSSION

Nanospanlastic as a New Drug Delivery System

Nanospanlastic nanovesicles have become a major concern in the development of topical and transdermal drug delivery systems (DDS), offering significant improvements in drug penetration, local bioavailability, and targeted delivery to different skin layers (Sharma et al., 2020b; Santuso et al., 2023). The unique membrane flexibility, resulting from the combination of nonionic surfactants (such as Span® 60) and edge activators (EA) such as Tween® 80 or Brij® 35, allows these vesicles to deform and pass through tight skin barriers, making them an ideal choice for dermatological and transdermal applications (Al-Mahallawi et al., 2017; El Hosary et al., 2024). The ability of Nanospanlastics to enhance drug penetration into and across the skin has been consistently demonstrated. Studies have shown that Nanospanlastics loaded with raloxifene HCl, a drug with low oral bioavailability, achieved high release (85%) and significant flux (4.24 µg/cm²/h) through the skin (Ansari et al., 2022). Similarly, the nanospanlastic formulation of itraconazole demonstrated better penetration and superior antifungal activity compared to commercial products. Nanospanlastics can also enhance the cutaneous retention of drugs, minimizing unwanted systemic penetration. Tazarotene nanospanlastic for psoriasis demonstrated 2.32 times greater cutaneous retention than the commercial gel, with high drug deposition in the stratum corneum, epidermis, and dermis, and without systemic detection (Elmowafy et al., 2019). This is important for chronic skin diseases, where local action targeting is highly desirable. Nanospanlastic containing curcumin showed good skin penetration (up to 112.5 µm) with gradual release (El Hosary et al., 2024). Nanospanlastic not only enhances penetration but also enhances the local pharmacological effects of the drug. In a rheumatoid arthritis model, topical celecoxib

Nanospanlastic showed superior anti-inflammatory effects, with a significant reduction in the expression of inflammatory biomarkers such as TNF and COX-2, even outperforming niosomes and commercial gels (Alaaeldin et al., 2021). This suggests that nanospanlastic can effectively deliver anti-inflammatory drugs to the site of inflammation in the skin and subcutaneous tissue. Dermatological application of tazarotene Nanospan resulted in a significant reduction in PASI (Psoriasis Area and Severity Index) scores in psoriasis patients, as well as a decrease in epidermal thickness from 360.7 µm to 115.8 µm (Elmowafy et al., 2019). This indicates better clinical efficacy compared to marketed products. In addition, nanospanlastic containing green tea extract exhibited strong antioxidant activity (IC_{50} = 7.63 ± 0.07 ppm), supporting its potential as a base ingredient for topical anti-aging products based on natural antioxidants (Santuso et al., 2023).

A key characteristic of nanosponges is their elastic membrane properties, which allow "penetration by squeezing" through skin pores smaller than the vesicle size (Al-Mahallawi et al., 2017). This was demonstrated in the optimal formulation of ciprofloxacin Nanosuspension using Brij 35 as an edge activator, showing significant permeation enhancement (Al-Mahallawi et al., 2017). Generally, nanospanlastic formulations have a nanoparticle size (160 nm – 419.70 nm), low polydispersity index, and high encapsulation efficiency (Ansari et al., 2022). The surfactant-to-edge activator ratio determines deformability and penetration performance.

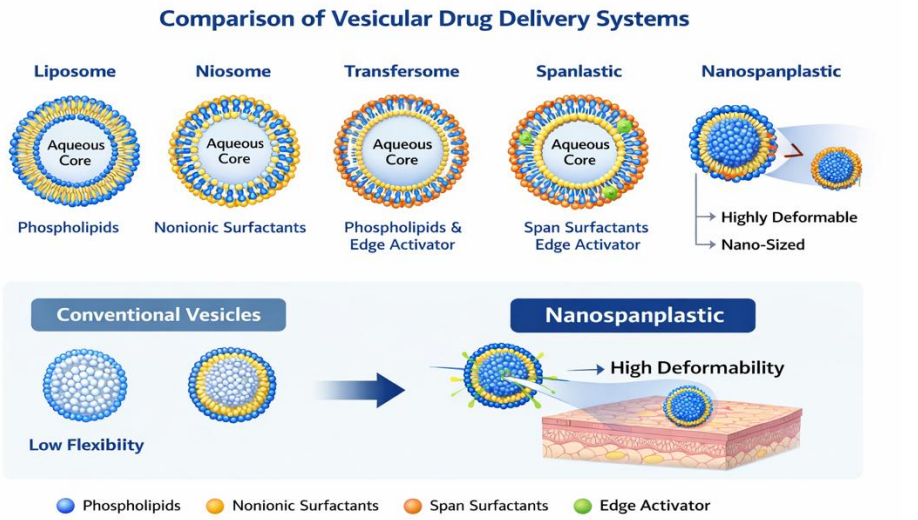

Figure 2. Schematic illustration comparing different vesicular drug delivery systems, including liposomes, niosomes, transfersomes, spanlastics, and nanospanlastics, highlighting their structural composition, deformability, and potential for skin penetration.

A schematic comparison of several vesicular drug delivery systems is presented in **Figure 2**, including liposomes, niosomes, transfersomes, spanlastics, and nanospanlastics. Each system possesses distinct structural compositions and physicochemical characteristics that influence their ability to

deliver drugs through biological barriers. Liposomes are composed primarily of phospholipid bilayers that surround an aqueous core, enabling the encapsulation of both hydrophilic and lipophilic drugs. However, their relatively rigid membrane structure often limits their deformability and penetration through the stratum corneum. Niosomes, which are formed from nonionic surfactants, offer improved stability compared with liposomes but still exhibit limited elasticity. Transfersomes are designed with phospholipids combined with edge activators, which increase membrane flexibility and allow vesicles to deform when passing through narrow intercellular pathways of the skin. Similarly, spanlastics are vesicular systems composed mainly of Span surfactants and edge activators, resulting in elastic vesicles with enhanced deformability and improved drug permeation properties.

Nanospanlastics represent a further development of spanlastic vesicles with nanoscale particle size and highly deformable membranes. The incorporation of suitable edge activators and optimized surfactant composition enhances vesicle flexibility, allowing the nanospanlastics to adapt their shape and penetrate more effectively through the skin barrier. As illustrated in Figure 2, the high deformability and nanosized structure of nanospanlastics facilitate deeper penetration into the skin layers compared with conventional vesicular systems. Overall, this comparison highlights that nanospanlastics combine the advantages of elastic vesicles and nanoscale drug carriers, making them a promising delivery system for improving topical and transdermal drug penetration.

Concept and Physicochemical Characteristics of Nanospanlastics

Most optimal spanplastic formulations have particle sizes in the nanorange (generally 100–450 nm), a low polydispersity index (PDI) (<0.4), a high encapsulation efficiency (EE%) (often 70–90%), and a negative zeta potential that supports colloidal stability. The presence of edge activators (e.g., Tween 80; Brij 35) is essential for imparting deformability. A high deformability index (DI) positively correlates with increased skin permeation. For example, ciprofloxacin spanplastic formulation with Brij 35 showed the highest deformability index and significantly increased trans-tympanic permeation. Preparation methods, such as thin film hydration (TFH) and ethanol injection, are the most commonly used to produce spanplastic with the desired characteristics (Yusuf et al., 2023; Safitri & Permana, 2023).

Several early toxicity studies (eg, skin irritation studies) have shown that nanospanlastic formulations generally have a good safety profile and minimal skin irritation, especially when compared to more aggressive chemical penetration enhancers. This suggests potential safety for long-term topical application (Safitri & Permana, 2023). The main mechanism behind the increased penetration of nanospanlastic involves the reversible deformation of the vesicles upon interaction with the stratum corneum. When nanospanlastic adheres to the skin surface, it tends to enter the intercellular gaps or pores of the pilosebaceous follicles. Due to their elastic properties, the vesicles can "squeeze" through

pores even smaller than their diameter. After passing through the stratum corneum, the vesicles can release their drug payload in the epidermis or dermis, or even enter the systemic circulation to produce transdermal effects. In addition, the composition of Nanospanlastic, which contains surfactants and edge activators, can interact with stratum corneum lipids and proteins, temporarily and reversibly disorganizing the intercellular lipid matrix and thereby facilitating drug penetration (Yusuf et al., 2023; Safitri & Permana, 2023).

Formulation and Manufacturing Methods

In developing nanospanlastic formulations, several essential criteria must be fulfilled to ensure successful vesicle formation. Key considerations include: (1) **Biocompatibility**: Nanospanlastic vesicles must be non-toxic and well tolerated by biological systems, which is supported by the use of environmentally friendly nonionic surfactants. (2) **Sustainability and Stability**: Vesicles must maintain chemical and osmotic stability to prevent degradation of the encapsulated drug during storage or application. (3) **Encapsulation Capacity**: The system should be able to entrap both lipophilic and hydrophilic active pharmaceutical ingredients within its vesicular matrices. (4) **Elasticity**: Adequate vesicle deformability is required to enable structural flexibility, thereby enhancing penetration through biological membranes and facilitating delivery to target tissues. (5) **Size and Distribution**: Vesicles must exhibit small and uniform dimensions to ensure efficient permeation and optimal distribution at the intended site of action. (6) **Safety**: All excipients, including surfactants and edge activators, must be non-irritating, particularly for sensitive routes such as ophthalmic administration. (7) **Delivery Efficiency**: The system should support controlled and targeted release of the drug, improving bioavailability while reducing potential adverse effects. (8) **Efficient Manufacturing**: Production techniques should be cost-effective and capable of generating vesicles with consistent quality, such as through ether injection, sonication, or microfluidization (Sharma et al., 2020a).

Nanospanlastic is a very effective topical drug delivery system that enhances skin penetration, local bioavailability, and therapeutic efficacy of various active substances. One example is raloxifene HCl, where the use of nanospanlastic significantly increased the drug's transdermal penetration, resulting in a drug release of around 85% and a flux of around 4.24 µg/cm²/h. This effect is largely attributed to Nanospanlastic's ability to modify the lipid structure of the stratum corneum layer, thereby increasing skin permeability. Meanwhile, for itraconazole, the nanospanlastic formulation showed a substantial increase in skin penetration and antifungal activity compared to conventional formulations. This was indicated by a larger inhibition zone against pathogenic fungi and increased therapeutic efficacy in vivo, making nanospanlastic a superior platform for treating fungal skin infections (Garg et al., 2018). In the tazarotene formulation, nanospanlastic provided 2.32 times higher cutaneous retention than commercial gels. Drugs delivered via nanospanlastic showed high deposition in the stratum corneum, epidermis, and

dermis layers without being detected in the systemic circulation, thereby reducing the potential for systemic side effects and increasing the safety of topical therapy (Sharma et al., 2020b; Gupta et al., 2017). The Celecoxib formulation in nanospanlastic has also shown promising anti-inflammatory effects as a therapy, particularly in rheumatoid arthritis models. Compared to commercial niosomes and gels, celecoxib nanospanlastic exhibited stronger anti-inflammatory effects with significant reductions in the expression of inflammatory mediators such as TNF-α, NF-κB, and COX-2, which are key targets in the pathogenesis of chronic inflammation (Sharma et al., 2020b; Patel et al., 2019). For phytotherapeutic agents such as curcumin, nanospanlastic allows penetration up to 112.5 μm into the skin and provides sustained release. This formulation can also maintain curcumin's antioxidant activity, making it an ideal choice for long-term dermatological applications that require controlled release and local antioxidant effects (Alnusaire et al., 2021; Sharma et al., 2020a). Finally, green tea extract formulated in nanospanlastic showed very strong antioxidant activity, with an IC_{50} value of 7.63 ± 0.07 ppm. This effect demonstrates the significant potential of green tea extract nanospanlastic as a base material for the development of anti-aging cosmetic and pharmaceutical products, thanks to its ability to maintain the stability and bioactivity of sensitive phenolic compounds (Alnusaire et al., 2021; Abdel-Salam et al., 2023).

Components of nanospanlastic:

1. **Vesicle Builder (Surfactant)**

   Surfactants act as active agents, lowering the surface tension at the interface between hydrophilic and lipophilic phases in a dispersion system. In nanospanlastic systems, nonionic surfactants such as sorbitan alkyl ester (Span) are key components in vesicle formation. Spans form concentric bilayers, and variations in fatty acid types in the group polyoxyethylene sorbitan differentiate Span types, for example, Span 20 (monolaurate), Span 40 (monopalmitate), Span 60 (monostearate), and Span 80 (monooleate). Selection: The type of span greatly influences the formulation of characteristics; spans with a chain saturated (e.g., Span 60) tend to produce more stable vesicles, while Spans with a chain not saturated (e.g., Span 80) are more prone to experiencing structural disruption. Stability is related to the characteristic lipophilic nature of vesicles, as well as the formation of monolamellar or multilamellar vesicles. Additionally, surfactant supports the performance of *edge activators* at lower voltages and facilitates a smoother particle size distribution (Yusuf et al., 2023; Sharma et al., 2020a).

2. **Edge Activator (EA)**

   Edge activators are surfactant chains with a high level of functionality, increasing the HLB and enhancing the deformability of the bilayer membrane through a mechanism of controlled destabilization. Therefore, his abilities lower the voltage interface, EA provides more flexibility, and is large on the membrane vesicles, as well as promotes the formation of particles with smaller sizes

and more spherical morphologies. In addition, hydrophilic surfactants such as Tween 80 can increase vesicle elasticity, improving their retention on the permeability membrane and facilitating their diffusion. Additionally, nature's hydrophilic EA can disrupt bilayer regularity, leading to varying degrees of deformability depending on the type and concentration (Yusuf et al., 2023; Sharma et al., 2020b).

Method Making Nanospanlastic

1. **Ether Injection Method**

   In this procedure, the surfactant is dissolved in ± 20 mL of ether. The organic solution is then injected gradually through a 14G needle at approximately 25 mL/min into the heated water phase, which contains the active substance and has been heated to 60 °C. After the injection process is complete, the organic solvent is removed by evaporation in a rotary evaporator. Evaporation of ether facilitates the formation of monolamellar vesicles, as a result of organizing repeat molecules of surfactant (Yusuf et al., 2023).

2. **Sonication Method**

   Method: sonication is performed with a prepared solution of the drug in an appropriate support system. The solution is then mixed with a component surfactant in a 10 mL glass receptacle. The mixture formed further when treated with an ultrasonic wave using a titanium probe, triggering the formation of smaller vesicles with more uniform structures (Yusuf et al., 2023).

3. **Hand-Shaking (Thin Film Formation) Method**

   This technique starts with dissolving a surfactant in an organic solvent, such as ether, chloroform, or benzene. The solvent was then removed under low pressure using a vacuum evaporator, leaving a thin surfactant film on the flask walls. This film was rehydrated with a drug-water solution while being shaken constantly, allowing a surfactant-swollen layer to form. This process causes amphiphiles to fold and form vesicles capable of encapsulating drugs (Yusuf et al., 2023).

4. **Extrusion Method**

   In this method, a mixture of surfactants and diacyl phosphate is evaporated with a rotary vacuum evaporator to produce a thin layer. The layer then rehydrated use solution medicine. Suspension vesicles that form are extruded through membrane polycarbonate pores ±0.1 μm, and this process is repeated eight times to get morphology uniform vesicles as well as a distribution consistent in size (Yusuf et al., 2023).

5. **Microfluidization Method**

   The microfluidization technique involves mixing two flow fluids — each containing drugs and surfactants — in a specially designed *interaction chamber*. High turbulent velocity interactions are based on the principle of submerged jets. This produces vesicles with a nanometer-sized distribution, characterized by narrow size and high reproducibility. This method is considered superior for

production scales, particularly large ones, and the formulation requires consistent particles (Sharma et al., 2020a; Yusuf et al., 2023).

1. Transdermal and Topical Applications

Nanospanlastics are highly deformable vesicular systems composed of nonionic surfactants such as span and edge activators, such as Tween, which reduce bilayer rigidity and greatly enhance membrane elasticity (Kumar et al., 2018). This structural modification produces vesicles capable of dynamic shape transformation, enabling them to efficiently transport both hydrophilic and lipophilic drugs. Their mechanism of action begins with their ability to encapsulate drugs within either the hydrophilic core or the lipophilic bilayer, providing a stable microenvironment for the active compound. The presence of edge activators destabilizes the bilayer thermodynamically but strengthens it mechanically, making the vesicle highly flexible and capable of passing through narrow gaps in the stratum corneum without rupturing (Ahmed et al., 2016). In addition, nanospanlastics act as protective carriers: the surfactant bilayer shields drugs from oxidative, hydrolytic, and photolytic degradation during transdermal transport, thereby maintaining drug integrity and enhancing therapeutic performance (Shaji & Lal, 2014; Mura et al., 2019). Nonionic surfactants also provide mild penetration-enhancing effects by loosening the tight lipid domains of the stratum corneum, thereby increasing lipid fluidity and improving drug permeation, while remaining largely biocompatible and non-irritating (Kaur et al., 2018). Thus, the overall mechanism of action of nanospanlastics involves multifunctional roles as drug carriers, stabilizers, penetration enhancers, and localized reservoirs.

The skin penetration mechanism of nanospanlastic vesicles involves multiple pathways and is considered superior to conventional vesicular systems due to their high deformability and osmotic energy–driven transport. As illustrated in Figure 3, the presence of edge activators increases the elasticity of the vesicle membrane, allowing nanospanlastics to pass through the intercellular lipid matrix of the stratum corneum. In addition to the intercellular pathway, nanospanlastics may also penetrate through follicular routes and subsequently release the encapsulated drug within the viable epidermis and dermis. This multipathway penetration mechanism enables nanospanlastics to enhance both localized drug delivery within the skin and transdermal drug transport into systemic circulation. The primary route is the intercellular pathway, where vesicles travel between the lipid matrices of the stratum corneum. Owing to their exceptional elasticity, nanospanlastics can elongate, compress, or flatten to fit into microscopic lipid channels, a phenomenon known as deformability-enhanced transport (Abdelbary & AbouGhaly, 2015). The second route is the transcellular pathway, in which vesicles partially fuse with or transiently disrupt the membranes of keratinocytes, releasing their drug cargo directly into the epidermal intracellular environment. The third route is the transfollicular pathway, in which vesicles traverse hair follicles and sebaceous glands—structures with significantly lower diffusion resistance

than the stratum corneum. Hair follicles also act as long-term reservoirs, allowing deeper, sustained drug deposition in the dermis (Müller et al., 2012).

Nanospanlastics have attracted considerable attention as flexible vesicular carriers for both transdermal and local skin drug delivery. Due to their nanoscale size and highly deformable membrane structure, nanospanlastics are capable of penetrating through the intercellular lipid matrix of the stratum corneum. The presence of edge activators in the vesicle composition enhances membrane elasticity, allowing the vesicles to squeeze through narrow skin pores without significant structural disruption.

In addition to facilitating systemic transdermal delivery, nanospanlastics also exhibit strong potential for localized drug delivery within specific layers of the skin. Depending on the formulation composition, vesicles may accumulate within different skin regions, such as the epidermis or dermis. For instance, formulations with relatively larger vesicle sizes tend to retain drugs within the upper skin layers, which is beneficial for topical therapeutic effects such as anti-inflammatory or antimicrobial activity. In contrast, smaller nanospanlastic vesicles with higher deformability can penetrate deeper into the dermal layer, enabling enhanced drug absorption and potentially systemic delivery.

Furthermore, the selection of surfactants, edge activators, and vesicle size plays an important role in determining the drug release profile and penetration depth within the skin. The optimized balance between vesicle elasticity, particle size, and drug–carrier interaction allows nanospanlastics to modulate drug localization across different skin layers, including the stratum corneum, viable epidermis, and dermis. Therefore, nanospanlastic formulations can be designed to achieve either localized therapeutic effects or enhanced transdermal drug delivery depending on the intended clinical application.

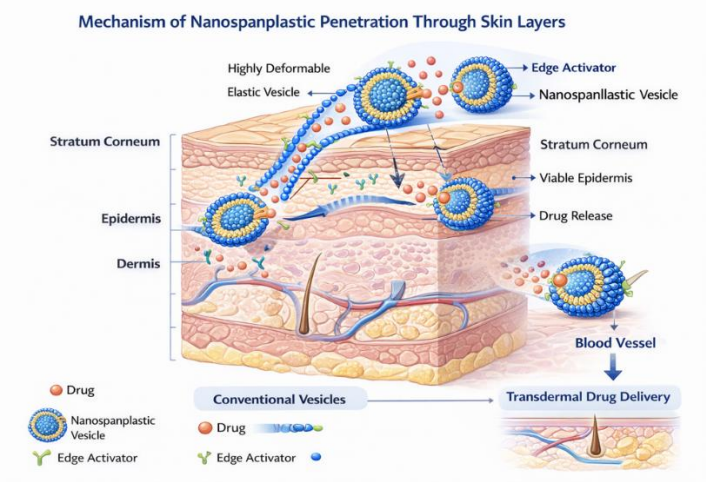

Figure 3. Mechanism of nanospanlastic penetration through skin layers showing deformable vesicles passing through the stratum corneum and releasing drugs in the epidermis and dermis, enabling both local and transdermal drug delivery

Beyond these anatomical routes, transdermal penetration of nanospanlastics is strengthened by elasticity gradients, osmotic pressure differences, and surfactant–lipid interactions. When applied to the skin, the mismatch between the highly elastic vesicle membrane and the rigid stratum corneum lipids generates a driving force that promotes deeper vesicular migration (El-Zaafarany et al., 2020). Edge activators further decrease the activation energy required for vesicle penetration by disrupting lipid–lipid packing, facilitating easier diffusion of both vesicles and drugs. Once nanospanlastics reach the viable epidermis or dermis, drug release occurs through passive diffusion, vesicle–cell membrane fusion, or vesicle rupture triggered by environmental pressure changes. These mechanisms collectively enable higher local drug concentrations, improved therapeutic outcomes, and reduced systemic exposure and side effects. Overall, nanospanlastics represent a highly efficient and modern transdermal drug-delivery platform, combining deformability, stability, and multipathway penetration to optimize drug transport across the skin.

2. Advantages and Disadvantages

Nanospanlastics represent an advanced transdermal drug-delivery system characterized by highly elastic vesicles composed of nonionic surfactants, such as span, and edge activators, like Tween. Their exceptional membrane deformability enables the vesicles to pass through the stratum corneum without disrupting skin integrity, thereby significantly enhancing drug permeation (Ahmed et al., 2016). This system can encapsulate both lipophilic and hydrophilic molecules, improving drug solubility, stability, and bioavailability (Moghddam et al., 2020; Abdelbary & AbouGhaly, 2015). Moreover, nanospanlastics protect against oxidative, hydrolytic, and photolytic degradation, prolonging the shelf life of the active compound (Shaji & Lal, 2014; Mura et al., 2019). Their ability to release drugs in a controlled manner may also reduce systemic side effects, while the use of nonionic surfactants ensures relatively low toxicity and good biocompatibility (Kaur et al., 2018).

Despite these advantages, nanospanlastics also present several limitations when applied as transdermal delivery systems. Their nanoscale vesicles are prone to physical and chemical instability, including fusion, aggregation, and drug leakage during storage, necessitating careful optimization of formulation parameters (Mura et al., 2019). Additionally, the transdermal route is suitable only for drugs with low daily dose requirements; high-dose drugs cannot be effectively delivered through this system. Although nonionic surfactants are relatively mild, they may still cause irritation or erythema at higher concentrations (Müller et al., 2012). From a manufacturing perspective, large-scale production of nanospanlastics requires precise control

over particle size, polydispersity, and stability, making the process more complex and costly compared to conventional topical formulations (El-Zaafarany et al., 2020). Thus, while nanospanlastics offer promising improvements in transdermal drug delivery, their practical application demands rigorous optimization and comprehensive evaluation.

3. Challenges, Stability, and Future Directions

Several important challenges still need to be addressed to support the widespread clinical application of nanospanlastic as a topical and transdermal drug delivery system. Long-term clinical trials in humans are still limited, so evaluating safety, efficacy, and optimal dosage on a large scale is still necessary (Lopes et al., 2019; Mehta et al., 2021). Additionally, the stability of the formulation for more than one year under various storage conditions is a significant concern for commercial applications (Pandey et al., 2020). The exploration of combining nanospanlastic with other therapeutic agents, such as antioxidants or anti-inflammatory agents, is believed to enhance efficacy in complex skin diseases (Lopes et al., 2019). A deeper understanding of the deformation mechanism of nanospanlastic and its interaction with the skin barrier is needed to design formulations more rationally and predictively (Mehta et al., 2021). Expanding the application to rare or chronic skin diseases that require sustained local drug delivery is also a research focus (Pandey et al., 2020). Efficient large-scale production methods that comply with Good Manufacturing Practice (GMP) standards should be developed (Lopes et al., 2019). Further research is needed to understand the interactions of edge activators with the skin, including their mechanisms of penetration and product safety considerations (Mehta et al., 2021). In addition, the regulation and standardization of characterization tests for elastic nanovesicles, such as Nanospanlastic, are still in development (Pandey et al., 2020).

Nanospanlastic nanovesicles represent a significant innovation in topical and transdermal drug delivery. Their ability to enhance penetration, local retention, and pharmacological effects while minimizing systemic side effects makes them a very attractive platform for the development of future dermatological and transdermal therapies. Further research should focus on clinical validation and optimization of formulations for human application.

Nanospanlastic is an advanced drug-delivery platform that entraps therapeutic agents within a central cavity surrounded by a bilayer membrane. This system, formed from a combination of Span surfactants and elasticizing components, was first introduced in 2011. Designed as a highly flexible, deformable carrier, it exhibits characteristics similar to those of transfersomes. As a vesicular system with high deformability, nanospanlastic offers superior permeability compared to conventional dosage forms. Its amphiphilic nature enables nonionic surfactants to assemble into vesicles that encapsulate drug molecules while maintaining remarkably small, microscopic vesicle sizes.

Nanospanlastic falls under a specialized class of nanovesicles engineered to overcome several limitations of liposomes, including chemical instability caused by oxidative degradation and variations in phospholipid purity and elasticity. Its enhanced deformability is attributed to edge activators incorporated into its structure (Sharma et al., 2020b). Morphologically, nanospanlastic vesicles possess a spheroidal form constructed from amphiphilic molecules that serve as an efficient encapsulation matrix. Similar to liposomes, Nanospanlastics can also be categorized by the number of bilayers (Sharma et al., 2020a).

The main classifications include: (1) Multilamellar Vesicles (MLV), the most commonly utilized type, consisting of multiple bilayer membranes with diameters ranging from approximately 0.5 to 1.0 micrometers. MLVs are simple to prepare and demonstrate strong mechanical stability during long-term storage. (2) Large Unilamellar Vesicles (LUV), which possess a high water-to-lipid ratio, allowing the encapsulation of larger volumes of bioactive compounds. (3) Small Unilamellar Vesicles (SUV), typically produced from multilamellar vesicles using sonication, French Press, or extrusion techniques (Sharma et al., 2020a).

Table 1. Research Gap with Similar Review Articles

No	Review Title	Review Results	Gap Analysis	Source
1	*Spanlastics: a novel elastic nanovesicular system for enhanced topical and transdermal drug delivery*	Explain the draft nanospanlastic, components surfactant –ea, mechanism of elasticity, as well as superiority compared to liposomes/niosomes. Includes an example of the drug being tested in vitro and in vivo.	Does not include cross-study comparative evaluation; does not discuss connection quantitative deformability – penetration; stability term long no discussed; safe use of ea term long not yet analyzed.	Sharma et al., 2020
2	*Spanlastics as nanocarriers for drug delivery: recent advancements and future prospects*	Comprehensive review of the latest nanospanlastic development, including formulation, pharmacological application, and some preclinical study results.	No formulation parameter synthesis cross-research is conducted; issues related to production scale are significant, and reproducibility is not thoroughly discussed; less emphasis is placed on skin retention; and the evaluation of pharmacodynamics across drugs is not analyzed in a structured manner.	Mehta et al., 2021

3	*Spanlastic vesicles: a promising approach for enhanced transdermal drug delivery*	To explain the ability of Nanospanlastics to increase transdermal penetration, the role of edge activators, and the mechanisms by which they weaken skin lipids.	Does not discuss the effect of surfactant variation (span 20/40/60/80); no evaluate performance method manufacturing (tfh vs ethanol injection vs microfluidization); not yet discuss toxicity chronic.	Lopes et al., 2019
4	*Elastic nanovesicles (spanlastics) for improved delivery of antioxidant natural extracts*	Explain the formulation of nanospanlastic for material nature, improvement in penetration and retention, as well as stability against degradation.	Focus narrowly on the material nature; no review stability term length >6 months; no discussion of technical parameters such as hlb and cpp; not yet compared the performance of drug synthetic vs natural.	Alnusaire et al., 2021
5	*Topical nanovesicular spanlastics: enhanced anti-inflammatory effect*	Review the effectiveness of nanospanlastic in inflammatory models, including the reduction of tnf-α, cox-2, and nf-κb, and revealed improvement in penetration and retention of the anti-inflammatory drug.	No general description of the cross formulation; no evaluation of how ea, particle size, and zeta potential influence response pharmacodynamics; issues related to security and long-term use are not explained.	Alaaeldin et al., 2021
6	Spanlastic as a Transdermal Drug Delivery System: a systematic review	Review formulation nanospanlastic, composition surfactant, method of manufacturing, and permeation testing; focus on aspects of the base formulation.	No review mechanism for deformability in the context of skin structure; no discussion of stability; no analysis of cross-study; no discussion of safety, toxicity, chronic issues, as well as gmp issues.	Annisa et al., 2025

A study of various international reviews reveals that development studies on nanospanlastic as a advanced drug delivery systems have increased; however, there remains substantial variation in coverage, depth of analysis, and contribution to knowledge across reviews. The table comparison indicates that the part remains descriptive, rather than a synthesis of cross-study results, and does not

explicitly integrate formulation parameters with pharmacological performance conditions. This confirms that, although interest in nanospanlastic is increasing, a truly scientific basis for a standardized approach is still limited.

Sharma et al.'s (2020) review, for example, is one of the main references that discuss the base draft of nanospanlastic and membrane elasticity mechanism. However, the review examines the quantitative relationship between vesicle deformability and skin penetration, as well as differences in performance between surfactants and edge activators across various studies. In fact, the technical aspects are highly influential on particle size, entrapment efficiency, and formulation stability. Similar findings are presented in Mehta et al. (2021), which, although providing a summary of the latest application, still do not yet map the optimal pattern for various types of lipophilic and hydrophilic drugs.

However, the review by Lopes et al. (2019) shows four strong mechanisms of penetration. However, it does not address variations in surfactant composition or manufacturing methods, so it cannot serve as a universal base formulation. This review indicates that the international literature still lacks a consistent, practical guide to the optimal formulation range or to the supporting composition-performance of nanospanlastic materials. On the other hand, experimental studies have shown that the difference in HLB value, the ratio of surfactant to EA, as well as the manufacturing method, significantly influence deformability, skin retention, and stability.

The reviews by Alnusaire et al. (2021) and Alaaeldin et al. (2021) also identify the same limitations, particularly narrow topic coverage. Both focus on groups with specific characteristics, allowing their contribution to be more nature-specific. There is no integration of anti-inflammatory, antifungal, and antipsoriatic drugs into a uniform formulation model. This is because nanospanlastic literature develops in a fragmentary way, with each study standing alone and lacking a comprehensive framework connecting the findings.

The analysis indicates that stability, long-term performance, and surfactant safety remain poorly addressed, even in international reviews. Even though the biggest challenge in commercializing nanovesicle technology is maintaining stability, both physical and chemical, during storage, there are risks such as particle fusion, medication leaks, and changes in size. Besides that, edge activators such as Tween 80 or Brij 35 potentially irritate when used chronically, but very few reviews discuss their toxicity subchronically or interaction terms with skin lipids.

Another limitation identified is the lack of discussion of the method's large-scale production. Most study laboratories use thin-film hydration or sonication, whereas the production industry requires a more consistent approach, such as microfluidization. No discussion about Good Manufacturing Practice

(GMP) exists for nanospanlastic. It is not yet ready for commercial stage translation. This is important, given the increasing significance of the potential use of nanospanlastic in dermatological, cosmetic, therapeutic, and anti-aging formulations.

Thus, the analysis comparative to various international reviews indicates that although nanospanlastic own potential big as system delivery drug topical and transdermal, still there is several important gaps : (1) lack formulation parameter synthesis cross research, (2) lack of discutain studies stability term length and safety chronic, (3) no standardized methods for deformability characterization, (4) limitations study translation industry, and (5) does not integrate pharmacodynamic performance with formulation parameters.

CONCLUSION

Based on the literature, optimizing edge activators and surfactants is crucial because nanospanlastic nanovesicles have been shown to directly control membrane elasticity, particle size, entrapment efficiency, and deformability index, which ultimately determine skin penetration and therapeutic performance in topical and transdermal delivery. The cross-study synthesis confirms that appropriate formulation design significantly enhances local bioavailability and pharmacological efficacy across various drug classes. However, important challenges remain, including long-term stability, chronic safety of edge activators, lack of standardized characterization methods, and scalability under GMP conditions. Therefore, although nanospanlastic represents a promising nanovesicular platform, further systematic optimization and clinical validation are essential to support its successful translational and industrial application.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Abdel-Salam, H. M., et al. (2023). Green tea extract loaded spanlastics for anti-aging cosmeceutical applications: Formulation, characterization, and in vitro evaluation. *Journal of Cosmetic Science*, 74(2), 241–255.

Abdelbary, A., & AbouGhaly, M. H. (2015). Design and evaluation of spanlastics for transdermal delivery of drugs. *AAPS PharmSciTech*, 16(1), 1–12.

Ahmed, T. A., Badr-Eldin, S. M., Ahmed, O. A., & Aldawsari, H. (2016). Nanovesicular systems for enhanced transdermal drug delivery. *Journal of Molecular Liquids*, 222, 301–310.

Al-Mahallawi, A. M., Khowessah, O. M., & Shoukri, R. A. (2017). Enhanced non-invasive trans-tympanic delivery of ciprofloxacin through encapsulation into nano-spanlastic vesicles:

Fabrication, in vitro characterization, and comparative ex vivo permeation studies. *International Journal of Pharmaceutics*, 522(1–2), 157–164.

Alaaeldin, E., Abouelmagd, S. A., Omar, M. M., & Elmowafy, E. (2021). Topical nano-vesicular spanlastics of celecoxib: Enhanced anti-inflammatory effect and down-regulation of TNF-α, NF-κB, and COX-2 in complete Freund's adjuvant-induced arthritis model in rats. *International Journal of Nanomedicine*, 16, 1749–1762.

Alnusaire, T. S., Sayed, A. M., Elmaidomy, A. H., Al-Sanea, M. M., Albogami, S., Albqmi, M., Alowaiesh, B. F., Mostafa, E. M., Musa, A., & Abdelmohsen, U. R. (2021). An in vitro and in silico study of the enhanced antiproliferative and pro-oxidant potential of *Olea europaea* L. cv. Arbosana leaf extract via elastic nanovesicles (spanlastics). *Antioxidants*, 10(12), 1860.

Annisa, R. (2025). Spanlastic as a transdermal drug delivery system: A systematic review. *Biomedical and Pharmacology Journal*, 18(1), 447–457.

Ansari, M. J., Anwer, M. K., Jamil, S., Ahmad, M., Alshahrani, S. M., & Alshetaili, A. (2022). Fabrication and optimization of raloxifene-loaded spanlastics vesicles for transdermal delivery. *Journal of Drug Delivery Science and Technology*, 70, 103226.

Elsherif, N. I., Shamma, R. N., & Abdelbary, G. (2017). Terbinafine hydrochloride spanlastics for transdermal delivery: Design, optimization and in vivo evaluation. *International Journal of Pharmaceutics*, 523(1), 273–281.

El Hosary, R. A., El-Say, K. M., Ahmed, O. A. A., & Bendas, E. R. (2024). Topical delivery of extracted curcumin as curcumin-loaded spanlastics anti-aging gel: Optimization using experimental design and ex vivo evaluation. *Saudi Pharmaceutical Journal*, 32(1), 34–45.

El-Zaafarany, G. M., Farid, R. M., & Helmy, M. W. (2020). Deformable nano-vesicles for dermal and transdermal delivery: Penetration mechanisms and formulation challenges. *Colloids and Surfaces B: Biointerfaces*, 194, 111156.

Elmowafy, E., El-Gogary, R. I., Ragai, M. H., & Nasr, M. (2019). Novel antipsoriatic fluidized spanlastic nanovesicles: In vitro physicochemical characterization, ex vivo cutaneous retention and exploratory clinical therapeutic efficacy. *International Journal of Pharmaceutics*, 568, 118505.

Garg, T., Singh, O., Arora, S., & Murthy, R. S. R. (2018). Itraconazole spanlastics for topical delivery: Formulation, optimization, and evaluation. *Journal of Liposome Research*, 28(4), 327–335.

Gupta, A., Bhardwaj, A., & Gupta, M. (2017). Enhanced skin retention of tazarotene via spanlastics for psoriasis: Preparation and evaluation. *Journal of Pharmaceutical Sciences*, 106(9), 2540–2547.

Santuso, E., Soeratri, W., & Purwanti, T. (2023). Characterization of spanlastic system loaded green tea extract as antioxidant for skin. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, 10(1), 30–37.

Kakkar, S., Kaur, I. P., & Kaur, A. P. (2018). Spanlastics - A novel nanovesicular carrier system for topical and transdermal drug delivery. *International Journal of Pharmaceutics*, 538(1–2), 79–92.

Kaur, G., Arora, S., & Sharma, A. (2018). Nonionic surfactants in topical formulations: Safety and applications. *Colloid and Interface Science*, 26(2), 78–89.

Kumar, L., Verma, R., & Singh, S. (2021). Spanlastic nanovesicles for enhanced dermal drug delivery: formulation, characterization and evaluation. *Journal of Pharmaceutical Investigation*, 51(4), 489–499.

Lopes, A. M., Batista, A. F., & Martins, J. P. (2019). Spanlastic vesicles: A promising approach for enhanced transdermal drug delivery. *Journal of Drug Delivery and Therapeutics*, 9(3), 122–129.

Mehta, M., Satija, S., & Sharma, S. (2021). Spanlastics as nanocarriers for drug delivery: Recent advancements and prospects. *Current Pharmaceutical Design*, 27(13), 1520–1529.

Moghddam, S. R., Fatemizadeh, M., & Ebrahimnejad, P. (2020). Nanospanlastics as a promising carrier for improved dermal delivery. *Journal of Drug Delivery Science and Technology*, 57, 101713.

Morrow, D. I. J., McCarron, P. A., Woolfson, A. D., & Donnelly, R. F. (2007). Innovative strategies for enhancing topical and transdermal drug delivery. *The Open Drug Delivery Journal*, 1, 36–59.

Müller, R. H., Keck, C. M., & Radtke, M. (2012). Nanocarrier penetration pathways through the stratum corneum: Role of surfactants and vesicle elasticity. *European Journal of Pharmaceutics and Biopharmaceutics*, 80(1), 25–34.

Mura, S., Maibach, H. I., & Couvreur, P. (2019). Nanocarriers for transdermal drug delivery. *Journal of Controlled Release*, 302, 93–112.

Pandey, M., Kumar, R., & Sawant, K. K. (2020). Stability and scalability concerns in nano-vesicular systems: An overview. *Asian Journal of Pharmaceutical Sciences*, 15(2), 143–155.

Patel, R. P., Patel, M. R., & Patel, N. M. (2019). Spanlastic formulation of celecoxib for topical delivery in rheumatoid arthritis: Preparation, characterization, and in vivo anti-inflammatory activity. *Drug Development and Industrial Pharmacy*, 45(12), 2037–2046.

Safitri, L. N., & Permana, A. D. (2023). Pengembangan sistem penghantaran obat berbasis spanlastik untuk aplikasi topikal dan transdermal. *Jurnal Ilmu Kefarmasian Indonesia*, 21(3), 215–230.

Shaji, J., & Lal, M. (2014). Nanovesicular carriers for transdermal delivery: A review. *Indian Journal of Pharmaceutical Sciences*, 76(4), 329–338.

Sharma, A., Gupta, R., & Sharma, S. (2020). Spanlastics: A novel elastic nanovesicular system for enhanced topical and transdermal drug delivery. *Journal of Drug Delivery Science and Technology*, 60, 101944.

Sharma, A., Pathak, K., & Sharma, S. (2020). Spanlastics: A novel nanocarrier for transdermal drug delivery. *International Journal of Applied Pharmaceutics*, 12(6), 1–8.

Yusuf, H., Maritza, S., & Meiyanto, E. (2023). Spanlastics: Potensi dan tantangan dalam sistem penghantaran obat topikal dan transdermal. *Jurnal Farmasetika Indonesia*, 7(2), 123–138.