

Spanlastic as a Transdermal Drug Delivery System: A Systematic Review

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Spanlastic is an innovative drug delivery system that traps drugs in a core cavity with a double-layer structure. The term spanlastic comes from the combination of Span and elastic, first introduced in 2011. This plastic is a development of liposomes and niosomes that have been modified sophisticatedly; several types of spanlastic include Multi Lamellar Vesicles (MLV) with a bilayer structure, size 0.5-1.0 microns, easy to make, frequently used, and long-term stable. Large Unilamellar Vesicles (LUV) measuring 100 nm-1 μ m have a high water or lipid ratio and can accommodate more drugs; Small Unilamellar Vesicles (SUV) measuring 20 nm-50 μ m, prepared from MLV by sonication. The growing interest in spanlastics for various administrative strategies has been evident. These nanovesicles, composed of a surfactant, are highly elastic and adaptable, encapsulating an aqueous solute solution. Studies have shown that spanlastics exhibit greater chemical stability and address several limitations of conventional dosage forms. They enhance drug delivery by enabling targeted distribution and controlled release of natural medicinal components, among other advantages. Spanlastics overcome many challenges associated with traditional drug formulations by facilitating the precise delivery of active pharmaceutical ingredients and regulating their release rate. This review highlights their significance, penetration mechanism, preparation methods, and applications.

Keywords: Edge Activators; Nanocarrier; Nanovesicles; Penetration; Spanlastics; Transdermal.

Spanlastic is one of the dosage forms that can be used for transdermal delivery in the form of a surfactant-based elastic vesicular nanocarrier consisting of nonionic surfactants (vesicle builders) and edge activators (EA).¹⁻² Spanlastic vesicles are a form of niosomes that have been sophisticatedly modified, utilizing the presence of EA, which provides high deformability or flexibility properties to vesicles.³ Several types of spanlastic include Multilamellar Vesicles (MLV) with a bilayer structure, size 0.5-1.0 microns, easy to make, often used, and long-term stable. Large Unilamellar Vesicles (LUV) are 100 nm-1 μ m in size, have a

high water/lipid ratio, and can accommodate more drugs. Small Unilamellar Vesicles (SUV) are 20 nm-50 μ m in size, prepared from MLV through sonication.

The manufacture of spanlastics is influenced by several main factors that determine the formation and characteristics of vesicles. One of them is the ratio of vesicle builder and edge activator, where this ratio affects particle size, entrapment efficiency, and vesicle stability. A higher ratio of edge activator tends to produce smaller and more elastic particles. In addition, the hydrophilic-lipophilic balance (HLB) value of the

surfactant is also important, whereas surfactants with HLB values between 4 and 8 are considered ideal.³ This value indicates that the surfactant has sufficient lipophilic properties to form a vesicle bilayer. Surfactants with HLB values above 14 are too hydrophilic and do not form a bilayer membrane well. Other factors, such as the ideal Critical Packing Parameter (CPP) range of 0.5–1.0 and the high Phase transition temperature at Span 60 (53°C), contribute to vesicle stability.⁴⁻⁵ Due to their advantages, nonionic surfactants are the most commonly used type in vesicle production. This material offers stability, compatibility, and lower toxicity than anionic, amphoteric, or cationic surfactants. Nonionic surfactants contain both polar and nonpolar components and exhibit excellent interfacial activity. Acting as vesicle formers, nonionic surfactants enhance the entrapment of active substances when used in large amounts. However, this also leads to an increase in vesicle diameter, resulting in larger vesicles. Particles smaller than 700 nm have been shown to penetrate deeper into the skin layers, offering benefits for psoriasis treatment and anti-inflammatory effects.⁶

Vesicles primarily composed of Span 80 (HLB value 4.3) and Span 40 (HLB value 6.7) exhibited high levels of disruption, aggregation, and instability. In contrast, vesicles based on Span 60 (HLB value 4.7) demonstrated greater stability. The lipophilic nature of Span 60 facilitates the formation of vesicles with a lamellar matrix structure. Additionally, Span 60 has a higher drug entrapment capacity than other nonionic surfactants. Studies indicate that Span 60 supports the formation of stable unilamellar and multilamellar vesicles with high entrapment efficiency (EE%) due to its lipophilic characteristics and saturated alkyl chains.⁷

Spanlastic formulations also include edge activators (EA), such as Tween and Brij, which enhance vesicle fluidity and deformability. The unique combination of vesicle formers and EA improves penetration, making spanlastic an innovative drug delivery system capable of crossing biological membrane barriers. This allows drugs to be transported to various tissues non-invasively via topical application. Increasing the concentration of EA in spanlastic reduces surface tension, enhancing deformability. However, excessive EA concentrations may increase vesicle membrane

permeability, leading to active ingredient leakage and reduced entrapment efficiency.⁷⁻⁸

Several techniques are used to prepare spanlastics, including ether injection, ethanol injection, thin film hydration, and modified spray methods. Based on the findings discussed, this review aims to highlight the significance of spanlastics, their penetration mechanisms, various preparation methods, and potential applications.⁹⁻¹⁰

MATERIALS AND METHODS

This study was systematically conducted using multiple databases, including a computer-based electronic search. The inclusion criteria encompassed publications from 2015 to 2025 in January – December, written in English or Indonesian and published in academic journals. Additionally, literature on polymeric hydrogel membranes and their applications in wound dressings was considered. Exclusion criteria included journal reviews and literary texts that were not fully accessible. The selected literature was obtained from original studies available on various accessible databases. ScienceDirect, Springer, PubMed, Sage, and Taylor & Francis Online were international sources. The search utilized keywords such as Film-forming, Hydrogels, Membranes, Wound Dressings, and Biomedical Applications. Data analysis followed a qualitative meta-synthesis approach due to the heterogeneous nature of the literature. The PRISMA Guideline diagram was used to filter relevant studies, resulting in the selection of 15 articles for detailed review. The PRISMA flow diagram summarizes the screening process visually. This chart initially records the number of articles found, then makes the selection process transparent by reporting decisions made at various stages of the systematic review. The number of articles was recorded at various stages. The review strategy is illustrated in Figure 1.

RESULTS

The approach for selecting and searching articles followed a structured and systematic strategy based on the PRISMA guideline method. This process involved four databases: ScienceDirect, Springer, PubMed, Sage, and Taylor & Francis Online. A total of 15 research articles

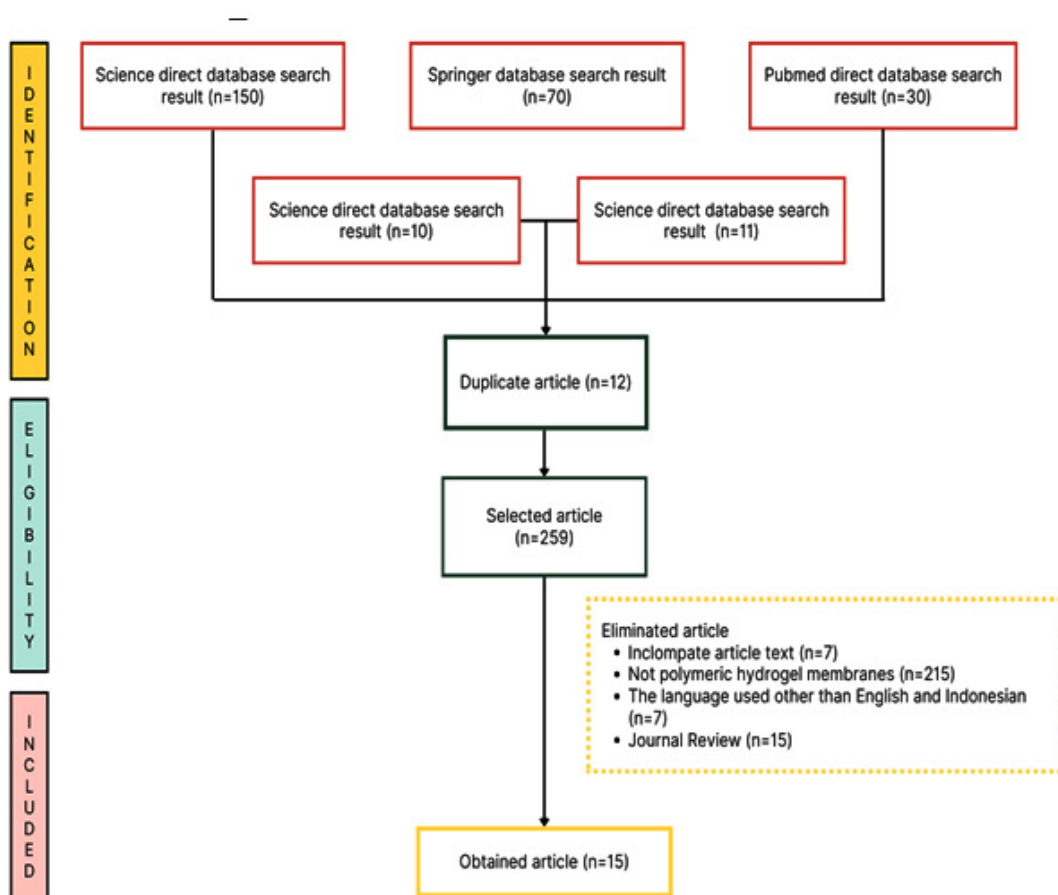
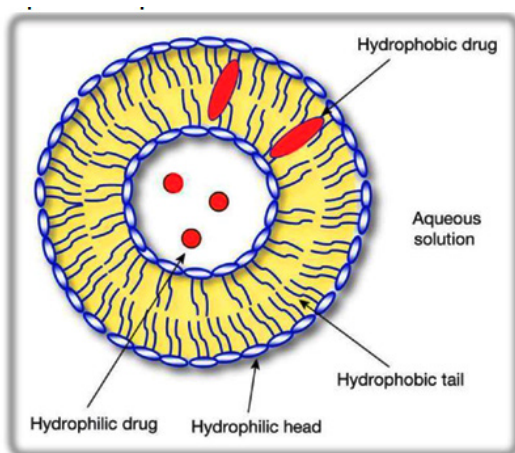


Fig. 1. Review strategy scheme

Fig. 2. Spanlastic Structure¹⁰

were identified as relevant to the topic of discussion (Figure 1).

Transdermal drug delivery systems have been the focus of intensive research over the past few years, drawing attention to researchers to overcome barriers to skin penetration to increase therapeutic effectiveness. One prominent innovation is using elastic lipid vesicles, such as spanlastic, designed to increase drug permeability through the skin. Spanlastics are lipid vesicles with high elasticity, allowing them to penetrate skin layers that are usually difficult for conventional vesicles. This flexible structure is obtained by adding certain surfactants into the lipid bilayer, increasing the deformability and penetration ability of the vesicles. Even though it has great potential,

using spanlastics in transdermal drug delivery systems faces several challenges, including the large-scale production process and stability for long-term use and storage. A consistent and efficient spanplastic manufacturing process on an industrial scale requires further optimization. Recent research focuses on improving spanplastic formulations and production methods to overcome

these challenges. In addition, further clinical studies are needed to confirm the safety and effectiveness of spanplastic use in humans. In the last five years, spanlastics have emerged as a promising transdermal drug delivery system, offering improved drug penetration and stability. Although several challenges still need to be overcome, technological and research developments in this

Table 1. Comparison system delivery spanplastic with niosome/liposome

Comparison System Delivery	Spanlastic	Niosome / Liposome
Stability formulation	Active ingredient in system spanplastic capable endure with existence changes in pH, temperature , and light	Material active in system spanplastic capable endure with existence changes in pH, temperature , and light
Size particle	No experience aggregation or change size particle during storage	Experience aggregation or change size particle during storage
Efficiency encapsulation	Drug can encapsulated with Good in system spanplastic	No all drug can encapsulated with Good in system spanplastic
Scalability production	Uniformity size particles and reproducibility of the process to be challenge in manufacturing mass	Uniformity size particles and reproducibility of the process to be challenge in manufacturing mass
Control release drug	Release controlled drug in accordance need therapy is very important	Release controlled drug in accordance need therapy is very important
Safety and biocompatibility	Able to minimize effect side system delivery drug	Able to minimize effect side system delivery drug
Method delivery	Use spanplastic in various route giving medication (oral, transdermal, or injection)	Use spanplastic in various route giving medication (oral, transdermal, or injection)

Table 2. Key Success Factors Formulation of Spanlastic

Spanlastic	Key Success Factors Formulation	Results Formulation
Component Carrier	Comparison vesicle builder and edge activator	Ratio component plastic span influence size particles, efficiency entrapment , and stability vesicles . The ratio is higher high on edge activator not visible produce more particles small and elastic .
Hydrophilic-Lipophilic Balance (HLB) of surfactants	Ideal HLB values 4 and 8	Surfactant with HLB value above 14 also hydrophilic and not to form bilayer membrane with Good
Critical Packing Parameters	Ideal Critical Packing Parameter (CPP) is in the range of 0.5–1.0	Maintain stability plastic sponge
Phase Transition Temperature (Tc)	High Phase Transition Temperature (Tc) at Span 60 (53°C)	Maintain stability plastic span

area continue to open up new opportunities for broader clinical applications.¹⁰

Spanlastic is an innovative drug delivery system that traps drugs in a core cavity with a double-layer structure. Spanlastic (a combination of Span and Elastic) was first introduced in 2011. This system is a highly elastic and deformable carrier, similar to transfersomes. As a flexible vesicular carrier system, spanlastic offers higher permeability than conventional drug preparations. This system is amphiphilic, where the drug is encapsulated in vesicles formed by nonionic surfactants. Its size is very small and microscopic. Spanlastic belongs to a special category of nanovesicles designed to overcome the weaknesses of liposomes, such as chemical instability due to oxidative degradation and variations in phospholipid purity. Its elastic properties come from the presence of edge activators in its structure. As a special vesicular carrier, spanlastic is a drug delivery system targeting specific sites. This system can be applied for ocular, oral, topical, nasal, and translingual treatments.¹²

Spanlastics are spheroidal structures composed of amphiphilic molecules that act as a suitable matrix for bioencapsulation. Spanlastics have concentric bilayers similar to liposomes. Spanlastics can be Unilamellar or Multilamellar (MLV). Depending on the size of the vesicle, it can be a small Unilamellar (SUV) (10-100 nm) or a large Unilamellar (LUV) (100-3000 nm). It has been reported that MLVs have longer retention than SUVs with the same lipid composition.¹⁰⁻¹¹

In the formulation of spanlastic production, several requirements must be met so that the success of spanlastic formation is met. Important considerations are: (1) Biocompatibility: Spanlastic must be non-toxic and compatible with biological systems. This is supported by the use of environmentally friendly nonionic surfactants. (2) Sustainability and Stability: To prevent drug damage during storage or use, vesicles must be chemically and osmotically stable. (3) Encapsulation Ability: Spanlastic must encapsulate active drug ingredients, both lipophilic and hydrophilic, in its vesicular matrix. (4) Elasticity: Vesicles must be elastic to allow deformation, thus facilitating penetration into target tissues through biological membranes. (4) Size and Distribution: Vesicle size must be small and uniform to ensure efficient penetration and optimal distribution at the target site. (5) Safety: Materials used, including surfactants and edge activators, must not irritate, especially for sensitive applications like the eyes. (6) Delivery Efficiency: The system must release the drug in a controlled and targeted manner, maximizing bioavailability and minimizing side effects. (7) Efficient Manufacturing Method: The manufacturing process must be economical and capable of producing vesicles of adequate quality, such as through ether injection, sonication, or microfluidization methods.¹²

Like liposomes, spanlastics can also be categorized based on their number of layers. (1) Multilamellar Vesicles (MLV): MLVs are the most commonly used type, consisting of multiple

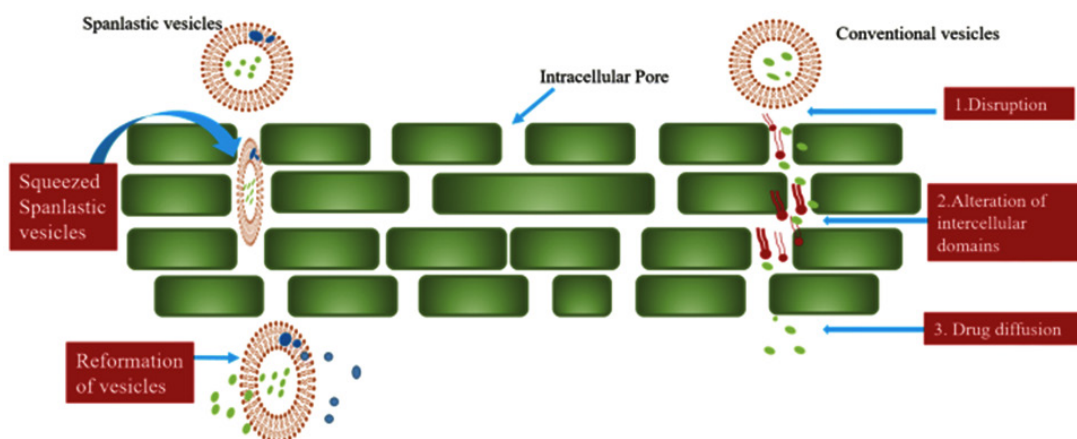


Fig. 3. Spanlastic Penetration Mechanism¹²

Table 3. General Summary of 15 Studies in the Systematic Review of Spanlastik

No	Scope Study	Summary of Contents	Evaluation Critical	Strengths & Weaknesses	Research Results	Relevance & Contribution	General Conclusion	Ref
1	System nanovesicular For delivery drug ophthalmologists	Review about various system nanovesicular For application ophthalmologists	Lack of clinical data For effectiveness term long	Comprehensive analysis but limited to laboratory studies	Nanovesicular increase bioavailability drug eye	Contribute to design system delivery drug ophthalmologists	Nanotechnology holds promise in improving eye therapy	1
2	Technology delivery modern medicine	Various studies technology delivery drug	Lack of Study empirical , more Lots based on Literature	Give view wide But No tested direct	Provide Turn technology latest	Useful for researchers and pharmaceutical practitioners	Technology delivery drug develop fast	2
3	spanish language in therapy pharmacy	Potential and trends latest in delivery drug based on spanplastic	Need study more carry on For application clinical	Give outlook deep But Still English	spanish language show efficiency tall in delivery drug	Give base For future research and applications	Spanlastik has great potential in therapy	3
4	Niosom as Carrier drug nanoparticles	Basic discussion and latest applications of niosome	Limited to exploration laboratory room	Give Review wide but minimal in vivo testing	Niosome has high stability and effectiveness	Useful in designing nanoparticle drug formulations	Niosom is alternative potential in delivery drug	4
5	Spanlastik with extract tea green For skin	Characterization and evaluation activity antioxidant	No clinical trials, limited to in vitro tests	Stable formulation but lack of long-term effect data	Spanlastik increase stability extract tea green	Useful in skin care product formulation	Spanlastik can used in cosmetics and pharmaceuticals	5
6	Delivery topical vitamin C use spanplastic	Stability and effectiveness studies For skin	Limited to short-term studies	Increase Vitamin C is stable but data less effect side	Spanlastik extend vitamin c stability	Relevant For product dermatology	Spanlastik can increase effectiveness therapy skin	6
7	Spanlastik For psoriasis therapy	Evaluation chemistry physics and retention skin spanplastic	Limited to initial experimental testing	Formulation show retention skin tall	Spanlastik effective in psoriasis target	Contributing to the development of psoriasis drugs	Nanotechnology opens up new opportunities in psoriasis therapy	7

8	Delivery topical Fenoprofen Calcium	Optimization in vivo formulation and evaluation	Long-term data is still lacking	The formulation shows high efficiency in skin permeation.	Spanlastik increase effectiveness delivery	Useful in therapy anti-inflammatory	Spanlastik can increase availability biological drug	8
9	Delivery of vanillic acid to eye	Characterization and evaluation of anti-inflammatory effects	Lack of Study clinical	Innovative formulation but lack of long-term effect data	Spanlastik increase bioavailability and effects	Contribution to formulation ophthalmologists	Spanlastik increases the efficiency of eye therapy	9
10	Potential spanplastic in delivery drug	Discussion benefits and challenges in use spanplastic	minimal experimentation, more nature theoretically	Give outlook But lack of empirical data	anti-inflammatory spanish language offer potential big in therapy	Useful for future drug developers	spanish language can increase delivery drug	10
11	Formulation spanplastic latest	Review approach formulation latest	n't any in vivo study	Discussion in theory good but minimal evidence clinical	Spanlastic formulation is superior to conventional methods	Useful in innovation pharmacy	Spanlastik offer solution modern formulation	11
12	Delivery drug based on spanplastic	Concept and benefits of learning spanplastic	practical tests	Great potential but not yet tested further	Better delivery stability and efficiency	Relevant for researcher pharmacy	Spanlastik have a future bright in industry pharmacy	12
13	Transdermal delivery of Haloperidol	Adsorption efficiency and particle size	long-term toxicity data.	Formulation show absorption tall	Spanlastik increase efficiency transdermal delivery	Useful in the formulation of neuropsychiatric drugs	Nanotechnology opens up new opportunities in therapy	13
14	Nanospanlastik for leukotriene inhibitors experience	Evaluation permeation skin and in vitro characterization	Limited to study laboratory	High potential but lack of clinical data	Improvement permeation skin and effectiveness therapy	Relevant for the development of inflammatory therapies	Nanospanlastik can increase therapy topical	14
15	Spanlastik For transdermal delivery of lidocaine	Formulation and evaluation efficiency	Lack of clinical trials man	Formulation show release good medicine	Spanlastik increase bioavailability lidocaine	Relevant in anesthesia local	Formulation spanplastic effective in delivery drug topical	15

bilayer layers with vesicle diameters ranging from 0.5 to 1.0 microns. They are easy to produce and exhibit mechanical stability over long storage periods. (2) Large Unilamellar Vesicles (LUV): LUVs have a high water-to-lipid ratio, enabling the encapsulation of a larger volume of bioactive compounds. (3) Small Unilamellar Vesicles (SUV): SUVs are typically derived from multilamellar vesicles through sonication, French Press, or extrusion processes.

DISCUSSION

Spanlastic has several advantages, making it a superior choice in drug delivery systems. One of its advantages is its biodegradable and non-immunogenic nature, making it safe for use in the body without causing toxic reactions. This system increases drug bioavailability by protecting the active ingredient from degradation until it reaches its target while providing controlled drug release. Spanlastic is also flexible and elastic, allowing better penetration through biological membranes such as the cornea, making it suitable for site-specific applications such as the eye, skin, and nasal. In addition, its chemical stability is better than liposomes, overcoming the problem of oxidative degradation that often occurs in conventional formulations. Its manufacturing process is economical, and the raw materials are easily available, making it efficient for large-scale production. However, spanlastics also have some drawbacks. The entrapment efficiency and stability of the vesicles depend highly on the manufacturing method and the type of surfactant used. In addition, the small size and elasticity of the vesicles may require special techniques to ensure uniform distribution and stability during storage. Another challenge is the need to optimize the formulation to suit the characteristics of a particular drug, which can be time-consuming and costly to develop.¹²

Spanlastic Mechanism as Transdermal Drug Delivery

A transdermal delivery system is a method of drug delivery through an application on the skin surface, where the drug is then absorbed into the body through the skin.¹² This method helps to extend the duration of drug release and reduce side effects that often occur in oral administration. The main advantages of transdermal delivery

include avoiding first-pass metabolism, increasing bioavailability, and ensuring longer effects, thereby reducing the frequency of drug administration, increasing patient compliance, minimizing side effects, and increasing therapeutic value. In addition, this method allows the drug to reach an effective concentration in the target area, providing direct therapeutic effects in the affected area. The success of transdermal delivery is influenced by the characteristics of the drug, including low molecular weight (<500 Dalton), low melting point (<200°C), octanol/water partition coefficient (log P) between 1-4, half-life ($t_{1/2}$) less than 10 hours, low oral bioavailability, and does not cause skin irritation. Drug penetration in the spanlastic system uses two mechanisms: (1) Elastic vesicles interact with the epithelial cell membrane, act as penetration enhancers, and then modify the intercellular lipid lamella. (2) Elastic vesicles can act as a drug carrier system, where intact vesicles carry drugs through the intercellular space and reach biological membranes. The following factors contribute to the successful passage of these carriers: Elasticity of the vesicle bilayer, which is high pressure dependent; the presence of an osmotic gradient; and Surfactants triggering solubilization (lysis) in a higher concentration range.¹²

Spanlastic Preparation Method

Ether Injection Method

This technique involves dissolving a surfactant in 20 ml of ether, which is then gradually introduced through a 14-gauge needle into 4 ml of an aqueous drug solution preheated to 60°C at a controlled rate of 25 ml/min. The ether is subsequently removed via evaporation using a rotary evaporator. Once the organic solvent is eliminated, a single-layer vesicle is formed.¹²

Sonication Method

This method prepares a drug solution in a suitable buffer and adds it to a surfactant mixture inside a 10 ml glass vial. The mixture is then subjected to sonication using a titanium probe, facilitating vesicle formation.¹²

Hand Shaking Method

The surfactant is first dissolved in an organic solvent such as ether, chloroform, or benzene. The solvent is then evaporated under reduced pressure using a vacuum evaporator in a round-bottom flask. The resulting thin film is subsequently hydrated with an aqueous drug

solution while continuously agitated. This process expands the surfactant layer, leading to the folding of amphiphilic molecules and the formation of drug-encapsulated vesicles.¹²

Extrusion Method

A mixture of surfactant and diacyl phosphate is prepared, followed by solvent removal using a rotary vacuum evaporator to form a thin film. This film is then hydrated with an aqueous drug solution. The resulting suspension is passed through a polycarbonate membrane with an average pore size of 0.1 microns. The extrusion process is repeated up to eight times to ensure uniform vesicle size.¹²

Microfluidization Method

This approach involves the interaction of two high-velocity fluid streams—one containing the drug and the other containing the surfactant within microchannels designed for controlled fluid dynamics. This process, known as the submerged jet principle, generates smaller, uniformly sized particles and ensures high reproducibility in spanlastic formulations.¹²

Components of Spanlastic Ingredients

Vesicle Builder

Surfactants act as surface-active agents, reducing interfacial tension between two immiscible liquids, such as oil and water. Nonionic surfactants, particularly sorbitan alkyl esters (Spans), do not carry charged head groups and play a crucial role in vesicle formation. The self-assembly of Spans results in a bilayer structure, with different types classified based on their fatty acid composition, including Span 80 (monooleate), Span 60 (monostearate), Span 40 (monopalmitate), and Span 20 (monolaurate). The choice of Span significantly affects the stability of the formulation. Vesicles based on Span 80 and 40 tend to exhibit higher instability, while the saturated alkyl chains in Span 60 contribute to increased structural stability. These lipophilic chains promote the formation of unilamellar and multilamellar vesicles. Additionally, the surface-active properties of these surfactants support the function of edge activators, which lower interfacial tension and aid in producing more uniform spanlastic dispersions.¹³

Edge Activators

Edge activators are surfactants with high hydrophilic-lipophilic balance (HLB) values,

contributing to vesicle flexibility. These single-chain surfactants disrupt vesicle structures by reducing interfacial tension, increasing membrane deformability, and forming more spherical vesicles with smaller particle sizes. Incorporating edge activators such as Tween 80 enhances vesicle elasticity, temporarily enlarging pore size in biological membranes. This improves drug penetration, facilitating transdermal delivery of slightly larger vesicles. Additionally, hydrophilic surfactants can destabilize vesicular membranes, increasing their deformability and altering their structural arrangement.¹³

Utilization of spanlastic as transdermal delivery

Recent studies have explored the potential of spanlastic formulations for transdermal drug delivery. One such investigation focused on enhancing the skin penetration of 3-acetyl-11-keto- β -boswellic acid (AKBA), a potent anti-inflammatory compound. However, due to its poor water solubility and low oral bioavailability, AKBA was incorporated into deformable elastic nanovesicles and nanospanlastic systems to improve transdermal absorption. Using the ethanol injection, researchers formulated nanospanlastic with Span 60 as the nonionic surfactant and Tween 80 as the edge activator. The study demonstrated that nanospanlastic technology holds promise for increasing the permeability and topical delivery of AKBA.¹⁴

Additionally, spanlastic formulations have been investigated for their ability to enhance the transdermal delivery of lidocaine, a local anesthetic. Studies have shown that spanlastic-based systems significantly improve lidocaine penetration into the skin, increasing its therapeutic effectiveness. However, further research is necessary to evaluate the long-term safety and efficacy of this approach.¹⁵

Based on results Review general of 15 articles done in discussion Review system delivery drug based on nanovesicular, in particular spanplastic can Advanced that technology This own potential big in increase bioavailability, stability, and effectiveness therapy various kinds of medicine applications, including ophthalmology, dermatology, and transdermal delivery. A number of study show that system nanovesicular capable increase retention drugs

at the target location, reduce effect side systemic, as well as extend duration action medicine. In addition, the formulation based on spanplastic has proven effective in increase permeation drug through membrane biological, making it promising solution in delivery topical and transdermal. However, most studies are still limited to the experimental stage and in vitro or ex vivo testing, with little clinical trial data in humans. Therefore, further research, especially clinical studies, is needed to ensure the safety, efficacy, and long-term stability of this nanovesicular-based drug delivery system before it can be widely implemented in the pharmaceutical and medical world. Overall, spanlastics technology is a promising innovation in the field of drug delivery, with great potential for further development in various pharmaceutical applications.

CONCLUSION

Spanlastic technology represents an advanced nanotechnology-based transdermal drug delivery system designed to improve drug penetration through the skin. Utilizing elastic vesicles composed of surfactants and other functional additives, spanlastic formulations offer high flexibility, enabling them to traverse the skin more effectively than conventional delivery systems.

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Conflict of Interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, so informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Not Applicable.

Authors' Contribution

The sole author was responsible for the conceptualization, methodology, data collection, analysis, writing, and final approval of the manuscript

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