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Spanlastics: An Emerging Elastic Technique for Enhanced Mucosal Drug Delivery

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ABSTRACT

Spanlastics are ultra-deformable nano-vesicular drug delivery systems that are mainly composed of non-ionic surfactants, especially sorbitan esters (Span), along with edge activators that provide high membrane flexibility and elasticity. Because of their special structure, spanlastic vesicles may bend and pass through biological barriers and small intercellular gaps, improving medication absorption and penetration. Because of these characteristics, spanlastics are particularly well suited for mucosal drug delivery, which has benefits like increased patient compliance, quick drug absorption, and avoidance of first-pass metabolism. However, medication permeability and bioavailability may be restricted by physiological barriers such as mucus turnover, enzymatic degradation, and tight epithelial junctions. The structure, composition, and classification of spanlastic vesicles are outlined in this article, along with the mechanisms underlying improved mucosal penetration. Along with important characterization metrics including vesicle size, zeta potential, shape, entrapment efficiency, and in-vitro drug release, common preparation techniques like thin-film hydration, ethanol injection, ether injection, and sonication are covered. Additionally, spanlastics' benefits and drawbacks are contrasted with those of traditional vesicular systems like liposomes and niosomes. Overall, the potential of spanlastics as adaptable nanocarriers for enhancing medication bioavailability and therapeutic outcomes is highlighted by recent applications in ophthalmic, transdermal, topical, intranasal, oral, and systemic drug delivery.

Keywords: Spanlastics, Mucosal drug delivery, Edge activator, Bioavailability, Permeability.

1. INTRODUCTION (1,2,3,4,5,6,7,11,18)

Mucosal drug delivery has attracted significant interest as a substitute for oral and injectable methods because it allows for quick absorption, bypasses first-pass metabolism, and enhances patient adherence. Mucosal tissues that are highly vascularized, including the nasal, buccal, ocular, and vaginal epithelia, offer direct access to the systemic bloodstream, making them particularly beneficial for drugs that have low oral bioavailability or undergo significant hepatic metabolism.

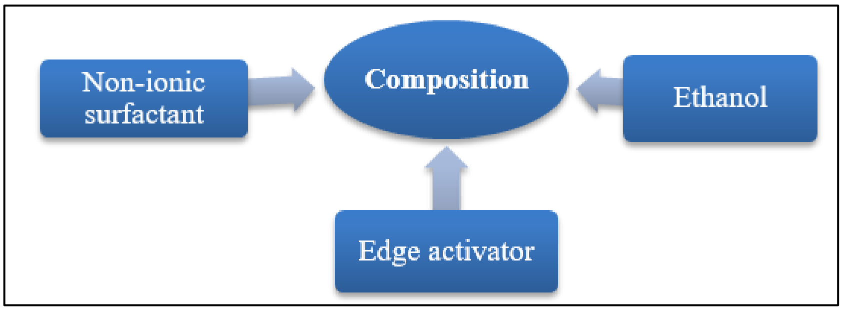
However, mucosal delivery encounters major biological challenges. The mucus layer consistently traps and eliminates foreign particles, which limits the amount of time drugs can remain in place. Tight junctions within the epithelium hinder the permeation of drugs, while local enzymes and clearance processes, such as mucociliary action and tear turnover, further diminish therapeutic effectiveness. These challenges highlight the need for flexible and stable carrier systems capable of enhancing drug transport across mucosal membranes.

Conventional vesicular systems, including liposomes and niosomes, enhance the encapsulation efficiency of therapeutic agents; however, they frequently encounter challenges related to restricted deformability and concerns regarding stability. In order to address these constraints, innovative elastic vesicular systems, exemplified by spanlastics, have been formulated. Spanlastics are nanovesicles derived from non-ionic surfactants, consisting of sorbitan esters (Span) and edge activators (such as Tween 80 or sodium cholate), which confer enhanced membrane flexibility. This inherent elasticity enables the vesicles to traverse through apertures smaller than their own dimensions while maintaining their structural integrity.

The groundbreaking studies of Kakkar and Kaur established spanlastics as a superior substitute for traditional niosomes by demonstrating that the concentration of edge activators plays a vital role in influencing vesicle deformability, entrapment efficiency, and drug release behavior. Their promise for nasal, buccal, and ocular distribution has been validated by later research, which has demonstrated superior pharmacokinetic performance and increased penetration. All things considered, spanlastics offer a flexible and promising platform for getting over the intrinsic obstacles of mucosal medication delivery.

1.1 The structure and composition of spanlastics (5,8,9,10,11,12,13)

Spanlastics are flexible bilayer vesicular structures designed to improve drug delivery across biological barriers. Non-ionic surfactants and edge activators make up the majority of their composition, however ethanol is commonly added during formulation to promote vesicle formation. In aqueous media, molecules of amphiphilic surfactants spontaneously form a closed bilayer structure. In order to form the membrane, the hydrophobic tails align inward while the hydrophilic heads face the external aqueous environment. Hydrophilic drugs can be enclosed in the central aqueous core formed by this arrangement, whereas lipophilic drugs are incorporated into the hydrophobic bilayer region.



Non-ionic surfactant:

The primary agents that generate vesicles are non-ionic surfactants like Span 60 (sorbitan monostearate) and Span 80 (sorbitan monooleate). Because of their amphiphilic characteristics, stable bilayer formation is possible. Since its longer saturated alkyl chain and higher phase transition temperature improve drug entrapment efficiency and membrane stability, Span 60 is frequently chosen among them.

Edge activator:

The bilayer is made more elastic by adding edge activators such as sodium cholate, sodium deoxycholate, Tween 80, and Tween 60. By intercalating between surfactant molecules, these substances increase the flexibility and decrease rigidity of membranes. Particularly in mucosal delivery systems, this structural alteration makes spanlastics more capable of deforming and overcoming biological barriers. To preserve vesicle integrity, their concentration must be carefully adjusted.

1.2 Ethanol:

Ethanol is frequently utilized in preparation techniques like ethanol injection. It improves membrane fluidity by reducing interfacial tension and serves as a solvent for the surfactants. Although too much ethanol may compromise vesicle stability, it also increases the solubility of medications that are poorly soluble in water, which can improve encapsulation efficiency.

Overall, ethanol supports membrane flexibility, edge activators provide deformability, and non-ionic surfactants build the bilayer in a synergistic manner to create a stable and versatile nano-vesicular system that can be used for improved mucosal drug administration.

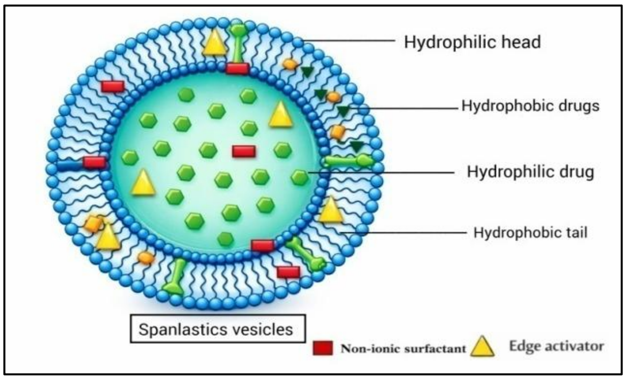
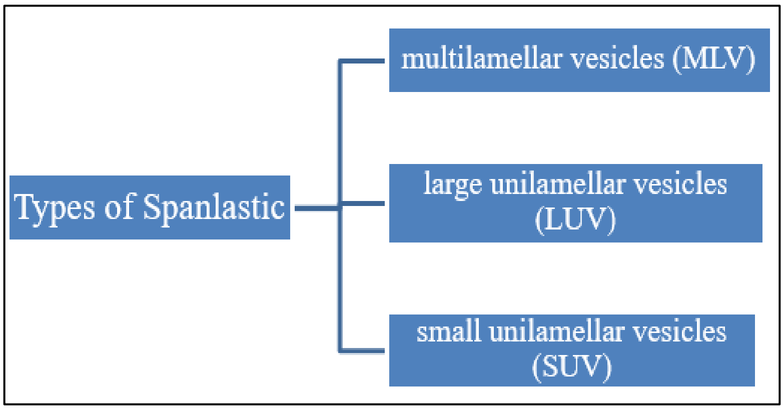


Fig. 1- Structure of spanlastic vesicles

1.3 Types of spanlastic vesicles (14,15,16)

Based on vesicle size and bilayer count spanlastic generally fall into three structural types –



1. **Multilamellar vesicles (MLV):**

Multilamellar vesicles have an onion-like structure due to the arrangement of several concentric bilayers on top of one another. Drug molecules can be trapped within many compartments because an aqueous layer separates each bilayer. MLVs typically feature large vesicles that range in size from roughly 0.5 to 1.0 µm. These vesicles are among the most frequently discussed forms in vesicular drug delivery systems because they are extremely simple to manufacture and exhibit good stability during storage. MLVs have a high drug-loading capacity due to the presence of several bilayers, especially for lipophilic compounds that can be integrated into the surfactant bilayer. The multilayer structure also functions as a diffusion barrier, allowing for regulated or prolonged medication release. However, compared to smaller vesicles, their capacity to deeply permeate biological membranes may be slightly reduced due to their larger particle size.

2. **Large unilamellar vesicles (LUV):**

A single surfactant bilayer surrounds a comparatively large aqueous core in big unilamellar vesicles. They have a high aqueous-to-lipid ratio inside the vesicle because their normal particle size ranges from 100 nm to around 1 µm.
Compared to smaller vesicles, LUVs are able to encapsulate more hydrophilic medicines due to their vast internal aqueous compartment. Furthermore, regulated drug molecule diffusion is made possible by the single bilayer membrane, which can enhance drug release kinetics. Thin-film hydration is frequently used to create LUV spanlastics, which are then extruded or homogenized. They are being investigated extensively for transdermal, ocular, and mucosal drug delivery systems due to their balanced size and loading capacity.

3. **Small unilamellar vesicles (SUV):**

The tiniest spanlastic vesicles are small unilamellar vesicles, which usually have a particle size of 20–100 nm. The aqueous core of these vesicles is smaller than that of LUVs, but they still have a single bilayer membrane. SUVs are typically produced from multilamellar vesicles using size-reduction techniques including sonication, extrusion methods. SUVs have excellent deformability and improved penetration into biological barriers, such as the stratum corneum and mucosal membranes, because of their nanoscale size and extremely flexible membrane. Despite their higher penetration capabilities, SUVs' restricted internal aqueous volume may result in a decreased drug loading capacity, especially for hydrophilic medicines.

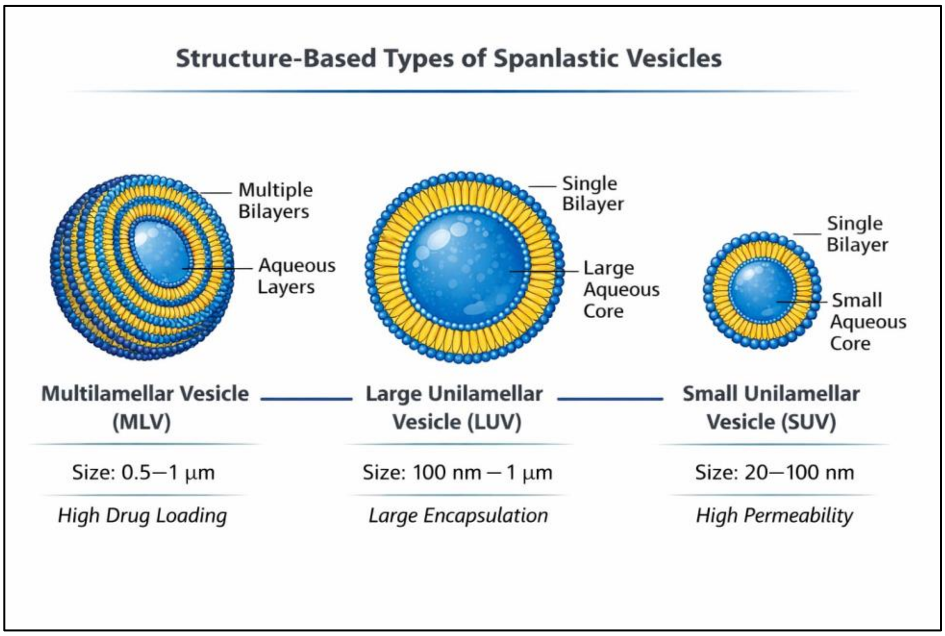


Fig. 2- Types of Spanlastics

1.4 Mechanism of mucosal permeation of spanlastics (18,19,20,21)

1. **Adhesion to mucosal surface**: Due to their small size and surfactant composition, spanlastics adhere to the mucus lining, extending their time near the epithelial cells and improving drug absorption.

2. **High deformability and squeezing through tight junctions:** The edge activators in spanlastics make the vesicles extremely flexible, allowing them to temporarily change shape and pass through narrow spaces between cells, improving permeation compared with rigid carriers.

3. **Interaction with the lipid membrane of the epithelium:** Spanlastics interact with the lipids in the membrane, slightly disrupting the packing of the membrane, increasing permeability and making it easier for the drug to pass through mucosal barriers.

4. **Drug protection from enzymatic degradation:** The vesicular structure protects sensitive drugs from mucosal tissue enzymes, maintaining their potency until they get to deeper absorption sites & beyond.

5. **Controlled drug release following permeation:** Spanlastics provide prolonged therapeutic activity and enhanced bioavailability by releasing the drug gradually after they have passed through the mucosal surface.

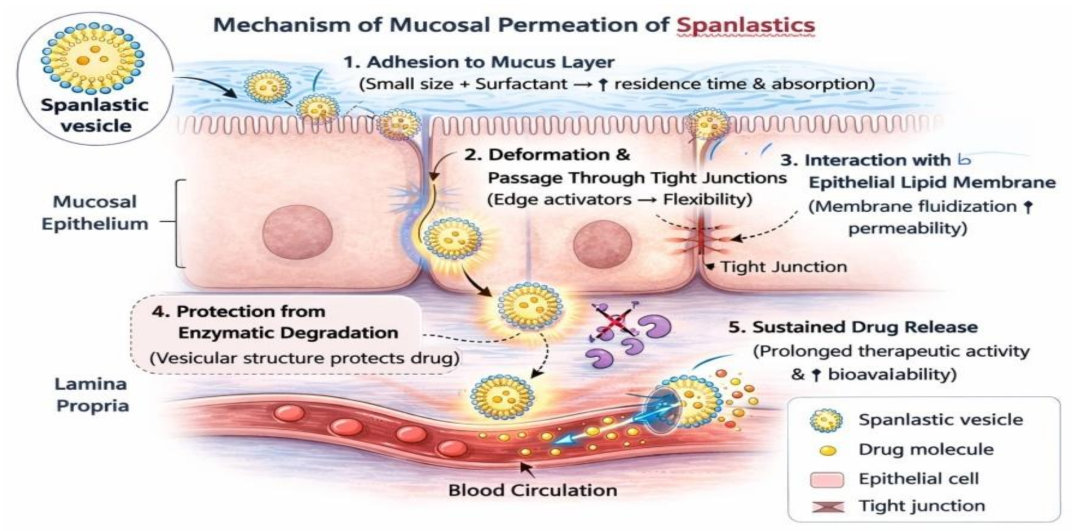


Fig. 3- Mechanism of mucosal permeation of Spanlastics

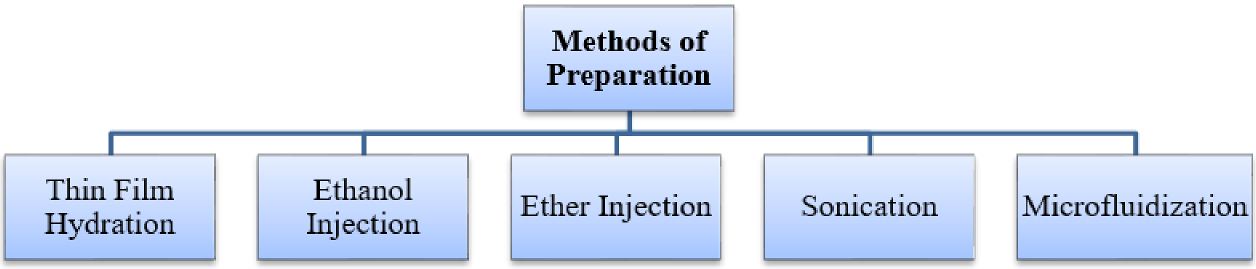
1.5 Advantages of spanlastics (5,9,10,13)

- High deformability: An elastic bilayer makes it possible to pass through restricted mucosal pores (5).
- Improved mucosal permeation: This enhances drug transport both transcellularly and paracellularly.
- Dual drug loading capability: Lipophilic medications are encapsulated in the bilayer and hydrophilic drugs in the core.
- Increased bioavailability: Better absorption and prolonged medication release enhance treatment effectiveness.
- Extended residence time: Improved interaction with the mucosal surface improves retention.
- Better chemical stability: Compared to phospholipids, non-ionic surfactants are less vulnerable to oxidative degradation.
- Improved solubility of poorly soluble medications: Surfactants and ethanol lead to better drug dissolution and entrapment effectiveness.
- Low irritability potential and biocompatibility: Non-ionic surfactants are typically gentle and suitable for mucosal tissues.

1.6 Limitations of Spanlastics (5,9,10,13)

- Stability issues: If it's extremely elastic structure is not adequately adjusted, it may cause aggregation or medication leakage during long-term storage.
- Formulation sensitivity: Because too much edge activator could destabilize the bilayer, the ratio of surfactant to edge activator needs to be carefully regulated.
- Scale-up challenges: Industrial production techniques are not yet fully standardized, and the majority of research is restricted to laboratory scale.
- Potential mucosal irritation: Sensitive mucosal tissues may become irritated by high surfactant or ethanol concentrations.
- Limited clinical data: Additional human research is necessary to validate the long-term safety and efficacy of the treatment.

2. Methods of preparation of spanlastics (17,22,23,24,25,26)



I. Thin Film Hydration:

This widely used laboratory technique involves dissolving the drug and non-ionic surfactant (like Span 60) in a volatile organic solvent, then using a rotary evaporator to remove the solvent under low pressure to create a thin film. This film is then hydrated with an aqueous phase that contains an edge activator (like Tween), creating a dispersion of elastic vesicles that can be sonicated to reduce size for uniform nanoscale distribution.

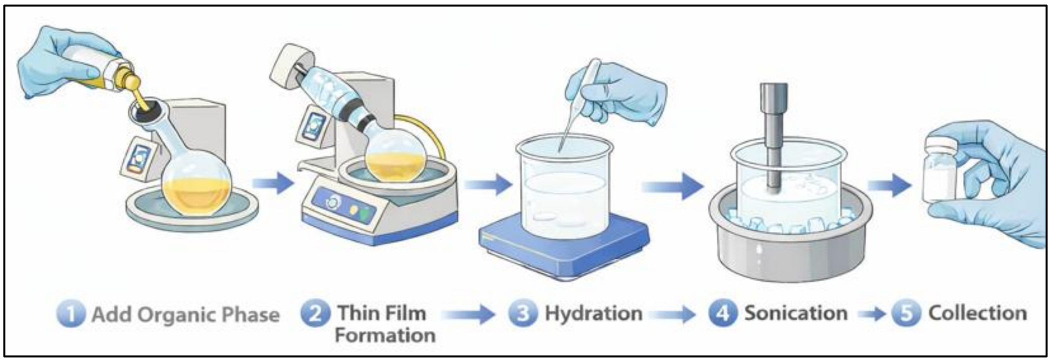


Fig. 4- Thin Film Hydration method

II. Ethanol Injection:

This method involves dissolving the drug and surfactant in ethanol to produce an organic phase, which is then gradually injected into a heated aqueous phase with an edge activator while being continuously stirred. Elastic spanlastic vesicles naturally form a milky suspension as the ethanol diffuses into the water. This approach is simple, reliable, and frequently used.

Fig. 5- Ethanol Injection method

III.Ether Injection:

This variation of the injection technique dissolves the surfactant in a more volatile solvent, such as diethyl ether, and then gradually introduces it into an aqueous drug phase at a high temperature, where quick solvent evaporation promotes the spontaneous formation of flexible nanovesicles. Sonication can then be used to improve vesicle size and homogeneity.

IV.Sonication:

It also known as "Post Hydration Size Reduction," is a common technique used to reduce larger multilamellar vesicles into smaller, more uniform nanosized particles after primary vesicle formation (from thin film hydration or injection techniques). This improves dispersion homogeneity and is essential for achieving a narrow size distribution, which is needed for stable formulations.

V. High Pressure Homogenization / Microfluidization:

These processes, which create highly consistent spanlastic particles through intense shear and collision forces generated within microchannels, can be used for more uniform particle size and better reproducibility. They also support scalability and improved batch to batch uniformity.

3. Characterization of spanlastics (27,28,29,30)

Spanlastics are elastic nanovesicles whose functional, chemical, and physical characteristics determine how well they work as drug carriers. The stability, homogeneity, and effective drug delivery of the vesicles are guaranteed by proper characterization.

3.1 Size Distribution and Vesicle Size:

The size of spanlastic vesicles plays a critical role in their ability to pass through biological barriers and get absorbed. They should have a restricted size distribution to provide homogeneity and are usually nanosized (100–300 nm). Dynamic light scattering (DLS) or laser diffraction methods are frequently used to evaluate particle size and polydispersity. Stability and reproducibility are enhanced by a homogeneous population of vesicles, which is demonstrated by a lower polydispersity index (PDI).

3.2 Surface Charge (Zeta Potential):

Zeta potential measures the surface charge of vesicles and is an indicator of high stability. Absolute zeta potential spanlastics (±30 mV or higher) exhibit resistance to aggregation and sustain their nanoscale size throughout time. A zeta sizer is used for measurement, and helps in determining stability during long-term storage.

3.3 Shape and Morphology:

The shape and surface characteristics of spanlastics are examined using Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM). Spherical, well-formed vesicles with smooth surfaces are ideal because they guarantee regulated release and reliable drug delivery.

3.4 Drug Loading and Entrapment Efficiency:

Two important factors influencing treatment effectiveness are drug loading and entrapment efficiency. The proportion of the original drug that is successfully encapsulated within the vesicles is known as entrapment efficiency (EE%), whereas drug loading is the actual amount of drug incorporated into the vesicles in relation to the total vesicle mass. These are quantified using UV-visible spectroscopy or HPLC after the unentrapped medication has been separated by centrifugation, dialysis, or ultrafiltration. Effective dosage is ensured by high drug loading, which also lowers the frequency of delivery.

3.5 In Vitro Drug Release:

Research on drug release sheds light on the drug's gradual release from the vesicles. In order to forecast therapeutic performance and comprehend controlled-release behavior, release profiles are periodically examined using dialysis bags or Franz diffusion cells.

3.6 Stability Studies:

To evaluate stability, the vesicles are stored in a variety of environments, including light, temperature, and humidity. Over time, changes in size, zeta potential, drug content, and physical appearance are observed. This assures that during its shelf life, the formulation will retain its therapeutic benefits.

3.7 Deformability of spanlastics:

Spanlastics are extremely elastic nanovesicles made of edge activators and non-ionic surfactants that greatly increase membrane flexibility by decreasing bilayer rigidity. The vesicles may bend and fit through tiny cellular pores without rupturing thanks to this suppleness. The deformability index (DI), which is based on the volume of suspension passing through and the ratio of vesicle size to pore size, is used to quantify deformability. It is calculated by extruding the vesicle suspension through membranes with specified pore sizes. A higher DI indicates increased vesicle flexibility and enhanced biological barrier penetration.

3.8 DSC:

The thermal behavior of spanlastic formulations is investigated and drug-excipient compatibility is assessed using differential scanning calorimetry (dsc). The crystalline form of the pure medication is typically shown by a prominent melting point in research studies. This peak may, however, change or vanish in spanlastic formulations, indicating that the medication is encapsulated and transformed into an amorphous state. The enhanced solubility and good medication integration are shown by this alteration. Additionally, Dsc aids in verifying that the medication and excipients are not significantly incompatible.

3.9 FTIR:

The chemical structure and interactions between the medicine and formulation ingredients are examined using Fourier transform infrared spectroscopy (FTIR). Ftir uses distinctive absorption peaks to identify functional groups. While minor shifts may imply physical interactions or drug encapsulation within the vesicles, the lack of significant peak shifts in spanlastic systems suggests that there is no chemical incompatibility. This validates the drug's integrity and the formulation's stability.

4. Table 1: Difference between Spanlastic, Noisome and Liposome: (31-35)

Parameter	Spanlastics	Niosomes	Liposomes
Definition	Elastic non-ionic surfactant vesicles modified with an edge activator to enhance deformability	Synthetic vesicles composed of non-ionic surfactant bilayers enclosing an aqueous core	Spherical vesicles composed of phospholipid bilayers enclosing an aqueous core
Type of vesicle	Second-generation deformable niosomes	Synthetic surfactant vesicles	Naturally derived phospholipid vesicles
Bilayer composition	Span (sorbitan ester) + edge activator (e.g., Tween)	Non-ionic surfactant (Span, Tween) + cholesterol	Phospholipids (e.g., phosphatidylcholine) ± cholesterol
Membrane flexibility	Very high (ultra-deformable)	Moderate	Low to moderate (rigid unless modified)
Particle size range	Typically50–300 nm (nano-range)	100 nm–several µm	10–3000 nm (wide range)
Penetration capability	Excellent penetration through skin and mucosal barriers due to elasticity	Moderate penetration; mainly enhances deposition	Limited penetration across intact barriers
Stability against oxidation	High (no phospholipid oxidation)	High	Lower (prone to oxidative degradation)
Cost of raw materials	Economical	Economical	Expensive (phospholipids costly)
Storage requirement	Relatively stable under normal conditions	Stable under normal storage	May require controlled storage (sensitive to oxidation/hydrolysis)
Toxicity profile	Generally low; depends on surfactant concentration	Low toxicity	High toxicity (Due to lipids)
Entrapment capability	High for hydrophilic and lipophilic drugs	Moderate to high	High, especially for hydrophilic drugs
Protection of biomolecules	Moderate protection	Moderate	Excellent protection (proteins, peptides, genes)

5. Applications of spanlastics (5,18,27,29,30,33)

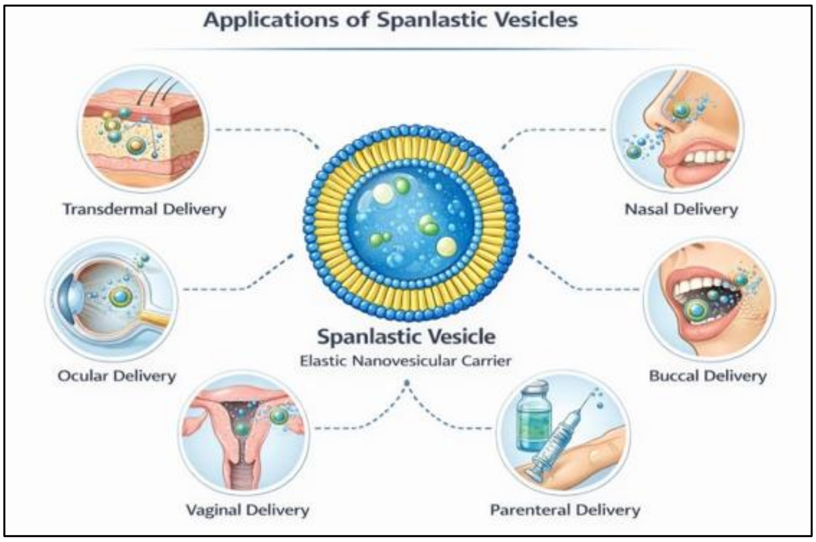


Fig. 6-applications of spanlastics

5.1 Ocular drug delivery:

Spanlastics' elastic vesicular structure and improved corneal penetration potential have made them promising nanocarriers for ocular medication administration. Their nanoscale size enhances interaction with the ocular surface, and their deformability permits passage through tight epithelial junctions. By increasing drug bioavailability, extending precorneal residence duration, and offering sustained release, they improve therapeutic outcomes in anterior and posterior segment illnesses by lowering dosage frequency.

5.2 Transdermal drug delivery:

Through lipid interaction processes and elastic deformation, spanlastics improve medication penetration through the stratum corneum. Because of its surfactant-based makeup, which improves medication diffusion and systemic absorption, skin lipid packing is disrupted. This pathway provides regulated plasma concentration profiles and avoids hepatic first-pass metabolism. Their better permeability and retention qualities as compared to traditional vesicular systems are highlighted in recent comprehensive reviews.

5.3 Topical dermal treatment:

Spanlastics enhance superficial medication deposition and local retention inside epidermal and dermal layers because of their nanoscale size and flexible bilayer. While reducing systemic exposure, sustained release behavior improves treatment efficacy. Their application in inflammatory infectious, and localized dermatological disorders is supported by these characteristics.

5.4 Intranasal administration:

By partially avoiding the blood–brain barrier, spanlastics enhance in mucosal penetration and can promote drug transport through olfactory and trigeminal routes. This approach lowers systemic toxicity while increasing bioavailability to the central nervous system. Spanlastics are described as sophisticated vesicular carriers for neurological targeting and brain medication delivery.

5.5 Oral Drug delivery:

Through boosting surface area and stabilizing drug dispersion at the absorption site, spanlastics increase the rate of dissolution and oral bioavailability of poorly water-soluble medications. Encapsulation promotes sustained release kinetics and shields medications from gastrointestinal breakdown. Improved pharmacokinetic performance of medications integrated into spanlastic systems has been shown in recent pharmaceutical research.

5.6 Injectable delivery:

Spanlastics have physical properties such nanoscale size, colloidal stability, and biocompatibility that make them appropriate for parenteral delivery. Because of their flexible membranes, injectable spanlastic dispersions may offer better tissue penetration, increased biodistribution, and controlled systemic release. Their potential for systemic drug delivery platforms beyond traditional topical methods is highlighted by recent reviews.

5.7 Peptide and protein delivery:

Spanlastics prevent denaturation and enzymatic breakdown of labile macromolecules including proteins and peptides. Encapsulation may increase the duration of systemic circulation and improve molecular stability. They are desirable carriers for biologics and hormone-based treatments because of their flexible membrane structure, which facilitates better absorption through non-oral routes.

5.8 Anticancer medication delivery:

As spanlastics can improve tumor tissue penetration and offer sustained drug release, they are being investigated as nanocarriers for anticancer drugs. Their deformability can allow deeper diffusion inside tumor microenvironments, and their nanoscale size facilitates passive targeting techniques. Systemic toxicity is decreased and the therapeutic index is enhanced by controlled release.

5.9 Targeted and regulated medication delivery:

In order to achieve prolonged release and possible ligand-mediated targeting, spanlastics vesicular architecture permits modification of bilayer composition and surface characteristics. Combination therapy and multifunctional delivery methods are made possible by their dual encapsulation capacity for hydrophilic and lipophilic medications.

5.10 Vaccine and biologics delivery:

Because spanlastics prevent the degradation of bioactive molecules and sensitive antigens, they could have value in the delivery of vaccines and biologics. Their vesicular structure may improve immunological stimulation and antigen stability through regulated release behavior. Spanlastics are attractive carriers for sophisticated biologic formulations, according to recent study.

Table no.2- Examples of spanlastics formulation

Spanlastics Formulation	Route	Method Used	Reference
Fluconazole spanlastic in situ gel	Ocular delivery (antifungal therapy)	Ethanol injection method	36
Felodipine nano-spanlastics (mucoadhesive wafers)	Buccal / mucosal systemic delivery	Ethanol injection followed by lyophilization	37
Famotidine spanlastic nanovesicles	Oral delivery	Ethanol injection method	13
Risperidone spanlastics	Intranasal / nose-to-brain delivery	Ethanol injection method	38
Oxiconazole nitrate spanlastic	Topical dermal antifungal therapy	Ethanol injection method	39
fenoprofen calcium-loaded spanlastics	topical (skin) delivery.	Thin film hydration (TFH) technique.	40
Meloxicam spanlastics	Transdermal anti-inflammatory delivery	Ethanol injection method	41
Glimepiride spanlastic gel	Transdermal antidiabetic therapy	coacervation phase separation method	42
Vanillic acid spanlastics	Ocular anti-inflammatory therapy	Ethanol injection method	27

6. Future perspectives (7,14,28,33)

Spanlastics are increasingly recognized as versatile nanovesicular carriers with strong potential in mucosal drug delivery. Due to their elasticity and permeation-enhancing properties, future research is expected to focus on improving site-specific targeting and clinical translation. Surface modification of spanlastics using mucoadhesive polymers, ligands, or receptor-specific molecules may enhance retention and targeted delivery across nasal, buccal, ocular, and vaginal mucosa, thereby improving therapeutic efficiency while reducing systemic exposure.

Their vesicular structure also provides protection to labile molecules, making them promising carriers for non-invasive delivery of peptides, proteins, and vaccines. In particular, spanlastics are being explored for nose-to-brain delivery as a strategy to bypass the blood–brain barrier and improve the treatment of neurological disorders.

Future developments may include integration into hybrid platforms such as in situ gels and bioadhesive systems to prolong mucosal residence time and enable sustained drug release. Additionally, next-generation spanlastic systems, including modified or stimulus-responsive variants, may further expand their application in targeted and precision therapies. With continued formulation optimization, safety evaluation, and scale-up validation, spanlastics may progress toward clinically viable mucosal delivery systems.

7. Conclusion

Promising elastic nano-vesicular carriers called spanlastics overcome the drawbacks of traditional vesicular systems like liposomes and niosomes. Their adaptable shape makes it easier for drugs to get across biological barriers, especially mucosal tissues. This review focuses on their composition, characterization, preparation techniques, and many uses in oral, transdermal, topical, intranasal, ocular, and systemic drug delivery. Despite stability issues and a lack of clinical research, spanlastics have great promise as cutting-edge nanocarriers for better medication delivery.

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