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Spanlastics Nanovesicles: An Emerging and Innovative Approach for Drug Delivery

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REVIEW

Spanlastics Nanovesicles: An Emerging and Innovative Approach for Drug Delivery

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Abstract

The use of vesicular structures as a drug delivery method has many advantages, including extending the duration of the drug's action in circulation, enhancing drug targeting, minimizing adverse effects, and boosting the bioavailability of a variety of medications. Spanlastics, which are elastic and can transport a range of pharmaceutical substances, are thought to be a subset of nanovesicles. They have drawn interest as a potentially effective medicine delivery method. They are a preferred choice for many administration routes because of their pliable and elastic nature, which allows them to pass through various cellular membranes. Non-ionic surfactants or a mixture of surfactants and a nanoscale edge activator make up these nanovesicles. Researchers have established that SPs improve drug bioavailability. The structure, composition, special qualities, and applicability as a cutting-edge drug delivery system for encapsulating a range of medications to treat various ailments are all covered in this review paper.

Keywords: Vesicular structures, Spanlastics, Non-ionic surfactants, Edge activators and characterizations

Vesicular drug delivery systems (VDDS) have been created recently in an effort to improve pharmacological properties and lessen negative effects. Recently, there has been an increase in interest in highly structured VDDS structures, which are made up of one or more concentric bilayers assembled by amphiphilic building blocks in the presence of water. VDDS can effectively address the heterogeneity between hydrophilic and hydrophobic components within a drug delivery system by serving as a link between the ideal and practical choices [1]. Vesicles can include drugs that are simultaneously hydrophilic, lipophilic, or both. Transporting various active moieties across epithelial membranes is made simple by the water's ability to maintain vesicles' appropriate colloidal stability and boost their membrane flexibility [2,3]. Numerous different types of VDDS have been developed, including liposomes, niosomes, transferosomes, cubosomes, ethosomes, virosomes, phytosomes, and spanlastics [4,5]. Kakkar and Kaur originally introduced spanlastics (SPs), a brand-new medicinal nanovesicular carrier based on surfactants, in 2011 [6]. SPs are elastic nanoscale vesicles based on non-ionic surfactants and edge activators [7]. The edge activator in SPs adds hydrophilic surfactant moieties that make the lipid bilayer membranes in SPs more flexible. This is brought on by the breakdown of the lipid bilayers and pore formation, which reduces the interfacial tension and ultimately increases the deformability of the vesicle [8]. SPs are more reasonably priced and chemically stable than liposomes. Additionally, SPs are more flexible and rigid than niosomal colloidal delivery techniques because they contain cholesterol and surfactant [6,9]. SPs can be given orally, intravenously, topically, transungally (nail lacquers), or by any number of other means.

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2. Structure of spanlastic

Spherical amphiphilic molecule-based structures known as spanlastics serve as effective bio-encapsulation matrices. The spanlastic structure in Fig. 1 is clearly identified and highlights the many components. Hydrophobic drugs are located in the hydrophobic tail of the vesicle, whereas hydrophilic pharmaceuticals are located in the middle area. The SPs vesicle typically ranges in size from 180 to 450 nm [10,11].

3. Composition of spanlastics

An edge activator and a non-ionic surfactant are SPs' two key components.

4. Non-ionic surfactant

Non-ionic surfactants are widely utilized as wetting agents while making vesicles due to their many advantages. Compared to anionic, amphoteric, or cationic surfactants, they offer better stability, compatibility, and less toxicity. The fact that non-ionic surfactants have both polar and non-polar portions contributes to their high interfacial activity [12]. The development of bilayer vesicles may be influenced by a number of factors, including the hydrophilic-lipophilic balance (HLB) of the wetting agent, the chemical composition of the contents, and the critical packing parameter (CPP) [13].

Vesicles based mostly on span 40 (HLB value 6.7) and span 60 (HLB value 4.7), which exhibit more stability, likely to be less disturbed, aggregated, and unstable than those based primarily on span 80 (HLB value 4.3). When compared to other non-ionic surfactants, span 60's lipophilic properties make it easier to form lamellar matrix vesicles and boost its potential to entrap drugs.

5. Edge activators

Many surfactants, including Tween 80 and (PVA), have the capacity to operate as edge activators. By including PVA, the vesicles' size can be reduced while their flexibility is increased. However, the application of these hydrophilic wetting agents has the potential to injure vesicular membranes [14–16], despite improving their deformability. When an edge activator is combined with SPs, flexibility is increased and interfacial tension is decreased, allowing large particles to pass readily through the tiny holes [17]. Various edge activators utilized in the creation of SPs are listed in Table 1.

6. Penetration of skin through SP vesicles

To enable SP vesicles to enter deeper skin layers, two mechanisms cooperate. The SP vesicles serve as a reservoir or carrier for medications and can safely and quickly pass through the skin's pores. As a result, medication molecules can enter the stratum corneum more quickly (Fig. 2). Another idea proposes that SP vesicles act as a penetration enhancer by disrupting the well organized intercellular lipids of the stratum corneum, allowing them to permeate deeper layers of the skin. The primary mechanism is determined by the nature of the active ingredient—hydrophilic or lipophilic—and the composition of the SP.

7. Notable characteristics of SPs [18–21]

SPs contain flexible vesicles that allow them to easily traverse biological membranes without causing injury, are biodegradable, non-immunogenic, continuously release medications, and they help improve patient adherence. SPs are non-irritating and capable of transporting both hydrophilic

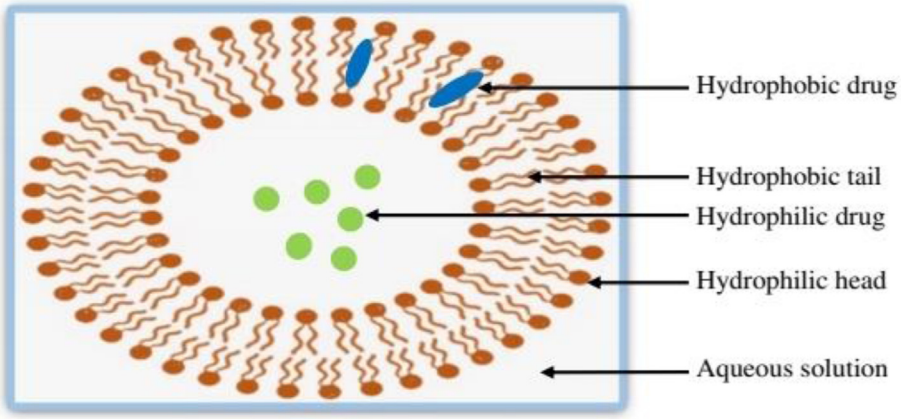

Fig. 1. The structure of SP vesicle.

Table 1. Edge activators used in formulation of SPs [7].

S.no	Name of edge activator	Category	HLB value	Molecular formula	Molecular weight (g/mol)
1	Span 20	Non- ionic	8.6	C18H34O6	346.47
2	Span 40	Non- ionic	6.7	C12H42O6	402.57
3	Span 60	Non- ionic	4.7	C24H46O6	430.6
4	Span 65	Non- ionic	2	C60H11408	963.54
5	Span 80	Non- ionic	4.3	C24H44O6	428.6
6	Span 85	Non- ionic	1.8	C60H108O8	957.51
7	Sodium cholate	Cationic	16.7	C24H39O5Na	430.55
8	Sodium deoxycholate	Cationic	16	C24H40O4	414.55
9	Oleic acid	Anionic	1	C18H34O2	282.46
10	Poly vinyl alcohol	Non- ionic	18	C2H4O	44.05
11	Tween 20	Non- ionic	16.7	C58H114O26	1227.5
12	Tween 40	Non- ionic	15.6	C62H122O26	1283.65
13	Tween 60	Non- ionic	14.9	C64H126O26	1311.7
14	Tween 80	Non- ionic	14.5	C64H124026	1310
15	Tween 85	Non- ionic	1.8	C100H188O28	1838.56

and hydrophobic medications because they contain non-ionic surfactants. SPs can be utilized as specialized medication delivery systems since they are adaptable delivery vehicles.

7.1. Preparation of SPs vesicles

There are several ways to make SPs.

1_Ethanol injection method

The first step involves injecting a precise amount of non-ionic surfactant and medicine is dissolved in ethanol into the preheated aqueous phase that also contains an edge activator for SPs. As seen in Fig. 3(a), the mixture is held at a temperature of 70–80 °C for 30 min while being continually whirled at 800–1600 revolutions per minute. The solution is then adjusted to the right volume using water as the last stage [22]. Because it forms an azeotrope with water(the term "azeotrope" describes a mixture of two or more substances that cannot be separated by simple distillation because the vapor phase has the same composition as the liquid phase. As a result, the components in the mixture evaporate and condense together, making it impossible to achieve further separation by traditional distillation techniques), leftover ethanol is challenging to remove with this method. Furthermore, ethanol poses the risk of deactivating

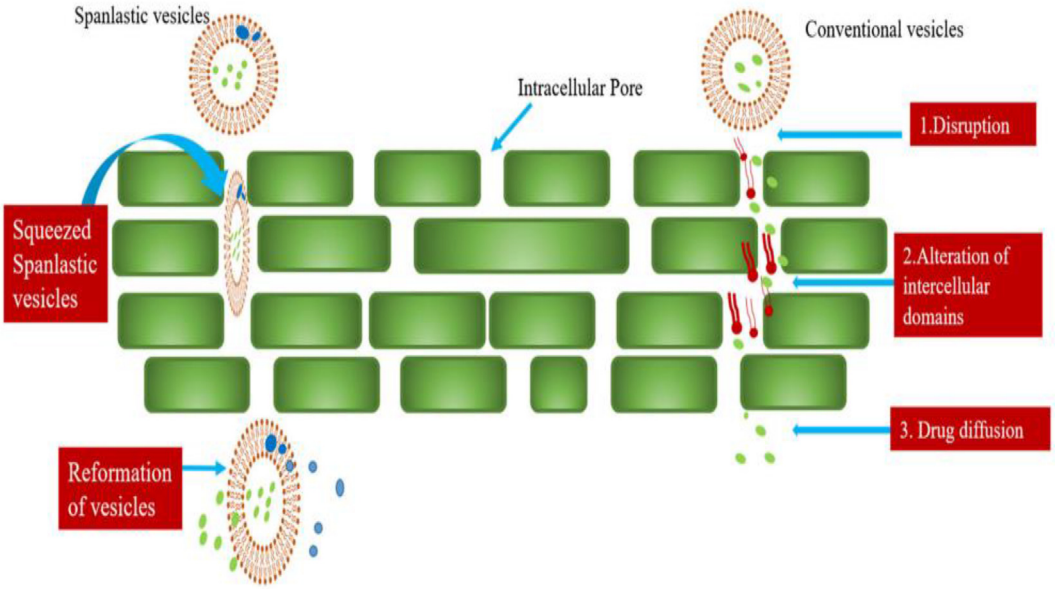

Fig. 2. The route that SP vesicles to infiltrate the skin [7].

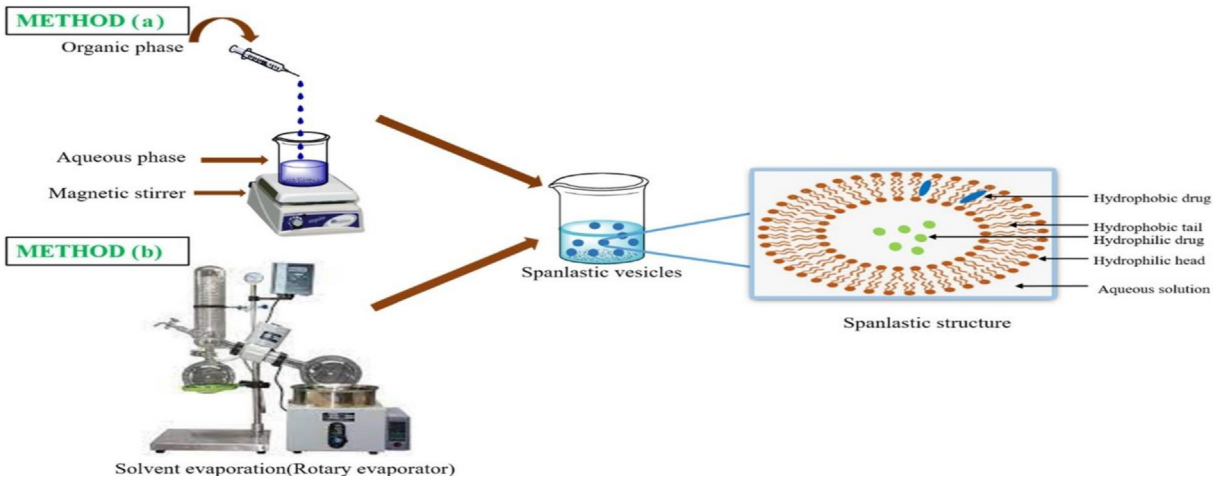

Fig. 3. Two techniques for creating SPs are the (a) ethanol injection method and (b) the thin film hydration method.

a variety of physiologically active macromolecules at even trace quantities [12].

2_Thin-film hydration method

Hydration is an easy technique for producing thin films. The wetting agents are dissolved in an organic solvent in a flask with a rounded bottom. A small layer is then left on the inner wall of the flask after the organic solvent has been evaporated using a rotary vacuum evaporator [23].

Fig. 3 (b) illustrates how an aqueous solution, such as water or phosphate buffer, is applied to the dry film at a temperature higher than the surface-active agent's transition temperature (Tc). During the hydration phase of the film, a hydrophilic medication may be added to the aqueous solution, whilst a lipophilic drug may be added to the organic layer [12].

3_Sonication:

In this process, the surfactant combination and a sample of the medication are mixed in a 10 mL glass vial after the appropriate buffer has been used to prepare the drug sample. A titanium probe is then used to sonicate the mixture [24].

4_Hand shaking method

Surfactants need to be dissolved initially in an organic solvent like ether or chloroform. The solvent is then removed using low pressure evaporation and vacuum evaporation inside a flask with a circular bottom. To rehydrate the layer, an aqueous drug solution is added, and the mixture is swiftly stirred. The gradual folding of the amphiphiles and formation of vesicles that trap the medication cause the surfactant layer to thicken [25].

5_Extrusion method

Starting with the creation of a thin layer, a spinning vacuum evaporator is used to evaporate a mixture of diacetyl phosphate and surfactant. Extrusion occurs through a polycarbonate membrane with a mean pore size of 0.1 microns that contains both the combined drug solution and the rehydrated drug solution. To obtain a consistent outcome, the combination is pushed over the membrane up to eight times consecutively [26].

6_Microfluidization method

Two fluidized streams—one containing the drug and the other the surfactant—interact in the interaction chamber at extremely high speeds through specially designed microchannels. This method, also called as the submerged jet principle, ensures that the energy supplied to the system stays within the spanlastic formulation zone. As a result, the formulation exhibits improved homogeneity, decreased size, and improved reproducibility [27].

7.2. Applications of SPs as carrier for drug delivery

As shown in Table 2 [10], numerous studies have shown that SPs have the potential to significantly improve therapeutic efficacy, increase drug bioavailability, promote patient compliance, and decrease adverse effects.

8. Description of the formulation of SPs

8.1. Drug content and entrapment efficiency (EE)

By combining a specific amount of SPs dispersion with an appropriate solvent volume, it was possible

Table 2. Examples on drugs that were formulated as SPS.

Drug	BCS class	Role of SPs	Ref.
Fluconazole	Class I	In contrast to Zocon® (a commercially available formulation containing 0.3% w/v fluconazole), administration of a fluconazole SPs solution showed a three-fold increase in ocular permeability without showing any negative effects on cells.	[18]
Vitamin C	Class I	In high-dose vesicles used in cosmeceuticals, SPs were discovered to positively affect the stability and skin penetration of vitamin C.	[28,29]
Clotrimazole, econazole, luliconazole	Class II	Additionally, compared to when they were in suspension form, SPs showed robust and long-lasting antifungal activities when prepared independently, and these vesicles were non-irritating in nature.	[9,30,31]
Terbinafine, efinaconazole	Class II	These medications' physical and chemical properties can be changed through the use of SPs, which improves how well they are delivered through the nails.	[32,33]
Haloperidol, glimepiride	Class II	The use of SPs for transdermal delivery of haloperidol and glimepiride shows potential as a sustained-release approach, which may lead to smaller dosages and less frequent administration.	[34,35]
Flibanserin, carbamazepine	Class II	Spanlastics have the potential to be an efficient medication delivery system when used to target the brain via the transnasal route.	[36,37]
Rasagiline	Class III	Due to its hydrophilicity and significant hepatic metabolism, this medicine has a limited oral bioavailability and has trouble crossing the blood–brain barrier, where it can have a pharmacological effect. If the medication is created as an SP, it can be administered to brain tissues without causing any harm, increasing both its safety and pharmacological effectiveness.	[38]
Granisetron hydrochloride	Class III	This study aimed to increase the drug's bioavailability and target it to the brain by developing mucoadhesive gels and intranasal inserts containing granisetron hydrochloride SP.	[39]
Ciprofloxacin	Class IV	The goal of encapsulating this antibiotic in an SP vesicle is to improve its delivery through a non-invasive trans-tympanic route for the topical treatment of acute otitis media.	[40]
letrozole and quercetin	Class I and IV	When loaded into SPs, letrozole and quercetin had greater cytotoxic effects and required lower dosages than their soluble free drug counterparts. It is possible that site-specific medication delivery is to blame for the improvement in cytotoxic effects and decrease in side effects.	[41]

to quantify the drug content, which included both unentrapped and entrapped amounts of drug. Then spectrophotometric analysis of the drug content is performed. Entrapment efficiency is the proportion of the medication that is contained within the SP, and it may be computed using the formula shown below(12):

$$EE = \text{Amount of entrapped drug} / \text{Total amount added} \times 100$$

To determine the entrapment efficiency, any substance that has not been captured by the SPs is extracted using a centrifugation technique. The leftover solution is separated, and the resulting supernatant is then collected. The collected liquid is then diluted to a particular concentration and tested in accordance with the appropriate method outlined in the pertinent drug monograph. The physicochemical characteristics of the medication and the production method are typically factors that affect the yield and effectiveness of SP entrapment [19,34].

8.2. Size, shape and morphology

8.2.1. Transmission electron microscopy (TEM)

TEM is employed to evaluate SP size, arrangement, and stacking. By making a suspension and

adding the appropriate amount of phosphotungstic acid at a concentration of 1%, the procedure is sped up. The excess liquid is then drained off, the mixture is placed on a grid covered in carbon, and the grid is allowed time to completely dry. The grid is then observed at the proper magnification while being photographed with a Philips TEM [42,43].

8.2.2. Elasticity measurement

Using a polycarbonate filter with pores that were 50 nm wide, vesicles were extruded using this technique under constant pressure. The technique involved the use of a 200 ml barrel and a stainless steel pressure holder with a 25 mm filter. The vesicular size of the extruded suspension was affected by the intervals before and after the extrusion technique. The ability of SP to squeeze itself and pass through the mucus barrier is demonstrated by the formulation's flexibility, which is an intriguing criteria for this vesicle type [44,45].

8.2.3. In-vitro release study

The dialysis membrane approach dominated in this trial. SPs were added in a specific quantity to the dialysis bag. A beaker containing the appropriate dissolving liquid and the dialysis bag were combined, and the mixture was stirred with a magnetic stirrer at a temperature of 37 °C. At regular intervals, fresh dissolving media was added to the beaker while a sample solution was removed. The samples were then spectrophotometrically analyzed for drug concentration at the maximum level for that drug [46].

8.2.4. Stability study

During storage, medication leakage from vesicles was evaluated in this investigation. By keeping the chosen elastic vesicular suspension in glass vials at 4–8 °C for three months, the drug's ability to be preserved was examined. Samples were periodically removed and checked for permeation, entrapment, and residual drug content [47].

9. Conclusion

Vesicles have gained popularity because they can solve a number of problems with traditional pharmaceutical delivery systems. Therapeutic compounds have been successfully delivered to the ocular, nasal, trans-lingual, brain, and epidermal layers using SPs, a type of nanoelastic vesicle. This may be due to their beneficial characteristics, such as biodegradability, non-irritating properties, and safe deformable nanovesicles. Future advancements in spanlastic vesicles should make it possible to administer medications site-specifically and increase the effectiveness of curing diseases.

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