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A NARRATIVE REVIEW ON SPANLASTICS WITH POTENTIAL APPLICATIONS

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ABSTRACT

The Spanlastics are a new type of elastic vesicular nanocarrier that is based on surfactants and composed of spans and edge activators. In 2011, a novel medication delivery method known as Spanlastics was released. They are elastic, deformable, surfactant-based nanovesicles. These are the special class of nanovesicles that overcomes the disadvantages associated with liposomes, such as chemical instability. They provide targeting and controlled release of natural pharmaceutical compounds and have improved several drawbacks of the conventional dosage form. The current review emphasizes the utility of Spanlastics advantages, disadvantages, structure, classification, preparation approaches, mechanism of penetration, evaluation parameters and applications.

KEYWORDS: Spanlastics, nanovesicles, edge activators, nonionic surfactants.

INTRODUCTION

SPs are elastic nanoscale vesicles based on non-ionic surfactants and edge activators. 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.

Kakkar and Kaur originally introduced Spanlastics (SPs), a brand-new medicinal nanovesicular carrier based on surfactants, in 2011 for targeting topically applied drug

Ketoconazole to the posterior segment of the eye.[1]

Spanlastic or modified niosomes are novel flexible-walled nanovesicular systems that differ from common niosomes in that they contain only non-ionic surfactant, usually Spans, in addition to an edge activator. The surfactant molecules are arranged in a bilayer membrane assembly that encloses the active agent. Inclusion of the edge activator induces destabilization of the bilayer membrane of the vesicular system by lowering the interfacial tension. Membrane destabilization imparts high elasticity and deformability to the vesicular system. Due to the ultra-deformability of Spanlastics, they possess the ability to squeeze themselves throughout the intracellular spaces of the stratum corneum and the skin layers that follow, passing into the target dermal tissues and thus, enhancing transdermal drug penetration. Spanlastics maintain acceptable stability compared to other dosage forms like liposomes. They are non-irritant compared to other dosage forms that contain cationic surfactants, and they provide enhanced delivery due to their highly elastic, deformable nature.[2]

Advantages of Spanlastics

- Spanlastics are non-immunogenic and biodegradable by nature.
- Increased Bioavailability: Because the medication has protected support, it reaches the targeted site without being shredded off, increasing bioavailability in comparison to the conventional one.
- The Spanlastics system allows hydrophilic or lipophilic drugs to pass through biological membranes such as the cornea.
- By encapsulating the medicine inside a lipid bilayer structure, they shield it from the biological environment.
- They improve the therapeutic execution of medicated particles by shielding the medication from the environment and limiting the impact on the targeted site.
- They boost the stability of the medicine that has been entrapped and are osmotically active and stable.
- They play an important role in delaying the clearance of drug molecules from the systemic circulation during sustained drug delivery.
- The presence of non-ionic surfactants in their structures lends them high compatibility with biological systems and imparts low toxicity.
- Handling and storage of surfactants require no special conditions.
- They can be made to reach the site of action by oral, parenteral or topical routes.[3]

Disadvantages of Spanlastics

- It has a poor water solubility
- It is easily degraded in an environment similar to that of the stomach, which is acidic. This makes it susceptible to first-pass metabolism in the liver**.**
- Extrusion and sonication are the most common methods for preparing multilamellar Vesicle (MLV), both take a significant amount of time and frequently necessitate the use of specialist machinery.

Structure and composition

Spanlastics systems are spherical structures made up of amphiphilic molecules that serve as bioencapsulation matrices. It consists of concentric bilayers, these can be unilamellar or multilamellar depending on the size of the vesicles; these can be (SUVs) Small unilamellar (10-100 nm) or (LUVs) Large unilamellar (100-3000 nm). Spanlastics are made up of a nonionic surfactant and an edge activator, which are both essential components. Since these vesicles are primarily composed of surfactants, they have been named Spanlastics.

- **Non-ionic surfactants**: Surface-active substances, also known as surfactants, work to reduce the interfacial tension between two liquids. In order to create the vesicular structure of spanlastic, spans form concentric bilayers. The polyoxyethylene sorbitan component of the molecule, known as the span, comes in various types, including Span 80 (monooleate), Span 60 (monostearate), Span 40 (monopalmitate), and Span 20 (monolaurate). The stability of the vesicular formulation can be predicted in large part by looking at the types of Span. Vesicles based on Span 80 and Span 40 exhibit significant disruption, aggregation, and instability. In contrast, the inclusion of saturated alkyl chains in Span 60 increases its sustainability.

- **Edge Activators**: These are a unique type of surfactant with high hydrophilicity, or the HLB value. These surfactants only have one chain. Edge activators are components that soften the bilayer, such as biocompatible surfactants, to which an amphiphilic substance is added to increase the permeability and flexibility of the lipid bilayer. It increases the deformability of the bilayer by lowering the interfacial tension between them. EAs have a propensity to produce larger spherical vesicles, which results in smaller particle sizes. Tween 80 is an edge activator that makes vesicles more elastic. Any vesicle larger than the pore size of the biological membrane can easily transfer from the outside to the inside

as a result of the Tween-80's temporary increase in pore size. Additionally, this promotes greater drug penetration and the transfer of larger amounts of drugs inside the vesicle. These hydrophilic surfactants can also destabilize vesicular membranes, make them more deformable, and create systems with different degrees of disruption in packing characteristics.[4]

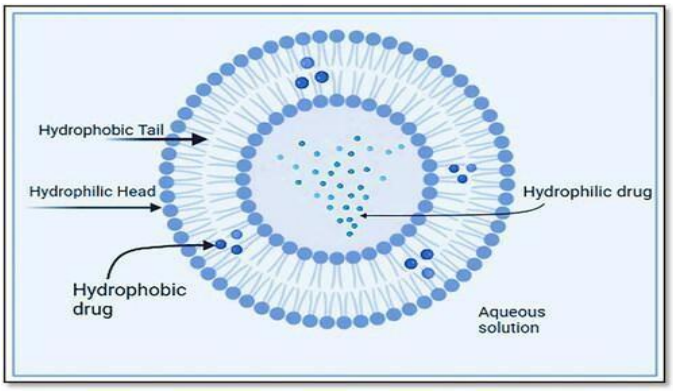

Fig. 1: structure of Spanlastic.

Classification of Spanlastics

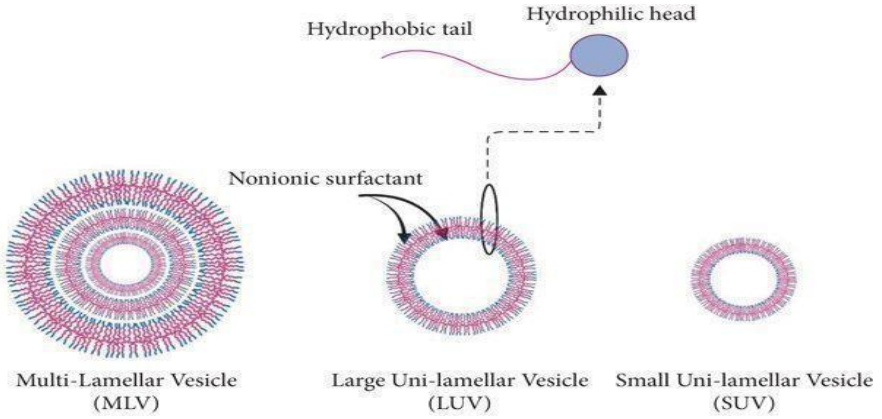

Fig. 2: Classification of Spanlastics.

Multi-Lamellar Vesicles (MLVs): are defined by their arrangement of multiple concentric bilayer membranes. These vesicles have a nested spherical appearance and find relevance in diverse fields. The size of MLVs typically falls within the range of 0.5 to 1.0 microns in diameter.

It is commonly employed, simple to produce, and maintains stability throughout extended periods of storage.

Large Unilamellar Vesicles (LUVs): Ranging in size between 100 nm and 1 µm.

Small Unilamellar Vesicles (SUV): generally have dimensions within the range of 20 nm to 50 µm. They are produced from multi-lamellar vesicles using the sonication method.[5]

Method of preparation

- **Ethanol injection method:** This technique can be used to create spanlastics with a set ratio of ionic surfactant to edge activator. The medicine to be encapsulated is dissolved in ethanol coupled with span. Five minutes are spent sonicating the lipid solution. Now, this solution is continuously injected into a heated aqueous phase containing an edge activator (such as Tween-80), which has been agitated at 800-1600 rpm and 70–80°C for 30 minutes on a magnetic stirrer. Another 30 minutes is spent stirring the mixture at a cool temperature. With distilled water, the final formulation is adjusted to 10 ml.[6]
- **Thin film hydration technique:** Span 60 that has been precisely weighed will be placed in a flask with a circular bottom and dissolved in chloroform. A thin coating will form on the flask walls as the organic solvent is evaporated at 55°C under vacuum using a rotary evaporator at 90 rpm. The chosen EA and cosolvent will dissolve a specific amount of medication in the aqueous phase. The deposited thin film will get the addition of this aqueous phase. Once more secured to the evaporator, the flask will be rotated for 30 minutes at normal pressure, 60°C, and 90 rpm to completely remove the lipid film from its walls. The distribution that results will be left overnight at 4°C after standing for a further 2 hours at room temperature to hydrate completely.[7]
- **Modified spraying technique:** This method is also used to prepare spanlastic. This approach involves forming the organic phase, which is subsequently transferred to a spray device, by dissolving non-ionic surfactants in 2 mL of ethanol. A closed system is used to heat the aqueous phase to 60 °C and prepare a sucrose solution (9% w/v in double-distilled water). The organic phase is then sprayed over the aqueous medium while being stirred at 1500 rpm and 60 °C at a rate of 250 L per 5 s. In order to improve the trapping of the medication inside the nano system, the resulting spanlastic vesicular systems.[8]
- **Ether Injection**: This method involves slowly injecting surfactant in 20 ml of ether using a 14-gauge needle at a rate of 25 ml per minute into a 4 ml aqueous phase that has been heated to 60°C. Using a rotary evaporator, the ether solution will be evaporated. Once the organic solvent has evaporated, it will produce single-layered vesicles.[9]
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Mechanism of penetration

There are two methods by which drugs penetrate the body.

The intercellular lipid lamellae are altered as a result of the elastic vesicles' interactions and penetration-enhancing functions with the epithelial cell membrane.

The elastic vesicles can function as drug-carrier systems, allowing intact vesicles containing the drug to breach the biological membrane and flow across intercellular spaces.

The following elements aid in these carriers' effective passage:

- The vesicle bilayers' extremely stress-dependent flexibility
- The existence of an osmotic gradient
- In the higher concentration range, the surfactant causes a solubilization (lysis).
- Edge activators (EAs) weaken the lipid bilayers, which makes the vesicles more deformable.

➢ In the below fig 4, figure A represents the spanlastic and the layers of the organ.
➢ In the figure, B we can see the interaction between the spanlastic system and the epidermis and the formation of pores inside the layers of the organ.
➢ The figure C represents the penetration of the spanlastic system through the layers.
➢ The figure D represents the release of drugs from the spanlastic system inside the organ.
➢ Due to this, the drug entrapped inside the system comes directly in contact with the infected part.[10]

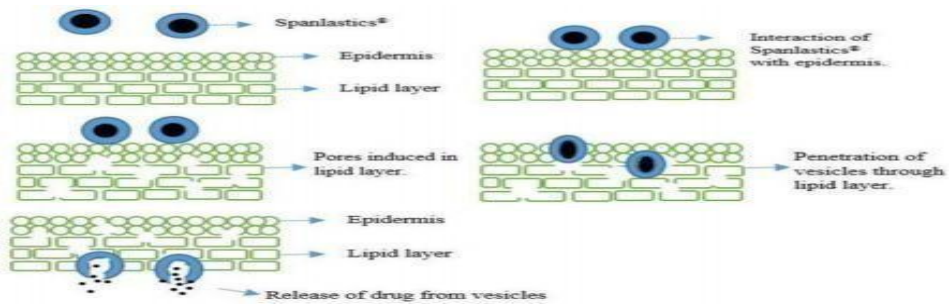

Fig. 4: Mechanism of penetration of Spanlastic system inside the epidermis and lipid Evaluation.

1. Particle Size[11]

The average particle size of the prepared drug-loaded Spanlastic nanovesicles was determined using a Biovis particle size analyzer. Samples of 0.1 mL of each formulation were diluted using distilled water to 10 mL before the measurements in order to avoid aggregation of particles. All measurements were performed in triplicate at 25°C, and the mean values ± standard deviation (SD) obtained were reported.

2. Zeta Potential[12]

The electrophoretic mobility of the charged vesicles was observed to measure the ZP using Zetasizer (Malvern Instruments, Malvern). All measurements were done at 25°C in triplicate after dilution of the formulations

3. Drug content[13]

0.2ml of Spanlastic dispersion equivalent to 2 mg of drug was dissolved in 25ml of Methanol and then measuring drug content was measured by UV Spectrophotometer at λmax.

4. Determination of Entrapment Efficiency[14]

The entrapment efficiency of the drug in the prepared novel Nanovesicular formulation was obtained using the ultracentrifugation method. The prepared formulation was centrifuged at 15000 rpm, 4°C for 60 mins. This causes the separation of free drug (appearing as supernatant) from drug-loaded vesicles (settled at the bottom). The supernatant was taken and was diluted with methanol. The amount of drug present in the supernatant was determined by ultraviolet (UV) spectrophotometer at λmax. The amount of free drug in the supernatant was then subtracted from the total amount of drug added during the preparation of Spanlastics.

All the prepared formulations were characterized for percent drug entrapment efficiency (%EE), using the formula:

$$\%EE = \frac{Total\ amount\ of\ drug - Free\ drug\ in\ supernatant}{Total\ amount\ of\ drug} \times 100$$

5. Optical microscopy[15]

The prepared drug-loaded Spanlastic was characterized using an optical microscope for structural attributes such as uniformity of size, lamellarity and shape.

6. In vitro diffusion studies[16]

An *in vitro* drug diffusion study was performed on Franz diffusion cells using an excised

cellophane membrane at a temperature of 37 ± 0.5°C. The receptor compartment was filled with buffer, which was magnetically stirred at 400 rpm throughout the experiment. The Spanlastics samples were mounted on the cellophane membrane. At regular time interval, 1ml of samples were withdrawn and replaced with fresh buffer to maintain sink conditions for 8 hrs. The concentration of drug was determined using a UV spectrophotometer at λmax.

APPLICATIONS OF SPANLASTIC

Nano-vesicles firstly emerge in the field of cosmetics and now attracting at a wide range as a vesicle drug delivery system. Due to their nature of entrapment of both hydrophilic (lipophobic) and well as hydrophobic (lipophilic) drugs. spanlastics can be an ideal system for drug delivery. Nano-vesicles system is already designed for drugs such as doxorubicin, vaccines, insulin, siRNA and many more; having a wide variation in usage. These vesicles can also be used as a co-delivery system as two different kinds of drugs can be easily loaded to achieve the desired therapeutic effects. As a formulation point of view, these vesicles possess biocompatibility, low toxicity, biodegradability, good stability, low cost and ease of storage. Various modifications of these nano-vesicles can also be used in the treatment of cancer due to their smaller size, leading to enhanced permeability and retention time in tumour tissue. They can be easily administered by various routes such as intravenously, orally and transdermally.

Following are some areas where this nano-vascular drug delivery system is being used:

- **Ocular delivery**: Due to numerous pre-corneal and corneal barriers, the ocular drug delivery system faces a number of difficulties that limit ocular bioavailability. Spanlastics, a unique class of vesicular carriers, serve as site-specific drug delivery systems for drugs that are intended for the posterior eye segment, which contains the choroid, epithelium, and vitreous cavity, as well as the anterior eye segment, which consists of the corneal membrane and aqueous humour. Both lipophilic and hydrophilic drugs can be delivered to the ocular tissues using spanlastics.[17]
- **Oral delivery:** The most preferred route for drug administration is the oral route but drugs administered by oral route undergo bioavailability problems due to various reasons such as poor solubility, frequent dosing, drug interactions, unpredictable absorption, first pass metabolism and systemic adverse effects. This lead to development of a novel surfactant based vesicular system. to overcome the barriers associated with oral drug delivery. for example: the encapsulation of Pravastatin sodium in enteric coated

spanlastics dispersions in order to achieve controlled release and targeted delivery at the duodenum. IT contributed in improvement of oral bioavailability of the drug as compared to aqueous drug solution.

- **Topical delivery:** Spanlastic system are used to deliver the drugs for the topical treatment of skin conditions such as fungal infections, cosmetics etc.
- **Transdermal delivery**: the spanlastics are also used in transdermal delivery of drugs .it exhibits various advantages like bypassing hepatic metabolism, which improves bioavailability and medicinal efficacy. To achieve a consistent drug release transdermal drug delivery is used.[18]
- **Nasal delivery**: Intranasal route is one of these strategies for drug delivery to the brain through three different pathways: systemically where the drug crosses the BBB, through the olfactory region and the trigeminal pathway where it is transported directly from nasal cavity to the central nervous system (Kumar et al., 2008). Spanlastic dispersion is one of the approach to transport the drug across the BBB to reach the brain to exert specific action.[19]
- **Peptides and Proteins**: Peptides and proteins such as bacitracin and insulin have important therapeutic activities but limited clinical applications due to low bioavailability and instability during administration and after storage. In order to avoid this problem, the nano-vesicular system has proven to be a better choice. Further, these formulations also contribute to the delivery of vaccines.

For example, Pardakhty studied the pharmacokinetic properties of the nanovesicular insulin formulation in diabetic rats via oral administration. The content of the drug was evaluated in simulated intestinal fluid and simulated gastric fluid. The results showed that the formulation has increased bioavailability and is protected from degradation.[20]

- **Vaccines:** Vaccine formulation is a powerful tool for the treatment of a number of diseases, but its use is limited due to its safety and efficacy problems. As a result, non-ionic surfactant-based nanovesicles formulation can help to avoid this degradation.
- **Gene Therapy**: Gene therapy, as a modern approach, is very powerful but has limited clinical applications due to the delivery problem. But now the nanovesicular approach is being experimented with to modulate the formulations. For example, DNA encoding**.**
- **Miscellaneous**: Experimental studies were carried out for multiple applications of sodium stibogluconate nano-vesicles, which were found to be effective against the parasite in the

liver, spleen, and bone marrow as compared to the solution of sodium stibogluconate.[21]

CONCLUSION

Development of novel surfactant based vesicles of Spanlastics provides a non-invasive tool for delivering the drug to its target site without the need for frequent drug administration. They tackle the issue of insolubility, instability, low bioavailability and fast debasement of medications. Thus, it can be concluded that Spanlastics can act as a breakthrough in the nano vesicular drug delivery system. These vesicular systems can be exploited to achieve site-specific action for both lipophilic and hydrophilic drugs. This system is being used now for delivering drugs to ocular, oral, topical, trans-ungual, nasal and to the middle ear.

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