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SPANLASTICS: A MODERN APPROACH FOR NANOVESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT: Drug delivery to targeted sites is restricted by various barriers. The conventional drug delivery systems like tablets, capsules, suspensions, emulsions, elixirs, lotions *etc*. are being encountered with a number of issues such as poor bioavailability, drug shelf life, drug-excipients incompatibilities and patient in compliance. Thus with the advent of novel drug delivery systems such as liposomes; nanoparticles are proving to be a better option nowadays. As evolution in the drug delivery system, a new system with lesser side effects was introduced in 2011 known as Spanlastics. They are elastic, deformable surfactant-based nanovesicles in which an aqueous solute solution is entirely enclosed. They are shown to be chemically more stable. 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, mechanism of penetration, different preparation approaches, their evaluation parameters and applications.

INTRODUCTION: The development of targeted drug delivery was initiated in the 1990s by Paul Enrilch; when he found out a drug delivery mechanism that would target directly to diseased cells [1, 2]. Spanlastics are a novel drug delivery system, which entraps the drug in the core cavity in the form of the bilayer. The term Spanlastic (Span + Elastic) was coined for the first time in 2011 [3]. These are highly deformable and elastic carriers similar to transfersomes. These deformable vesicular carrier systems show improved permeability in contrast to drug solution. These are amphiphilic in nature, in which the medication is encapsulated in a vesicle which is made by non-ionic surfactant. The size of spanlastics is very small and microscopic [4]. These are the special class of nanovesicles which overcome the disadvantages associated with liposomes such as chemical instability. Chemical instability in liposomes is due to their predisposition to oxidative degradation and variable purity of phospholipids. The elastic nature of these vesicles is attributed to the presence of edge activators in their structure.

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Spanlastic is a special class of vesicular carriers that act as site-specific drug delivery systems for targeting drugs to the target sites including ocular, oral, topical, nasal and transungual application [5]. The article represents some salient features along with an overview of the preparation technique and the current application associated with.

Salient Features of Spanlastics: [6, 7]

1. Spanlastics can entrap solutes, osmotically active and stable.
2. They discharge medication in a controlled way by means of its bilayer which gives supported the arrival of encased medication.
3. They exhibit flexibility in their structural characteristic and hence can be modulated according to the desired specifications.
4. Spanlastics provide better availability of the medication at the site just by protecting it from a biological environment.

Advantages: [8]

1. Spanlastics are biodegradable and non-immunogenic in nature.
2. Bioavailability Improvement: Since the medication has shielded support hence it goes to the targeted site without being shredded off and provides medication to the targeted site to improve bioavailability as compared to the traditional one.
3. Target Specific: They enhance the restorative execution of medicated particles; shielding the medication from the natural conditions and limiting impact on the targeted site.
4. They are osmotically active and stable, as well as increase the stability of the entrapped drug.
5. Handling and storage of surfactants require no special condition.
6. They can be made to reach the site of action by oral, parenteral as well as topical route.
7. They play an important role in delaying the clearance of drug molecules from the systemic circulation in sustained drug delivery.
8. The presence of non-ionic surfactants in their structure renders them high compatibility with biological systems and imparts low toxicity character.
9. These vesicular systems are highly elastic and deformable in nature which provides them better corneal permeability in contrast to niosomal formulations.
10. They are designed to achieve site-specific action. The elastic nature of these vesicles enables them to squeeze through the corneal membrane, thus, they can reach the anterior segment of an eye as well as to the posterior segment of eye to target the retinal pigment epithelium, vitreous cavity, choroid.
11. They are chemically stable as compared to liposomes.
12. The irritation power of surfactant decreases in the following order: cationic > anionic > ampholytic > nonionic so the nonionic surfactant based spanlastics are non-irritant to the eyes.
13. Economic method of preparation.
14. Access to raw materials is convenient.

Classification of Spanlastics: [9, 10] Likewise liposomes; they can also be classified based on the numbers of layer it composes of; which is illustrated as follows:

Multi-Lamellar Vesicles (MLV): MLVs are the types that are most widely used. It consists of a number of the bilayer. The approximate size of vesicles is 0.5 to 1.0-micron diameter. It is simple to make and are mechanically stable upon storage for a long period.

Large Unilamellar Vesicles (LUV): LUVs are having a high aqueous/ lipid component ratio, so that larger volumes of bio-active materials can be entrapped.

Small Unilamellar Vesicles (SUV): SUVs are mostly prepared from multilamellar vesicles by sonication method, French Press and extrusion method.

Components of Spanlastics: [11, 12] Spanlastics have a structural analogy with conventional liposomes. These are similar to Transfersomes which are highly deformable and elastic liposomes. Spanlastics are composed of two integral parts, a

nonionic surfactant and an edge activator. Since these vesicles are primarily composed of Spans (Surfactants); hence, they have been named as Spanlastics.

Non-ionic Surfactant: [13, 14] Surface active agents (Surfactant) aim at reducing the interfacial tension between two liquids (aqueous phase and oily phase). A nonionic surfactant has no charged group in its head. Sorbitan alkyl esters (Spans) form an important class of non-ionic surfactants. The vesicular structure of Spanlastics is formed by the arrangement of Spans in the form of concentric bilayers. Depending on the type of fatty acid associated with polyoxyethylene sorbitan part of the molecule, spans are of different types like Span 80 (monooleate), span 60 (monostearate), span 40 (monopalmitate) and span 20 (monolaurate). The types of Span have an important role in predicting the stability of the vesicular formulation. Span 80 and Span 40 based vesicles show a high degree of disruption, aggregation and instability. Whereas, the presence of saturated alkyl chains in Span 60 imparts more sustainability to the developed vesicles. It is the lipophilic nature of saturated alkyl chains in Span 60 that permits the formation of unilamellar or multilamellar matrix vesicles. The surface-active properties of this surfactant would augment the action of the edge activator allowing for a reduction in the interfacial tension and subsequent development of fine spanlastic dispersions.

Edge Activators: [15, 16] These are a special class of surfactants with high HLB value or hydrophilicity. These are single chain surfactants which destabilize the vesicles and increase the deformability of the bilayer vesicles by lowering their interfacial tension. Hence, they provide flexibility to the lipid bilayer membranes of these vesicles. EAs tend to form vesicles that are more spherical and hence have a smaller particle size. The incorporation of an edge activator (Tween 80) would potentiate the elastic nature of the vesicles allowing them to temporarily increase the pore size of the biological membranes such that slightly bigger vesicles can squeeze in and promote better drug penetration. Furthermore, these hydrophilic surfactants can destabilize the vesicular membranes, increase their deformability and create systems having different degrees of disruption in packing characteristics.

Ethanol: [17] Ethanol has positive impacts on the properties of these nano-vesicular carriers. It contributes towards improving the drug partitioning and entrapping within the vesicles. The membrane condensing ability of ethanol causes a decrease in thickness of the vesicular membrane, thus, reducing the vesicular size and finally *via* modifying the net charge of the system toward a negative zeta potential resulting in some degree of steric stabilization.

Morphology: [18, 19] Spanlastics have concentric bilayers similar to liposomes as seen in **Fig. 1**. These can be Unilamellar or Multilamellar (MLVs). Depending on the size of vesicles, these can be (SUVs) Small unilamellar (10-100 nm) or (LUVs) Large unilamellar (100-3000 nm). It has been reported that MLVs have prolonged retention as compared to SUVs of the same lipid composition. Spanlastics systems are spheroid structures consisting of amphiphilic molecules acting as suitable matrices for bio encapsulation.

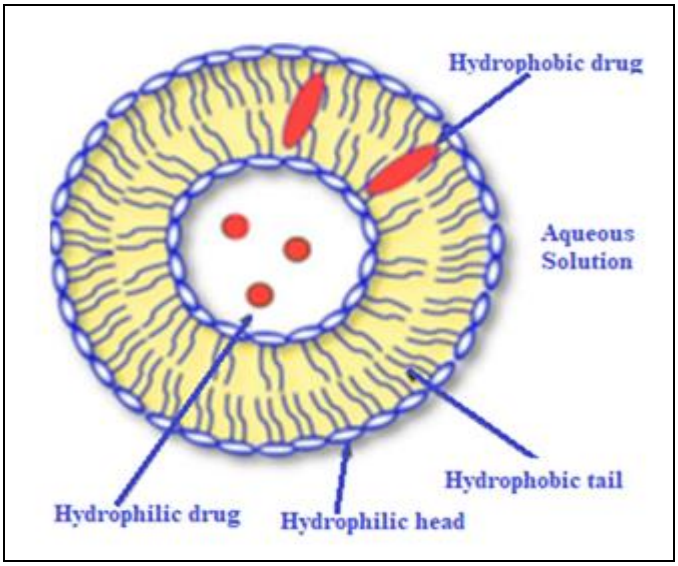

FIG. 1: STRUCTURE OF SPANLASTIC VESICLE

Mechanism of Penetration of Spanlastics: [20, 21] Edge activators (EAs) destabilize the lipid bilayers and in turn, increase the deformability of the vesicles. The surfactant present in these vesicles causes them to induce pores in lipid structures, such as membranes and also provokes solubilization (lysis) in the higher concentration range. Thus, elastic vesicles can squeeze themselves through intercellular regions under the influence of water gradient based on the membrane bending energy that depends on its composition.

There are 2 mechanisms for drug penetration as seen in **Fig. 2**.

1. The elastic vesicles interact with the epithelial cell membrane and act as penetration enhancers, and subsequently modify the intercellular lipid lamellae.

2. The elastic vesicles can act as drug-carrier systems, whereby intact vesicles carrying the drug pass through the intercellular spaces and reach across the biological membrane.

Two factors contribute towards successful passage of these carriers: [22]

1. The highly stress-dependent elasticity of the vesicle bilayers and

2. The existence of an osmotic gradient.

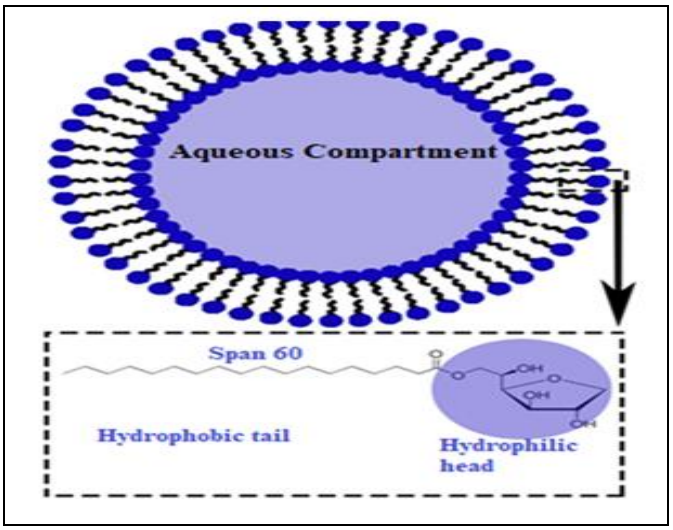

FIG. 2: STRUCTURE OF SURFACTANT BASED VESICULAR CARRIER

Method of Preparation: [23, 24]

Ether Injection: In this method, slow injection of surfactant in 20 ml ether through a 14 gauze needle (25 ml/min) in preheated 4 ml aqueous phase containing the drug is maintained at 600 ºC. The ether solution will be evaporated using rotary evaporator, after evaporation of the organic solvent it forms single layered vesicles.

Sonication: In this method, an aliquot of drug in suitable buffer is prepared which is then subsequently added to the surfactant mixture in a 10 ml glass vial. Probe sonication of the mixture is made by titanium probe.

Hand Shaking Method: [25] Firstly surfactants are dissolved in some organic solvent (like ether, chloroform, benzene). After that, the solvent is evaporated under reduced pressure in a vacuum evaporator in a round bottom flask. The layer is rehydrated with an aqueous solution of drugs with continuous shaking which results in swelling of the surfactant layer. Swelled amphiphiles eventually fold and form vesicles which entrap the drug.

Extrusion Method: In this method, a mixture of surfactant and diacetyl phosphate is prepared and the solution is evaporated using a rotary vacuum evaporator to leave a thin film. The drug solution is rehydrated with aqueous drug solution thus obtained mixture is extruded through the polycarbonate membrane (mean pore size 0.1 micron) and then kept in series up to eight passages to obtain a uniform result.

Microfluidization Method: [26] In this method, one containing drug and the other surfactant *i.e.* two fluidized streams get interacted with ultrahigh velocity, in strictly defined microchannels within the interaction chamber such that the energy supplied to the system remains in the area of spanlastics formulations. This is called submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation.

Factors Affecting the Physico-Chemical Properties of Spanlastics: [27, 28]

Membrane Additives: The stability of spanlastics can be increased by the number of additives into the formulation along with the main surfactant and drug. The membrane stability, morphology, and permeability of vesicles are affected by numbers of additives *e.g.* tweens enhance the flexibility of the formed vesicles to easily enter into targeted area.

Temperature of Hydration: Shape and size is also influenced by the hydration temperature. Assembly of the vesicles is affected by the temperature change of the system. The temperature change can also induce vesicle shape transformation. Polyhydral vesicles of C16G2: solulan C24 (91: 9) is formed at 25 °C, but it is converted into spherical vesicles at 45 °C and on cooling from 55 to 49 °C, the vesicles produced a cluster of smaller spherical nano-vesicles.

Characteristic of Drugs: [29] Molecular weight, chemical structure, hydrophilicity, lipophilicity as well as the hydrophilic-lipophilic balance (HLB) value of the drug can affect the drug entrapment efficiency. Vesicle size may increase due to the entrapment of drugs. The surfactant head group does the interaction with drug particle, which probably leads to increase the charge on polymer and thus causes repulsion of the surfactant bilayer which further results in an increase in vesicle size.

Content and Surfactant Type: The mean size of vesicles got increased proportionally as we increase the HLB value of surfactants like span 85 (HLB 1.8) to span 20 (HLB 8.6). It could be because of surface free energy that will decrease with the increment of hydrophilicity of surfactant. Alkyl chain is present in a well-ordered structure in a gel state, while in the liquid state the structure of the bilayer is more disordered. The gel–liquid phase transition temperature (TC) is used for the characterization of surfactant and lipids [30]. Phase transition is also the reason for affecting Entrapment efficiency *i.e.* span 60 having higher TC, provide better entrapment efficiency. The entrapment efficiency of the spanlastics is affected by the HLB value for e.g. spanlastics have high entrapment efficiency at HLB value 8.6 but HLB value 14 to 17 is not suitable for their formulation.

Structure of Surfactants: The geometry of the vesicles formed during the preparation also depends upon the critical packing parameter (CPP). According to CPP, the geometry of the vesicles can be predicted. CPP can be calculated using the following equation:

$$\text{Critical packing parameter (CPP)} = v/ lc*a0$$

Where; *v* hydrophobic group volume, *lc* the critical hydrophobic group length, *a*0 the area of hydrophilic head group.

CPP is helpful in predicting the structure of vesicles in following way [31];

1. Spherical micelles formed if CPP<1/2
2. Bilayer micelles is formed if ½<CPP<1
3. Inverted micelles is formed if CPP>1.

Resistance to Osmotic Stress: [32] Addition of hypertonic salt solution to the formulation of spanlastics brings the decrease of vesicle diameter. In hypotonic salt, there is a slow release and slight swelling of the spanlastic vesicles which could be due to inhibition of eluting fluid from vesicles, then by faster release, which perhaps due to loosening of vesicles structure under osmotic stress.

Method of Preparation: [33] Preparation methods of spanlastics such as handshaking, ether injection or sonication hamper the final formulation characteristic an appreciable degree. For example, vesicles made up by ether injection are smaller when compared with the vesicles prepared by handshaking method. Therefore hydrating the above mixture and then vortexing will help to reduce the vesicles made by hand-shaken method.

***In-vivo* Behaviour of Spanlastics:** [34, 35] *In-vivo* spanlastics have been found equiactive to nano-vesicles and their distribution follows the same pattern as that of colloidal drug delivery system. The level of disposition of these constituents is appreciably high in life because of the natural vectoring process. Size variation also affects the pattern of drug disposal from blood; as larger sized vesicles get entrapped in the alveolar section of lungs due to retention or perhaps phagocytic action. While small-sized vesicles can easily pass through sinusoidal epithelium and will have better access to the spleen.

Characterizations of Spanlastics: [36, 37]

Entrapment Efficiency (EE): It is defined as the percentage amount of drug which is entrapped by the spanlastics. Entrapment efficiency is calculated by using the formula:

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

For the determination of entrapment efficiency, the un-entrapped drug is first separated using a suitable method (*e.g.* by centrifugation method). The resulting solution is then separated and the supernatant liquid is collected. The collected supernatant is then diluted as specified and estimated using an appropriate method as described in a monograph of that particular drug. Both the entrapment efficiency (EE) and yield of spanlastics depend on the method of preparation as well as the physicochemical properties of a drug. The number of double layers, vesicle size and its distribution, entrapment efficiency of the aqueous phase, and the permeability of vesicle membranes are influenced

by the methodology used for formulation as well as the addition of tweens as they make the spanlastics less leaky. Bhaskaran and Lakshmi reported that the transmembrane pH gradient method had higher EE with respect to other processes like ether injection method and film hydration method. In this process, the presence of a net charge, whether negative or positive can increase water uptake within the double layer. Such hydration leads to an increase with respect to uncharged vesicles of loaded hydrophilic molecules that can probably be located within the bilayer as well as in the core of the aggregated structures.

Size, Shape and Morphology: [38, 39]

Transmission Electron Microscopy (TEM): TEM is used to determine the size, shape and lamellarity of spanlastics. In brief, a suspension is prepared and mixed with 1% phosphotungstic acid (in sufficient amount). A drop of resultant was then used on carbon-coated grid, draining off the excess and then the grid was observed and images are taken under suitable magnification under TEM after complete drying (Philips TEM).

Freeze Fractured Microscopy: [40] The size and shape of spanlastics were found to be dependent on the drug entrapment, nature of drug used and the nature of surfactant. For the determination of size, vesicles are generally freeze-thawed and then visualized under freeze fractured electron microscope. Liquid propane is generally used for the cryofixation of the vesicular suspension (glycol may be used as cryoprotectant) at low pressure (10_2 Pa). The cryofixed vesicles are fractured at a specified angle. The resultant surface is then shadowed using platinum or carbon vapors at an angle of 45°. Carbon coating used in this method strengthens the formed replica. Replica is cleaned and then observed and examined using TEM.

Optical Microscopy Technique: [41] This technique is also used for observation of size and shape. Nearly 100 spanlastics are used for particle size determination. In this method size of the stage micrometer coinciding with the eyepiece micrometer is recorded and the size of formulation is then calculated. Nowadays laser beam based mastersizer is used for the determination size distribution, mean surface diameter and mass distribution of spanlastics. Dynamic light scattering (DLS) analysis using Malvern zeta sizer is also used for the determination of size distribution, mean diameter and zeta potential.

***In-vitro* Release Study:** [42] In this study dialysis membrane method is generally used. In this method, a small amount of spanlastics are taken into dialysis bag and are tied at both ends. Another beaker containing suitable dissolution media is maintained at 37 °C and the dialysis bag is put into it and stirred by a magnetic stirrer. A sample solution is taken from the beaker at specified time intervals and replaced with fresh dissolution media. The samples were analyzed for the concentration of drug at specified wavelength reported in a respective monograph of that particular drug.

Tissue Distribution / *In-vivo* Study: [43, 44, 45] Tissue distribution profile has been studied using suitable animal models. Bhaskaran and Lakshmi, used three groups of healthy albino rats (100-150 gm.) for tissue distribution profile, each group contain three animals. The first group was treated as a control in which free spanlastics without drug were injected, to the second group free drug was injected. The third group was treated by formulation. After sacrificing the animals, various tissue like liver, lungs, spleen, kidney and heart were removed. After washing the tissue with phosphate buffer (pH 7.4) the organs were homogenized and centrifuged. The supernatant thus obtained was used for the determination of drug content using a suitable method. Similarly, Jadon *et al.*, used male albino rats for this study. After the administration of the free drug and drug entrapped in spanlastics, the amount of drug in plasma was determined. The animals were divided into three groups, each group contains five animals. The first group was treated as control and was injected with PBS (pH 7.4), the second and third groups were treated with the pure drug and nanovesicles containing drug respectively by the oral route, after predetermined time intervals, blood samples were collected, centrifuged and frozen immediately and then analyzed using HPLC.

Applications of Spanlastics: [46] 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); 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. 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:

Chemical Drugs: Nano-vesicles is most commonly being used as a carrier for many chemical drugs due to their most advantageous properties. They possess both hydrophobic shell and hydrophilic cavity; hence suitable chemicals can be easily loaded on these vesicles. 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.

For example, Carvediol is a chemical drug that is most commonly used in the treatment of congestive heart failure and coronary artery diseases [46]. But the systemic availability is limited due to 1st pass metabolism and short half-life [47]. Therefore, nano-vesicles are the suitable carrier for this kind of drug because these provide the loaded drug from degradation, control the release profile through component optimization and rendering 1st pass metabolism. The formulation was prepared by fil hydration technique with vesicle size around 167 nm and highest encapsulation efficiency (77.7%).

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 tumor tissue.

Peptides and Proteins: [48, 49] Peptide and protein 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 been proven a better choice. Further, these formulations also contribute to the delivery of vaccines.

For example, Pardakhty investigated the nano-vesicular insulin formulation and studied pharmacokinetics property of the resulted formulation on diabetic rats through oral administration. The content of the drug was evaluated in simulated intestinal fluid (SIF), simulated gastric fluid (SGF). The results showed that the formulation has increased bioavailability and protected from degradation.

Another example of successful delivery of peptide/protein is peroral administration of 9-deglycinamide 8-arginine vasopressin (DGAVP); investigated [9]. *The in-vitro* study was performed to evaluate the vesicular formulation with drug solution and better bioavailability was observed.

Vaccines formulation is a powerful tool for the treatment of a number of diseases, but limited due to their safety and efficacy problem. Hence non-ionic surfactant based nano-vesicles formulation is a way to avoid such degradation.

Gene Therapy: [50] Gene therapy as a modern approach; is very powerful but has limited clinical applications due to the delivery problem. But now the nano-vesicular approach is being experimented to modulate the formulations. For example, DNA encoding

Miscellaneous: [51, 52] Experimental studies were carried out for multiple doing of sodium Stibogluconatenano-vesicles was found to be effective against the parasite in liver, spleen and bone marrow as compared to the solution of Sodium Stibogluconate.

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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