Spanlastics- A Novel Drug Delivery System

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ABSTRACT :

A novel drug delivery technique called spanlastics traps the drug in a central chamber in the shape of a bilayer. Nanocarriers are used in this innovative method of drug delivery to improve the bioavailability and therapeutic effectiveness of pharmaceuticals. These elastic, nanoscale vesicles are made of edge activators and non-ionic surfactants and offer regulated medication release, flexibility, and stability.

Spanlastics are particularly helpful for delivering hydrophobic drugs since they can penetrate biological barriers including the skin and mucous membranes. Their elasticity allows them to deform and fit into tiny pores, making them suitable for transdermal, ophthalmic, and other site-specific drug delivery applications. This approach has shown promise in improving drug solubility, reducing side effects, and ensuring sustained therapeutic benefits.

INTRODUCTION:

For the past few decades, researchers have focused on developing innovative drug delivery systems (NDDS). A few of the conventional carriers are by nature inflexible (1). In order to increase permeability on biological membranes, current research has focused on improving the deformability of nanovesicles (2).In 2011, spanlastics were first introduced. The combination of [Span+Elastic] and [Span] is pronounced as "Spanlastics." Kakkar and Kaur developed the first surfactant-based deformable nanocarriers. Edge activators E.A. and non-ionic surfactants, which are part of spanlastics, destabilize nanocarrier vesicular membranes and encourage flexibility and permeability through a range of biological membranes without breaking them (3).

In comparison to liposomes, nano-spanlastics are chemically more stable, biodegradable, non-immunogenic, and made of deformable nano-vesicles (4,5). The nano vesicle carrier is called nano spanlastics.

since they are easily compressed and deformed, nano-spanlastics add stability to lipophilic medications by encasing them in nanocarriers and increasing their permeability through the microscopic gaps of biological membranes (7,8). This type of nano-vesicular carrier delivers the drug to a specific site and can be used in a number of ways, such as oral, nasal, transdermal, and ocular applications.(9).

STRUCTURE OF SPANLASTIC:

Spanlastics are spherically shaped, amphiphilic molecule-based structures that function as efficient bioencapsulation matrices. Pharmaceuticals that are hydrophilic are found in the central section of the vesicle, while hydrophobic medications are found in the hydrophobic tail. The size of the SPs vesicle normally falls between 180 and 450 nm.

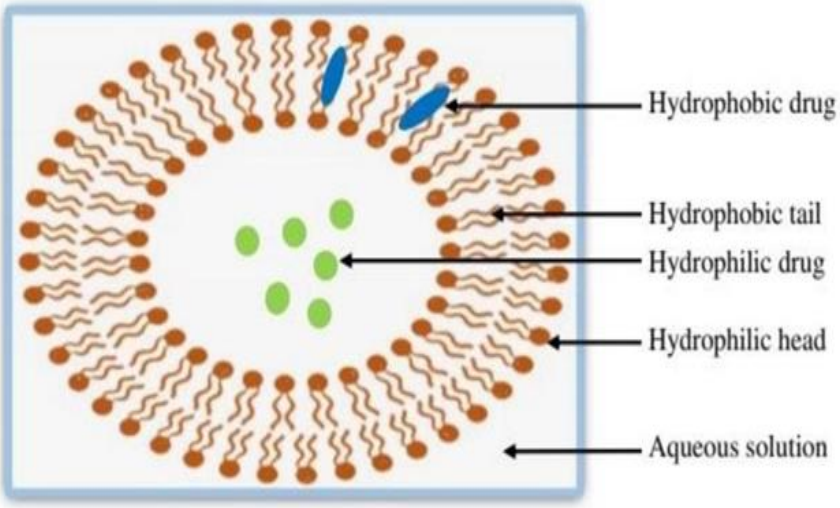

Fig 1

COMPOSITION (12):

The two essential components of spanlastics are a nonionic surfactant and an Edge activator. Substances that are not ionic:

Because of their various benefits, non-ionic surfactants are frequently used as wetting agents while creating vesicles. They are less toxic, more stable, and more compatible than cationic, amphoteric, or anionic surfactants (13). Nonionic surfactants' strong interfacial activity is a result of their combination of polar and non-polar components.

Several parameters, such as the critical packing parameter (CPP), the chemical makeup of the contents, and the hydrophilic-lipophilic balance (HLB) of the wetting agent, may affect the formation of bilayer vesicles. Compared to vesicles based mostly on span 80 (HLB value 4.3), those based primarily on span 40 (HLB value 6.7) and span 60 (HLB value 4.7) show greater stability and are probably less disturbed, aggregated, and unstable14.
The lipophilic characteristics of span 60 increase its capacity to entrap pharmaceuticals and facilitate the formation of lamellar matrix vesicles in comparison to other non-ionic surfactants.

EDGE ACTIVATORS (15): A variety of surfactants, such as Tween 80 and PVA, can function as edge activators. PVA can be added to the vesicles to increase their flexibility while decreasing their size. Despite increasing the deformability of vesicular membranes, the use of these hydrophilic wetting agents may cause damage to them [14e16]. Combining SPs with an edge activator increases flexibility and reduces interfacial tension, which makes it easier for big particles to fit through the tiny pores.

PENETRATION OF VESICLES THROUGH SKIN[16,17]:

The lipid bilayers become unstable due to edge activators (EAs), which increases the deformability of the vesicles. The surfactant in these vesicles stimulates lysis (solubilization) at greater concentrations and creates porosity in membranes and other lipid structures.

Therefore, elastic vesicles can compress themselves over intercellular regions with different membrane characteristics when there is a water gradient present.

With the use of elastic vesicles, undamaged drug-carrying vesicles can pass through biological membranes and intercellular gaps.

Two factors influence these carriers' ability to travel successfully:

1. Vesicle bilayer flexibility is strongly dependent on stress.
2. There is an osmotic pressure gradient.

SPANLASTICS CLASSIFICATION:

The number of layers that spanlastics are formed of determines their classification. For example: i. Multi-Lamellar Vesicles (MLV): These are the most commonly utilized type. It is made up of many bilayers. Vesicles range in diameter from 0.5 to 1.0 microns. It is easy to build and maintains its mechanical stability over time.

ii. Large Unilamellar Vesicles (LUV):

LUVs can entrap higher amounts of bioactive molecules because of their high aqueous/lipid component ratio.

iii. SUVs, or small unilamellar veins:

There is just one bilayer vesicle in it. The size is between 20 nm and 50 µm

ADVANTAGES (10,11):

1. Unlike regular spanlastics, which have shielding support, nano-Spanlastics deliver medication to the targeted spot without being torn off, improving bioavailability.

2. Nano-Spanlastics naturally decompose.

3. Compared to the traditional form, nano-Spanlastics have a higher bioavailability.

4. They deliver the medication at the intended location without harming the pores or cell membranes.
5. They are very compatible with biological systems due to the non-ionic surfactants that are a part of their composition.
6. These formulations are more cost-effective than others.

7. They improve the stability of the medicine that is entrapped and are osmotically stable and active.
8. The vesicles are less harmful when a non-ionic surfactant is present.

9. These spanlastics enable hydrophilic or lipophilic medications to cross biological membranes, including the skin, oral, topical, or parentral.

10. They are made to accomplish site-specific goals. These vesicles' elastic properties allow them to pass through the corneal membrane and target the retinal pigment epithelium, vitreous cavity, and choroid in both the anterior and posterior segments of the eye.

11. The following is the order in which surfactant's irritating strength declines: spanlastics based on nonionic surfactants are non-irritating to the eyes because they are cationic > anionic > ampholytic > nonionic.

12. In prolonged drug delivery, they are crucial in postponing the removal of drug molecules from the systemic circulation.

DISADVANTAGES:

1. Because of their surface negative charge, spanlastics may have poor mucoadhesion properties, particularly in applications like ocular administration. This may make it more difficult for the target surface to absorb the material.

2. Toxicology associated to surfactants: Because surfactants make up the majority of spanlastics, large quantities may cause irritation or toxicity at the application site, depending on the surfactant's characteristics.

3. Limited drug loading capacity: Some medications may not easily integrate into spanlastic vesicles due to their physicochemical characteristics, which restricts the quantity of medication that may be administered.
4. Stability issues: Over time, spanlastic formulations may deteriorate as a result of interactions with other formulation ingredients, temperature swings, and pH variations.

PREPARATION OF SPANLASTICS VESICLES :

There are several ways to make spanlastics :

a) ETHANOL INJECTION METHOD:

A precisely measured amount of non-ionic surfactant and medication dissolved in ethanol are injected into the heated aqueous phase, which also contains an edge activator for spanlastics, in the first stage. At 800-1600 revolutions per minute, the mixture is continually swirled while being maintained at 70-80 degrees Celsius for 30 minutes. As the final step, water is added to the solution until the proper volume is achieved [18].

Because it combines with water to form an azeotrope (the word "azeotrope" refers to a mixture of two or more substances that cannot be separated by straightforward distillation because the liquid phase and the vapour phase have the same composition), It is therefore difficult to remove leftover ethanol using this process, because the components in the mixture evaporate and condense together, making further separation by conventional distillation techniques impossible. Additionally, ethanol has the potential to deactivate a number of physiologically active macromolecules in even minute amounts.[19].

b) THIN FILM-HYDRATION TECHNIQUE:

It is a simple technique for creating thin films. Wetting agents, like span 60, are accurately weighed in a round-bottom flask and dissolved in organic solvents, like chloroform, to create a thin coating on the flask walls [20].

A rotary evaporator running at 90–100 rpm is used to evaporate the organic solvents at 60°C. The aqueous phase containing the edge activators is then added, and after 30 minutes of regular rotation at 90 rpm, the solvents evaporate and the film is separated from the walls. While lipophilic medications are added to organic layers, hydrophilic drugs can be introduced to aqueous solution when an aqueous phase is added to the film [21].

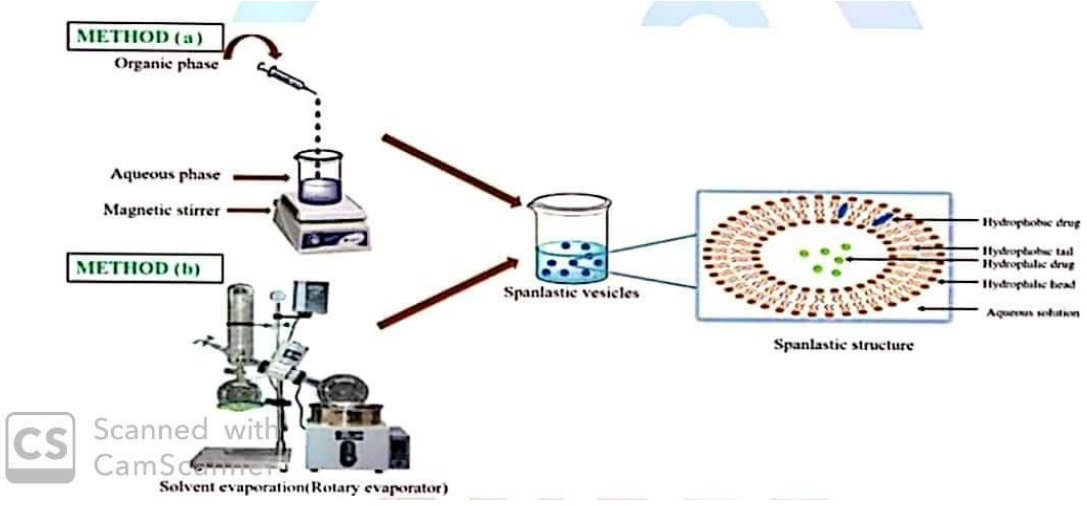

Fig 2

c) SONICATION:

This procedure involves preparing a drug sample using the proper buffer, then mixing the surfactant mixture with a sample of the medication in a 10 mL glass vial. The liquid is then sonicated using a titanium probe[22].

d) HAND SHAKING METHOD

It is necessary to first dissolve surfactants in an organic solvent, such as ether or chloroform. After that, the solvent is eliminated inside a flask with a circular bottom by vacuum and low-pressure evaporation. An aqueous drug solution is added to rehydrate the layer, and the mixture is quickly swirled. The surfactant layer thickens as a result of the amphiphiles' slow folding and the creation of vesicles that trap the drug[23].

e) ETHER INJECTION:

The surfactant is injected into an aqueous phase that has been heated to 600 degrees Celsius at a rate of 25 milliliters per minute using a 14-gauge needle. For this approach, 20 milliliters of ether must be used to dissolve the surfactant. A rotary evaporator will be used to remove the ethanol from the ether solution. Vesicles with a single layer will occur as a result of the procedure once the organic solvent has been totally eliminated[24].

f) Microfluidization Method:

With this technique, two fluidized streams—one holding a drug and the other a surfactant—interact at extremely high speeds inside pre-designed microchannels in an interaction chamber. In order to keep the energy supplied to the system within the range needed for spanlastic compositions, it is carefully regulated. The submerged jet principle is the term used to describe this phenomena. As a result, the formulation has improved reproducibility, decreased dimensions, and improved homogeneity[25].

FACTOR AFFECTING OF PHYSIO-CHEMICAL PROPERTIES OF SPANLASTICS[26]

i. Membrane supplements:

In addition to the active agent and primary surfactant, additional chemicals can be added to the formulation to increase the stability of the spanlastics. Numerous alterations can impact the stability, shape, and permeability of vesicle membranes. For example, tweens might increase the produced vesicles' flexibility, which facilitates their entry into the targeted region.

ii. Properties of Drugs:

The drug's hydrophilicity, lipophilicity, hydrophilic-lipophilic balance, molecular weight, and chemical structure are some of the factors that can impact its entrapment efficiency. The medications being trapped may cause the vesicle to enlarge.

iii. Hydration Temperature:

The temperature at which an object is hydrated can also affect its size and shape. The temperature differential across the system has an impact on the vesicle assembly process. Vesicles' shapes can also alter as a result of temperature fluctuations. At 25 degrees Celsius, the polyhydral vesicles of C16G2: solution C24 (91:9) develop; however, at 45 degrees Celsius, they transform into spherical vesicles.

After cooling from 55 degrees Celsius to 49 degrees Celsius, the spherical vesicles form a cluster of spherically formed but significantly smaller nano-vesicles.

CHARACTERIZATIONS OF SPANLASTICS[27]:

i. Entrapment Efficiency (EE):

This refers to the proportion of medication that gets absorbed by the polymers. Entrapment efficiency is calculated using the formula below:

EE is equal to the total amount added x 100 divided by the amount of drug trapped. The unentrapped drug must first be separated using a suitable method (such as centrifugation) in order to calculate the entrapment efficiency. The liquid supernatant is collected after the resulting solution has been separated. The supernatant is collected, diluted as instructed, and then calculated using an appropriate method described in the drug's monograph.

The yield and entrapment efficiency (EE) of spanlastics are influenced by the physicochemical properties of a drug and its production method. The formulation procedure and the addition of tweens, which lessen the leakiness of the spanlastics, have an impact on the aqueous phase's entrapment efficacy, the quantity of double layers, the size and distribution of vesicles, and the permeability of vesicle membranes. A net charge, either positive or negative, can improve the double layer's capacity to absorb water during this process. More uncharged vesicles of loaded hydrophilic molecules are produced as a result of this hydration, and these are probably present both inside the bilayer and at the center of the aggregated formations.

ii. Size, Shape and Morphology(28,29):

Transmission Electron Microscopy (TEM): TEM is used to assess spanlastics' dimensions, form, and lamellarity. In short, enough 1% phosphotungstic acid is combined with a prepared solution. Following thorough drying, a drop of the resulting was applied to a carbon-coated grid, draining off any excess. The grid was then examined and pictures were taken under the appropriate magnification under a TEM (Philips TEM).

iii. Drug entrapment, drug kind, and surfactant type were found to influence the size and shape of spanlastics using freeze-fracture microscopy (30). To measure their size, vesicles are frequently freeze-thawed and then inspected using a freeze-fractured electron microscope. Usually, liquid propane is used to cryofix the vesicular solution at low pressures (10_2 Pa); glycol can be employed as a cryoprotectant. The cryofixed vesicles shatter at a specific angle. After that, carbon or platinum vapors are used to shade the resultant surface at a 45° angle. The carbon coating used in this procedure strengthens the manufactured copy. Following cleaning, TEM is used to view and examine the replica.

iv. Measurement of elasticity (31,32)

Using this technique, vesicles were extruded using a polycarbonate filter with 50 nm-wide holes under constant pressure. The process made use of a 200 ml barrel and a stainless steel pressure holder fitted with a 25 mm filter. The vesicular size of the extruded suspension was affected by the durations prior to and following the extrusion operation. The formulation's adaptability shows that SP can squeeze itself and pass through the mucous membrane, which is an intriguing need for this type of vesicle.

v. Technique for Optical Microscopy (33).

This method is also applied to size and shape observation. The particle size is determined using almost 100 spanlastics. Using this method, the size of the formulation is estimated by recording the size of the stage micrometer that coincides with the eyepiece micrometer. These days, the size distribution, mean surface diameter, and mass distribution of spanlastics are determined using a laser beam-based masterizer. The size

distribution, mean diameter, and zeta potential are also determined by dynamic light scattering (DLS) analysis utilizing a Malvern zeta sizer.

vi. Study of In-vitro Release (34)

The dialysis membrane method is typically employed in this study. This technique involves putting a tiny quantity of spanlastics inside a dialysis bag and tying them at both ends. The dialysis bag is placed in a second beaker with appropriate dissolving medium that is kept at 37 °C and agitated with a magnetic stirrer. At certain intervals, a sample solution is removed from the beaker and replaced with brand-new dissolving medium. The samples were examined to determine the drug concentration at a given wavelength as stated in the relevant monograph for that specific drug.

APPLICATIONS :

1.Therapy of gene:

A more modern approach, gene therapy, is highly effective, but delivery issues limit its practical applicability. To alter the formulations, the nano-vesicular method is presently being researched and tried. One excellent example is DNA encoding (35).

2. Peptides and proteins:

Although peptides and proteins such as bacitracin and insulin have strong therapeutic effects, their clinical uses are limited because of their low bioavailability and instability during and after delivery. It is now evident that the best way to get around this problem is to employ the nano-vesicular system.

Additionally, these formulations aid in the spread of vaccines (36).

Oral administration of 9-deglycinamide 8-arginine vasopressin (DGAVP), which was investigated 9, is one efficient peptide or protein delivery method. Improved bioavailability was found in the in-vitro investigation used to evaluate the vesicular formulation with the drug solution.

3. Immunizations:

Despite the fact that vaccines are an effective treatment for a variety of diseases, their use is restricted due to worries about their efficacy and safety. To help stop this degradation, non-ionic nanovesicles based on non-ionic surfactants can be developed (37).

4. Chemical Medication: Due to their various benefits, nano-vesicles are increasingly being used in the pharmaceutical industry as carriers for chemical therapies. Because these vesicles have a hydrophilic interior and a hydrophobic exterior, it is simple to load the appropriate chemicals onto them. These vesicles can also be employed as a co-delivery method because it is easy to load two distinct types of medications into them to achieve the intended therapeutic effects. From the standpoint of formulation, these vesicles have a number of advantageous qualities, including low toxicity, biocompatibility, biodegradability, high stability, cost, and ease of storage.

5. OCCURRING DELIVERY [41, 42]

Because of the many pre-corneal and corneal barriers, the ocular drug delivery system faces several difficulties that limit ocular bioavailability. A unique type of vesicular carrier known as spanlastics is used to deliver site-specific medications. distribution strategies for drugs intended for the anterior portion of the eye, which contains the corneal membrane and watery humor, and the posterior portion, which contains the choroid, vitreous cavity, and epithelium. Apart from lipophilic Hydrophilic drugs can be administered to the eyes. elastic-banded tissues.

6. DELIVERY BY ORAL MEANS [43,44,45]

Despite the fact that oral pharmaceutical delivery is the most widely used technique, a number of factors, including poor solubility, frequent dosage, medication interactions, irregular absorption, first-pass metabolism, and unpleasant systemic reactions, can affect a drug's bioavailability. A new vesicular system based on surfactants was created in order to overcome the difficulties involved in the delivery of oral medications. For instance, encapsulating sodium pravastatin in spanlastic dispersions coated in enteric allows for precise distribution and controlled release. to the abdomen. It improved the drug's oral bioavailability when compared to an aqueous pharmaceutical solution.

7. DELIVERY OF TRANSDERMAL [46,47]

The transdermal Spanlastics are utilized for giving medication. It has many benefits, including preventing hepatic metabolism, improving the material's bioavailability, and improving the effectiveness of medication. Transdermal application is a method of drug delivery that produces a continuous release of the drug.

8.NASAL DELIVERY [48,49]

The intranasal pathway is one method that goes directly from the nasal cavity to the central nervous system. Trigeminal route after crossing the blood-brain barrier crossing the area known as the olfactory barrier (BBB). One method of getting medicine is by crossing the blood-brain barrier and entering the brain to accomplish a specific goal. spanlastic dispersion is the mode of action.

[50,51] TOPICAL DELIVERY

The spanlastic system is used to supply drugs for topical skin therapy conditions such fungal infections and inflammation, among others.

10. PROTEIN DELIVERY AND PEPTIDES [52,53,54]

Due to their fragile nature and low bioavailability both during injection and after storage, proteins and peptides like insulin and bacitracin have substantial therapeutic potential but few real-world applications. To avoid The nano-vesicular system has proven to be a better solution for this problem. Furthermore, these formulae also facilitate the process of immunization. examined the pharmacokinetic properties of the insulin formulation in nanovesicles, for example, by administering them orally to diabetic rats.

11. Miscellaneous: It was demonstrated that the efficacy of multiple dosages of sodium stibogluconate nano-vesicles in preventing spleen, liver, and bone marrow parasites was noticeably greater than that of the sodium stibogluconate solution (39, 40).

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