Spanlastic advanced approach as nanovesicular drug delivery system

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***Abstract*- In the field of drug delivery system advancements, a new approach was introduced in 2011, called Spanlastics, which aims to minimize adverse effects. Spanlastics are deformable nanovesicles based on surfactants, enclosing an entire solution of aqueous solutes. Notably, they exhibit improved chemical stability and enable the targeted and controlled release of natural pharmaceutical compounds. Spanlastics consist of two essential components: a nonionic surfactant and an edge activator. These vesicles are primarily constituted of Spans (surfactants), which is why they are referred to as Spanlastics. This Drug delivery systems find applications in numerous fields, including optics, oral administration, dermatology, nasal delivery, and transungual delivery for medications with various applications.**

***Keywords*: Spanlastic, Optic, Oral, Dermal, nasal, transungal.**

INTRODUCTION

Spanlastics stand as a novel approach to drug delivery, where drugs are confined within a bilayer structure in the core cavity. The term "Spanlastic" (formed by merging "Span" and "Elastic") was first introduced in 2011. These carriers exhibit significant deformability and elasticity akin to transfersomes. These vesicular carrier systems, known for their malleability, demonstrate enhanced permeability compared to conventional drug solutions.Spanlastic vesicles (SVs) represent a distinct variety of niosomes utilized in drug delivery. These vesicles incorporate substances like Span or Tween as edge activators, rendering them notable for their deformability and elasticity. The elasticity of SVs has been extensively documented in various studies, and this particular trait plays a pivotal role in facilitating drug permeation through diverse mucosal membranes, including the nasal mucosa. (1, 2, 3).These structures exhibit an amphiphilic nature, where the medicinal compound is enclosed within a vesicle formed by a non-ionic surfactant. The elasticity of these vesicles is attributed to the incorporation of edge activators within their structure. In comparison to liposomes, these nanovesicles surpass them in certain aspects such as resistance to chemical instability. Liposomes are susceptible to chemical instability due to factors like oxidative breakdown and variable phospholipid purity.This unique category of vesicular carriers functions as targeted drug delivery systems, particularly suitable for medications designed for ophthalmic, oral, topical, nasal, and transungual applications(4,5).

Spanlastic classification

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.

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

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

Small Unilamellar Vesicles (SUV), short for, generally have dimensions within the range of 20 nm to 50 µm. They are produced from multi-lamellar vesicles using the sonication method.(4,6)

Advantages of spanlastic

1 Spanlastics are naturally non-immunogenic and biodegradable. Their ability to provide a protective carrier ensures that medications can reach their target site without degradation, leading to increased bioavailability when compared to conventional methods.

2 The spanlastics system facilitates the passage of hydrophilic or lipophilic drugs through biological membranes, including the cornea.

3 spanlastic enclosing the medication within a lipid bilayer structure, it is protected from the surrounding biological environment.

4 They boost the therapeutic efficacy of medicated particles by providing protection to the medication from the surroundings and mitigating its effect on the targeted site.

5 They enhance the stability of the entrapped medicine and exhibit osmotic activity while maintaining their stability.

6 Spanlastic have significant role in prolonging the retention of drug molecules within the systemic circulation when implementing sustained drug delivery methods.

7 Presence of non-ionic surfactants in the composition of spanlastic makes it highly compatible with biological systems and results in minimal toxicity (4, 7).

Components of Spanlastic

Non ionic surfactants: Non-ionic surfactants consist of sorbitan alkyl esters, often referred to as Spans. To establish the vesicular structure of spanlastics, Spans arrange themselves into concentric bilayers. Conversely, the incorporation of saturated alkyl chains in Span 60 enhances its longevity.

Edge activators are like special ingredients that make the outer layer of lipids more flexible. They do this by adding substances that mix well with both water and fat. This makes it easier for things to pass through the layer. Edge activators also help make the layer more bendable by reducing the tension between the layers. When we use edge activators, they tend to form larger round structures, which can result in smaller particle sizes.Tween 80 is a special substance that acts as an edge activator, making vesicles more stretchy. When you have vesicles that are bigger than the tiny holes in a biological membrane, Tween 80 can temporarily make these holes bigger. This allows vesicles to easily move from the outside to the inside of the membrane.

Ethanol It helps to improve the way drugs are trapped and distributed inside the vesicles. It also makes the membrane of these vesicles thinner, which helps the spanlastic system trap drugs more effectively. Furthermore, it changes the overall charge of the system to become more negative and stablize the formulation(4, 8).

Application of spanlastic

1 Optic drug application

The delivery of drugs to the eyes is quite challenging because of various barriers in front of and within the eye itself. These barriers make it difficult for drugs to reach their intended target effectively. Spanlastics, a unique type of carriers, are designed to overcome these challenges and deliver drugs precisely to specific parts of the eye.

Spanlastics can transport drugs to both the front and back parts of the eye. The back part includes structures like the choroid, epithelium, and vitreous cavity, while the front part consists of the corneal membrane and aqueous humor. The versatility of spanlastics allows them to deliver both fat-soluble and water-soluble drugs to various parts of the eye, helping to improve the bioavailability of medications for eye treatments (7).

Case study: Elazreg and his research team devised a method using spanlastics to contain methazolamide. They combined Span 60 with various edge activators, including Tween 80, Tween 60, Brij 35, and Brij 58, in different proportions. The outcomes of their study demonstrated that the finely-tuned formulation had the right particle size and encapsulation efficiency, making it a promising candidate for future studies exploring drug delivery systems for other anti-glaucoma medications(9).

2 Oral administrations

Oral medications encounter bioavailability challenges due to several factors, such as limited solubility, the need for frequent dosing, potential drug interactions, unpredictable absorption rates, initial metabolism in the liver, and the possibility of causing side effects throughout the body.

Case study:

The data gathered suggests that a 1% CMC transbuccal wafer formulated with nano-spanlastics offers a promising enhancement in the delivery of CRV (presumably a drug) through the buccal route. This improved delivery method appears to be more effective in protecting heart tissue when compared to the current product, Carvid®(10).

3 Dermal drug administrations

Transdermal medication administration utilizes spanlastics and offers several advantages. One of these benefits is the avoidance of hepatic metabolism, which leads to improved drug bioavailability and effectiveness. Transdermal medication delivery is utilized to achieve a continuous and consistent release of the drug (11).

Case study

The pharmacokinetic study revealed a substantial improvement in the bioavailability of the optimized gel containing Fluvastatin sodium (presumably a drug) when compared to the oral drug solution, with an approximately 2.79-fold increase. Furthermore, the half-life (t1/2) of the drug was extended to approximately 6.49 ± 0.67 hours with the gel.

In addition to these findings, the developed transdermal formulation exhibited strong positive effects in a rat model of CFA-induced arthritis. These effects were characterized by a significant reduction in rheumatoid markers, as well as anti-inflammatory and antioxidant properties. Most importantly, there was a notable suppression of p38 MAPK expression when compared to both the arthritic control group and the group treated with oral FVS.

These results highlight the potential of SNVs (presumably a delivery system) for facilitating non-invasive transdermal delivery of FVS and providing a platform for the treatment of rheumatoid arthritis (12).

4 Nasal medication administrations

One approach is the intranasal route, where a substance travels directly from the nasal cavity to the central nervous system through the trigeminal pathway. This happens after crossing the blood-brain barrier (BBB) and passing through the olfactory region. A method to facilitate the delivery of medication across the BBB and into the brain for a specific purpose involves the use of spanlastic dispersion.

Case study

The novel carbamazepine spanlastic formulation was developed successfully with a high viscosity, making it suitable for use in the nasal route without the need for a gelling agent. Furthermore, it displayed an improvement in in-vitro drug release characteristics and remained stable for six months when stored at 25°C.

In behavioral assessment tests using the elevated plus Maze test, the optimized spanlastic formulation exhibited a reduced latency time. Additionally, when compared to the oral CBZ suspension, F0 showed a decrease in serum eNOS and TNF-α levels and an increase in GSH levels. Histopathological analysis revealed greater CBZ uptake by the brain.

This indicates that the novel CBZ spanlastic vesicles have been successfully formulated and evaluated for administration via the nasal route to target the brain (13).

5 Transungal drug delivery

The size of spanlastics plays a crucial role in transungual applications, affecting permeability, biological behavior, and effectiveness. Smaller particle sizes facilitate deeper penetration of the nanovesicles. Nanosized spanlastics, owing to their ease of penetration and diminutive size, can readily traverse the transungual barrier.

Case study

The optimized spanlastic vesicles loaded with efinaconazole exhibited specific characteristics, including a particle size of 197 nm, a transparency level of 91%, a relative deformability of 12.5 minutes, and a dissolution efficiency of 81.23%. These spanlastic vesicles were then integrated into a gel and assessed for transungual delivery in an ex vivo setting.Hence this vesicles considered as treatment through transungal drug delivery (14).

Methods to prepare Spanlastic

1 Ether injection technique

This method involves the slow injection of a surfactant into 20 ml of ether, using a 14-gauge needle, at a rate of 25 ml per minute. This is done into a 4 ml aqueous phase that has been heated to a temperature of 60 degrees Celsius. Afterward, a rotary evaporator will be employed to remove the ether solvent. As the organic solvent evaporates, it will lead to the creation of single-layered vesicles (15).

2 Ethanol injection technique

This method can be employed to produce spanlastics with a predetermined ratio of non-ionic surfactant to edge activator. The medication intended for encapsulation is dissolved in ethanol along with the non-ionic surfactant. The lipid solution is then subjected to sonication for five minutes.

Next, this lipid solution is steadily introduced into a heated aqueous phase that contains an edge activator, such as Tween-80. The aqueous phase is continuously stirred at 800-1600 rpm and maintained at a temperature of 70–80°C for 30 minutes, using a magnetic stirrer. Subsequently, the mixture is stirred for an additional 30 minutes at a lower temperature. To reach the desired volume, the final formulation is adjusted to 10 ml using distilled water (16).

3 Thin film hydration techniques

The procedure begins with the precise weighing of Span 60, which is then introduced into a flask with a flat bottom. In this flask, Span 60 is dissolved in chloroform, leading to the formation of a thin coating on the inner walls of the flask as the organic solvent evaporates. This evaporation process occurs under vacuum conditions at 55°C, utilizing a rotary evaporator set at 90 rpm.

Following this step, a specific quantity of medication is dissolved in an aqueous phase using a combination of the chosen Edge Activator (EA) and a co solvent. This prepared aqueous phase is then added to the flask containing the previously deposited thin film.

The flask is once again attached to the rotary evaporator and rotated for 30 minutes under normal pressure conditions, at a temperature of 60°C, and a speed of 90 rpm. This rotation ensures the complete removal of the lipid film from the inner walls of the flask.

The resulting mixture is then left at room temperature for 2 hours to allow for thorough hydration. Finally, it is placed in a refrigerator at 4°C overnight for further processing (17).

4 Hand Shaking Technique

To begin the process, surfactants are first dissolved in an organic solvent, such as ether, chloroform, or benzene. The subsequent step involves evaporating the solvent under reduced pressure, typically using a vacuum evaporator in a round bottom flask. This evaporation results in the creation of a surfactant layer.

Following this, the surfactant layer is rehydrated by adding an aqueous solution containing drugs, all while continuously agitating the mixture. This rehydration process causes the surfactant layer to expand and swell. Over time, these swollen amphiphiles within the layer reorganize themselves, ultimately forming vesicles that encapsulate the drug (18).

5 Micro fluidization Techniques

In this approach, two separate streams, one containing the drug and the other containing the surfactant, are brought into contact at extremely high speeds within precisely defined micro channels located within an interaction chamber. The energy supplied to the system during this process remains concentrated within the realm of spanlastics formulations. This method is referred to as the submerged jet principle. It leads to improved consistency, reduced particle size, and greater reproducibility in the formulation (19).

6 Sonication Techniques

In this procedure, a portion of the drug is prepared in a suitable buffer, and this preparation is then added to the surfactant mixture in a 10 ml glass vial. The mixture is subjected to probe sonication using a titanium probe (20).

Characterization of Spanlastic

1 Transmission electron microscope

TEM the is employed for morphological analysis to assess and identify characteristics such as lamellarity, size uniformity, shape, and physical stability properties of spanlastics (21).

2 Zeta potential

The zeta potential of the spanlastic formulation is determined using a zeta sizer instrument. This analysis helps in understanding the causes of flocculation, aggregation, or dispersion in the formulation(22).

3 Optical Microscopy Technique

This method is also applied for observing and measuring the size and configuration of spanlastics. About 100 spanlastics are utilized to gauge their particle dimensions. In this process, the size of the stage micrometer aligning with the eyepiece micrometer is noted, and subsequently, the size of the formulation is calculated.

Modern techniques, such as laser-based mastersizer, are currently employed to determine the spanlastics' size distribution, average surface diameter, and mass distribution. Dynamic light scattering (DLS) analysis using tools like the Malvern zeta sizer is also utilized to evaluate size distribution, mean diameter, and zeta potential (23).

4 Vesicle Size & PDI

Utilizing dynamic light scattering, it is possible to measure both the size and the polydispersity index (PDI) of the formulation (24).

5 Measurement of elastic properties

Elasticity is quantified through the deformability index (DI). To assess the elasticity of nano-spanlastics, an extrusion method is employed. Nano-spanlastics are generated and extruded for a duration of 10 minutes under a consistent vacuum pressure using a polycarbonate membrane featuring 200-nanometer pore width, which serves as the filtering membrane.

Deformability index (DI)= J[rv/rp]2×100

•J represents the weight of the sample in grams that has been pressed and passed through a polycarbonate filtration membrane in a span of 10 minutes.

•rv denotes the size of spanlastic vesicles after the extrusion process.

•rp signifies the pore size of the polycarbonate membrane filter(25).

6 Differential scanning calorimetry

Differential scanning calorimetry (DSC) is utilized to determine the thermal characteristics of a specimen. In this study, a 40-liter aluminum crucible is accurately weighed, and it contains a sample ranging from 5 to 10 milligrams of the extrudate. The crucible is then sealed tightly. All tests are conducted within a temperature range of -20 to 150 degrees Celsius, with a heating rate of 10 degrees Celsius per minute, under a nitrogen atmosphere. The resulting thermograms are scrutinized for any anomalies, such as significant shifts or the emergence or disappearance of new peaks (26).

7 In vitro drug release studies

In the in vitro drug release experiments, Franz diffusion cells were utilized. These cells consisted of two compartments: the donor compartment and the receptor compartment, separated by a cellophane barrier.

In the setup, the receptor compartment was filled with phosphate buffer of pH 6.8. On one side of the dialysis membrane, a precisely weighed amount of spanlastic was placed. The temperature was maintained at 37°C, and the contents were constantly mixed by magnetic stirring at a rate of 500 rpm.

At specified time intervals, samples from the acceptor chamber were withdrawn and immediately replaced with an equal volume of buffer solution. The collected samples were then analyzed spectrophotometrically at their maximum absorption wavelength (max) after appropriate dilution (27).

Conclusion

The development of innovative vesicles based on surfactants, specifically Spanlastics, presents a non-invasive approach to drug delivery that eliminates the need for frequent dosing. Spanlastics effectively address challenges related to drug insolubility, instability, low bioavailability, and rapid degradation. As a result, Spanlastics represent a significant breakthrough in nanovesicular drug delivery systems. These versatile vesicular systems have the potential to enable precise drug delivery for both lipophilic and hydrophilic drugs. Currently, this system is in use for delivering drugs to various areas, including ocular, oral, and topical.

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