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THE EVOLUTION OF VESICULAR CARRIERS: SPANLASTICS AS A BREAKTHROUGH PLATFORM

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ABSTRACT

The drug distribution to the target areas can be limited due to the presence of biological and physiological barriers which hinder therapeutic effectiveness. Various conventional dosage forms, such as tablets, capsules, solutions, suspensions, and emulsions, are generally used in treatment of disease; But, these systems usually have bioavailability issues and poor patient compliance, resulting in poor clinical outcomes. Novel drug delivery system (NDDS) has been created to overcome this limitation, such as nanoparticles, nanoemulsions, liposomes, and dendrimers, which results in enhanced drug stability, controlled release, and efficiency in drug targeting. A further improvement in vesicular drug delivery technology, i.e, Spanlastic was presented in 2011 by Kakkar and Kaur. These are extremely elastic and deformable vesicular carriers consisting of non-ionic surfactants & Edge activators. In this, aqueous drug presented in a core which is entrapped in a flexible bilayer membrane due to the self-assembly property of surfactant. These system ensures effective penetration across biological membranes as it is possessing extraordinary deformability. This paper provides an overview of the structural properties, content, preparation processes, evaluation criteria, and therapeutic applications of Spanlastics. Their potential role as effective carriers for site-specific medication delivery and better therapeutic performance is especially highlighted.

KEYWORDS: Spanlastics, Non-ionic surfactants, Deformable vesicles, Elastic vesicular systems, Edge activators, etc.

INTRODUCTION

A vesicular drug delivery system (VDDS) refers to well-organised structures made up of one or several concentric bilayers, created through the self-assembly of amphiphilic components when water is present. These are especially crucial for the precise delivery of medications due to their capability to concentrate the drug's effects at the specific site or organ of action, thus reducing its concentration in other areas of the body.[1] Lately, there has been a growing fascination with well-organised VDDS, consisting of one or more concentric bilayers formed by amphiphilic building blocks in the presence of water. Many various forms of VDDS have been created, such as liposomes, niosomes, transferosomes, cubosomes, ethosomes, virosomes, phytosomes, and spanlastics.[2]

Spanlastics (SPLs) are innovative drug delivery systems that are newly developed surfactant-based small carriers, exhibiting remarkable elasticity, introduced by Kakkar and Kaur in 2011. The word “Spanlastic” is derived from span + elastic, with the medication (core) being encapsulated in a bilayer. SPLs consist of a surfactant, primarily span, along with edge activators like Tween 80 and ethanol, which enhance drug entrapment in the vesicle, improve stability through steric stabilisation, increase treatment efficacy, and minimize the adverse effects of drugs.[3,4] These novel nanovesicles are intended to address the limitations of liposomes, such as chemical instability. Liposomes are chemically unstable due to their tendency to oxidize and fluctuate in phospholipid purity. Edge activators give these vesicles their flexibility. Recently, interest has resurfaced in employing spanlastics to administer ophthalmic, oral,

topical, nasal, and trans-ungual medications site-specifically.[5,6]

CHARACTERISTICS OF SPANLASTIC

1. Spanlastics promote drug efficacy by increasing stability, bioavailability, and lowering degradation rates.
2. Spanlastics aid in drug delivery to numerous body parts, including the eyes, mouth, skin, nose, and nails.
3. Spanlastics are stable and osmotically active, allowing them to entrap solutes.
4. The bilayer in the enclosed medicine allows for regulated delivery.
5. Their structural flexibility allows for customization to meet specific requirements.
6. Spanlastics shield medications from biological environments, improving their availability at the location.[7,8]

ADVANTAGES

- The spanlastics system allows hydrophilic or lipophilic medications to permeate biological membranes, including the cornea.
- Spanlastics are naturally biodegradable and do not cause an immunological reaction.
- Spanlastics boost bioavailability by protecting the medicine and allowing it to reach the target region without being shredded, compared to conventional methods.
- They sustain osmotic activity and stability, improving drug stability after encapsulation.
- Prolonged medication administration causes delays in drug clearance from the systemic circulation.
- Lipid bilayers safeguard medications from harsh biological conditions.
- These medications can be administered orally, parenterally or topically.
- Surfactants do not require specific handling or storage conditions.[9]

DISADVANTAGES

- Surfactants employed in SP production have low water solubility.
- SPs are unstable in acidic environments, as the membrane readily breaks down.
- The two most popular ways for creating MLVs are sonication and extrusion, both of which take a lot of time and specialized equipment.[10]

MORPHOLOGY[11]

Spanlastic has a similar structures compared to liposomes having concentric layers. It can either be unilamellar and multilamellar. Depending on their size, these can be small unilamellar vesicles (SUVs) measuring 10-100 nm or large unilamellar vesicles (LUVs) ranging from 100-3000 nm. Studies show that MLVs have longer retention times than SUVs with the same lipid content. The term "spanlastic systems" describes spherical structures made of amphiphilic molecules that have great properties for bioencapsulation.

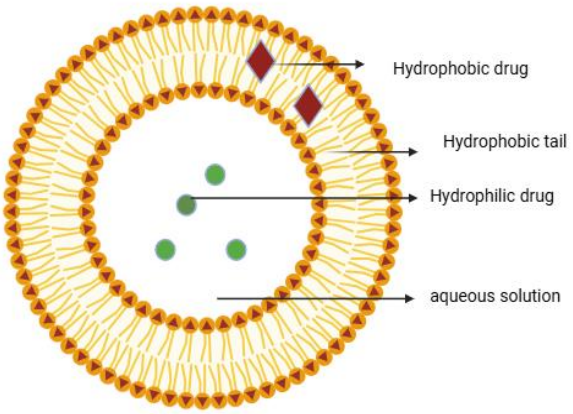

Fig 1: Structure of Spanlastic.

CLASSIFICATION OF SPANLASTICS[12]

Similar to liposomes, nano-spanlastics can be classified into three categories based on the quantity and dimensions of the vesicles they comprise, as illustrated in Fig 2.

1. Multi-lamellar vesicles [MLV]: Presence of several bilayers is the structural attributes of multi-lamellar vesicles. MLV usually exist in the size range of 0.5 to 1.0 µm in diameter. These are generally easy to prepare and also remain stable for extended period of life.

2. Large unilamellar vesicles [LUV]: Compared to MLV's these LUV consist of only single layer. The size of LUV varies between 100 nm and 1 µm. This type of vesicle has a high aqueous-to-lipid component ratio, which aids in the entrapment of a significant quantity of drugs within the core.

3. Small unilamellar vesicles (SUV): These are comparable to large unilamellar vesicles (LUV) as they also consist of a single bilayer; however, they are smaller in dimension. Their size can range between 20-100nm. SUVs are generated from multilamellar vesicles (MLVs) using several techniques, including the sonication method, French press method, and extrusion method.

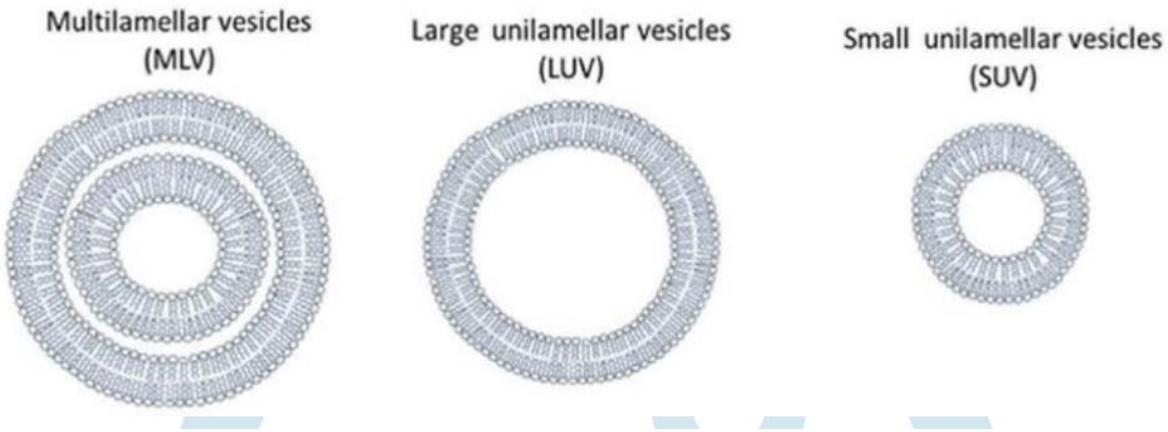

Fig 2: Classification of Spanlastic.

COMPONENTS[13,14]

Spanlastics composed of essential ingredients such as non-ionic surfactants and edge activators.

Non-ionic surfactants: These are surface-active substances that reduce the interfacial tension between two liquids. Their heads lack charged groups, making them non-ionic. A key type of non-ionic surfactants includes sorbitan alkyl esters, known as Spans. To form the vesicular structures of spanlastic, spans arrange themselves into concentric bilayers. The polyoxyethylene sorbitan part of the molecule, called Span, varies and includes types such as Span 80 (monooleate), Span 60 (monostearate), Span 40 (monopalmitate), and Span 20 (monolaurate). The stability of these vesicular formulations largely depends on the type of Span used. Vesicles with Span 80 and Span 40 tend to break down, aggregate, and are unstable. Conversely, using saturated alkyl chains in Span 60 enhances stability.

Edge activators: These are ingredients that increase the flexibility of the outer lipid layer by incorporating substances that blend well with water and fat. This integration facilitates easier passage through the layer. Additionally, edge activators reduce tension between layers. When we use edge activators, they often form larger, rounder structures, which can lead to smaller particle sizes. Tween 80 is a specific edge activator that enhances vesicle elasticity. When vesicles are larger than the openings in a biological membrane, Tween 80 can temporarily enlarge these openings, allowing vesicles to move more easily from the outside to the inside membrane.

Ethanol: It helps to improve how drugs are trapped and distributed inside the vesicles. It also makes the membrane of these vesicles thinner, which allows the spanlastic system to trap drugs more effectively. Additionally, it changes the overall charge of the system, making it more negative and stabilising the formulation.

MECHANISM OF ACTION OF SPANLASTIC[15]

Edge activators promote the vesicles to deform by inducing the reduction in the stability of lipid layers thereby increased vesicle deformability in presence of edge activators can be seen. The creation of holes in the membranes as well as other lipid structures contributed by surfactants. If the concentration exceeds beyond a normal range, results in the lysis of membrane. As a result, elastic vesicles can squeeze through intercellular spaces due to the membrane's variable bending energy when a water gradient is present.

Drug vesicles can penetrate through membrane via two mechanism.

- The elastic vesicles interact with the epithelial cell membrane and act as penetration enhancers. They also change the intercellular lipid layers.
- The elastic vesicles can serve as drug-carrier systems. Intact vesicles carrying the drug pass through the intercellular spaces and cross the biological membrane.

  Several factors help these carriers pass through successfully:
  - The elasticity of the vesicle bilayers, which is highly dependent on stress.
  - The presence of an osmotic gradient.
  - The surfactant causes solubilization (lysis) at higher concentrations.

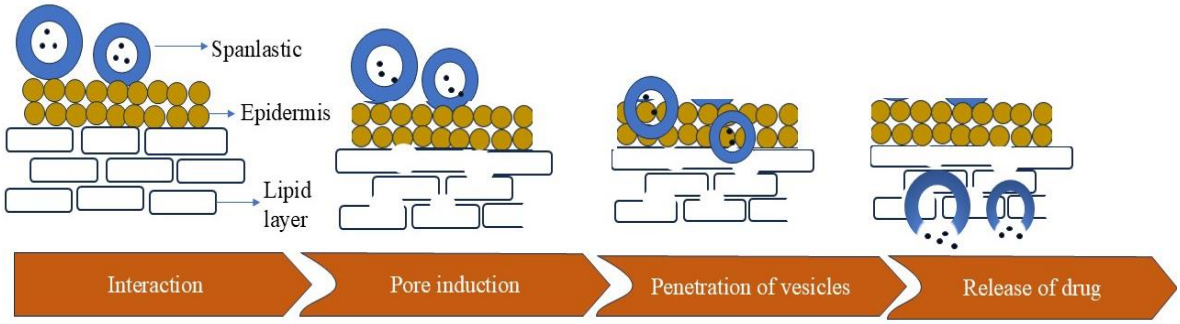

Fig 3: Mechanism of action of Spanlastic.

Factors affecting physico-chemical properties of spanlastics[16]

1. Membrane supplements

The stability of the spanlastic can be increased by adding more additives to the formulation in addition to the main surfactant and active ingredient. The stability, shape, and permeability of vesicle membranes are all influenced by various additives; tweens, for instance, can make the generated vesicles more flexible, making it easier for them to enter the desired area.

2. Drug Characteristics

The chemical structure, molecular weight, lipophilicity, hydrophilicity, and hydrophilic-lipophilic balance of the medication can all affect its entrapment efficiency. The size of the vesicle may rise as a result of pharmacological entrapment. The drug particle interacts with the surfactants' head group, which probably causes the polymer's charge to rise. The size of the vesicles increases as a result of the surfactant bilayers being repelled from one another.

3. Hydration Temperature

The size and shape of an object can also be influenced by the temperature at which it is hydrated. The vesicle assembly process is affected by temperature variations throughout the system. Temperature variations can also cause changes in vesicle morphology. At 25 ^{0}C, C16G2:solulan C24 (91:9) polyhydral vesicles are created; however, at 45 ^{0}C, these vesicles change into spherical vesicles. A cluster of spherical but considerably smaller nano-vesicles forms after the spherical vesicles are cooled from 55 ^{0}C to 49 ^{0}C.

4. Surfactant Type and Content

The mean size of the vesicles grew in proportion to the HLB value of the surfactants, for example, from span 85 (HLB 1.8) to span 20 (HLB 8.6). It could be because the surface free energy of the surfactant decreases as its hydrophilicity increases. If the substance is in a gel state, the alkyl chain has a tidy and well-ordered structure, whereas in a liquid condition, the bilayer structure is more disordered. The gel-liquid phase transition temperature, often known as the TC, is used to characterize lipids and surfactants. The HLB value influences the entrapment efficiency of spanlastics; for example, spanlastics have a high entrapment efficiency at an HLB value of 8.6, whereas an HLB value of 14 to 17 is unsuitable for their formulation.

5. Surfactant Structure

The essential packing value also has an impact on the geometry of the vesicles produced throughout the process. The critical packing parameter indicates that vesicle geometry is predictable. The formula for determining the critical packing parameter is as follows.

Critical packing parameter (CPP) = v/ lc*a0

Where, V = volume of hydrophobic group,
lc = length of hydrophobic group at critical point,
a0 = hydrophilic head group area.

Method of preparation

Ether Injection Method[17]

This involves preparation of organic phase, where the surfactant dissolved in a ether which is injected slowly into aqueous phase maintained at 60^{0}C via syringe to form tiny droplets. Ether evaporates quickly as it enters the hot aqueous solution results in the self-assembly of single layered vesicles (unilamellar vesicles) by surfactants. Further ether is been removed using rotary evaporator ensures no solvent left and stable vesicle formation.

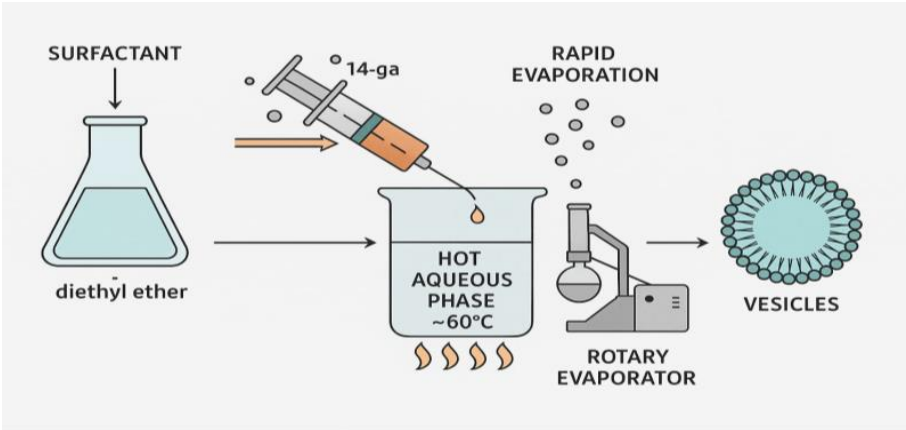

Fig 4: Ether injection method.

Ethanol injection method[18]

Here, Ethanol constitutes the major component. In this, lipid components and drug is dissolved in a ethanol which is injected into aqueous phase containing surfactants. As there's a contact between organic and aqueous phase, leads to the sudden diffusion of solvents into water due to variation in the solubility profile of lipids thereby, formation of vesicles with appropriate lamellarity and size.

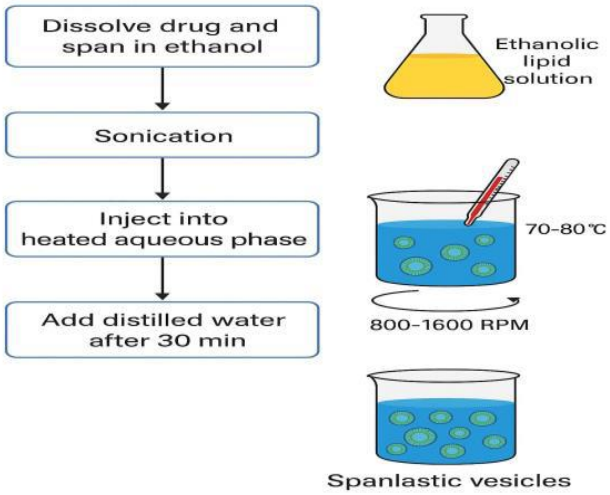

Fig 5: Ethanol injection method.

Thin film hydration method[19]

Lipid / surfactant is dissolved in a organic solvent using a round bottom flask and evaporated under vacuum using a rotary evaporator at 60^0C and 90 rpm. Which results in the formation of thin dried film and it is hydrated with aqueous solution preferably phosphate buffer saline (PBS) containing drug and non-ionic surfactant. Due to hydration, film swells, and forms a tiny spherical vesicles containing the drug. Followed by sonication of prepared dispersions, to optimize particle size and underwent four consecutive freeze-thaw cycles –8 °C for 8 hours and 25 °C for 1 hour for the better entrapment of drug inside the nanosystem.

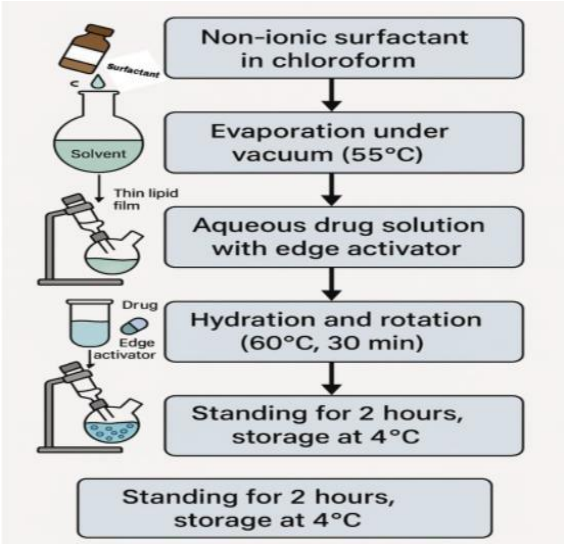

Fig. 6: Thin film hydration method.

Extrusion Method[20]
The component like surfactant and charge inducing agent dissolved in an organic solvent which is then removed using a rotary vacuum evaporator to create a thin film. Further it is hydrated with an aqueous drug solution. The resulting suspension is passed through a polycarbonate membrane with an average pore size of 0.1 microns. The extrusion process is repeated up to eight times to ensure the vesicles are of uniform size.

Microfluidization Method
This works on high- pressure fluid interaction. Containing two liquid streams one with drug in aqueous phase and other stream contains surfactant/lipid components which are forced at a very high pressure through microchannels using a device known as microfluidizer. As a result of collision beween two streams at a very high shear rates thereby, large vesicles breaks down to uniform sized vsicles and ensure better drug encapsulation.

Evaluation
To assess the in vitro and in vivo properties of the Spanlastics formulation, it is essential to implement a precise and consistent quality control procedure.

1. Morphological Examination[21]
For the morphological analysis, transmission electron microscope is used to identify the lamellarity, size, shape, and physical stability properties of spanlastics.

2. Determination of vesicle size and PDI[22]
The diluted formulation's vesicle size and polydispersity index (PDI) were measured using a Zetasizer. The measurements took place at a temperature of 25 ± 2 °C. To obtain accurate measurements, the samples were diluted by a factor of 10 with distilled water before analysis.

3. Number of spanlastic vesicles per cubic millimetre[23]
To determine the number of spanlastic vesicles per cubic millimetre, the produced formulation was diluted, and the vesicles were counted in 80 counting chamber squares with a Neubauer haemocytometer under an optical microscope. The total number of spanlastic vesicles per cubic millimetre was obtained using,

$$\text{Total number of vesicles per cubic mm} = \frac{\text{Total no. of vesicles counted X Dilution factor X 4000}}{\text{Total no. of squares counted}}$$

4. Entrapment efficiency[24]
The indirect approach and ultracentrifugation were used to calculate spanlastics' entrapment efficiency (EE%). The spanlastic dispersion (1.5 mL) was centrifuged at 4°C and 15,000 rpm for 1.15 hours. Spectrophotometric analysis was used to calculate the supernatant's free drug concentration by reading at the maximum absorbance wavelength of spanlastics in the appropriate solvent and after adequate dilutions.

To calculate the (EE%) of drug loaded spanlastics,

$$\% \text{ EE} = [(\text{Total amount of drug} - \text{free drug in supernatant}) / \text{Total amount of drug}] \times 100.$$

5. Zeta potential[25]
Spanlastic formulation was diluted with deionized water (1:100) and homogenized at 25°C, and the zeta potential was determined using Malvern Zetasizer.

6. Elasticity measurement[26]
The elasticity of the Spanlastics aqueous dispersion was evaluated using the extrusion technique. Under a constant pressure of 2.5 bar, the formulation was diluted and extruded through a microporous filter with 220 nm pores. The percentage of deformation was computed by comparing the particle size before and after extrusion.

7. Drug content[27]
A known volume of formulation is diluted with solvent and stirred to disrupt vesicles. The solution is filtered, suitably diluted, and analyzed spectrophotometrically at λmax.

8. Differential scanning colourimetry[28]
For the thermal examination of spanlastic formulation and to understand the compatibility of medication and other spanlastic constituents differential scanning colorimetry which is calibrated previously is used. Standard aluminium pan is used to hold the spanlastic formulation and heated between 10 and 300 ^{0}C at a rate of 10 degrees Celsius per minute while nitrogen is continuously purged at a rate of 25 millilitres per minute.

9. In vitro release study[29]
Modified Franz diffusion cell method is the most commonly used method to evaluate in-vitro release study of formulations. Mainly, it consists of donor and receptor compartment, the former is sealed with previously soaked dialysis membrane and loaded with specific amount of drug induced spanlastic formulation and the latter consist citrate–phosphate buffer serves to be a receptor medium to influence diffusion of drug through membrane. The entire set up is maintained at a temperature of about 37 ± 0.5 °C and continuously stirred at 50 ± 10 rpm using a thermostatic shaker. At a specific time interval, over a period of 6 hours, from the release medium 2ml is withdrawn, and replaced with equivalent volume of fresh buffer solution in order to maintain sink condition. Further, the amount of drug diffused form formulation is determined using UV Spectrophotometrically.

10. Stability studies[30]
Stability studies for the spanlastic formulation were conducted for a period of 3 months. At 40 ± 0.5 °C and 75 ± 5% relative humidity (RH), the stability investigation was conducted. At the conclusion of the three-month study period, the physicochemical parameters of the tested formulations were assessed.

Measurements made in triplicate were reported as the mean ± SD (n = 3).

APPLICATIONS

Nano-vesicles first emerged in the cosmetics industry and are currently gaining popularity as a vesicle drug delivery technology. Due to their ability to entrap both hydrophilic (lipophobic) and hydrophobic (lipophilic) medicines. Spanlastics may be a great mechanism for drug delivery. The nano-vesicle system has already been designed for pharmaceuticals such as doxorubicin, vaccines, insulin, siRNA, and many more, with a wide range of applications. These vesicles can also be employed as a co-delivery method because they can easily accommodate two distinct types of medications to provide the necessary therapeutic effects. In terms of formulation, these vesicles have biocompatibility, low toxicity, biodegradability, good stability, low cost, and are easy to store. Because of their small size, various alterations of these nano vesicles can be used in cancer treatment, resulting in increased permeability and retention duration in tumor tissue. They can be conveniently delivered by different ways, including intravenously, orally, and transdermally. The following are some of the applications for this nano-vascular medication delivery system.

1. Ocular delivery[31]3

Many eye illnesses are related with bacterial infections, including conjunctivitis, blepharitis, endophthalmitis, and keratitis. One disadvantage of topically applied conventional ocular delivery systems is the substantial and rapid loss of medication due to nasolacrimal outflow and fast tear fluid turnover. Recently, spanlastics (SLs) have been developed, a surfactant-based nanovesicular elastic carrier system. Researchers have previously employed SLs to improve both corneal penetration and skin delivery of different medications, thus it can be a viable technique for ocular delivery.

2. Oral delivery[32]

The oral route is the most common method of medicine administration, although oral drugs have bioavailability concerns for a variety of reasons, including low solubility, frequent dosing, drug interactions, variable absorption, first-pass metabolism, and systemic side effects. To overcome the problems of oral medication delivery, a novel surfactant-based vesicular system was developed. Using enteric-coated spanlastic dispersions, such as pravastatin sodium, provides for controlled release and precise distribution to the duodenum. When compared to an aqueous medication solution, it increased the medicine's oral bioavailability.

3. Transdermal delivery[33]

The transdermal route is widely regarded as a patient-friendly approach because it eliminates GIT side effects, fluctuating pH values along the GIT, and first-pass metabolism, which frequently requires oral medication administration. It also gives a consistent and persistent pharmacological action in the body. Nonetheless, the barrier aspect of the stratum corneum (SC) is considered the most significant hurdle to transdermal distribution. Because of their ultra deformability, spanlastic nanovesicles can breach the SC fence and enter deeply into the target dermal tissues by squeezing themselves through SC intercellular domains. This new nanocarrier can improve transdermal medication penetration.

4. Nasal delivery[34]

Several investigations have shown that spanlastics can transport certain medications to the brain via nose-to-brain transfer. For example, Saleh et al. reported increased drug penetration across the nasal membrane in zolmitriptan-loaded spanlastic formulations, confirming the promising impact of intranasal dosing for brain delivery.

5. Transungual delivery[35]

Onychomycosis (tinea unguium) is a fungal infection of the nails of the toe or finger. Topical treatment of onychomycosis is challenging because locally applied drugs show poor permeability across the nail plate and most antifungal drugs have poor solubility and permeability.

Contrast to conventional drug delivery sytem, topically applied systems with nanosized drugs offer the benefits of improved transungual penetration with minimal systemic adverse effects. Spanlastic particles efficiently accommodate poorly water-soluble drugs and show improved encapsulation and, therefore, were selected for exploring the improvement in transungual penetration.

6. Peptides and Proteins[36]

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 (SIF) and simulated gastric fluid (SGF). The results showed that the formulation has increased bioavailability and is protected from degradation.

CONCLUSION

The development of innovative surfactant-based vesicles by Spanlastics provides a non-invasive technique for delivering drugs to their target sites without the need for repeated drug administration. They address drug insolubility, instability, limited bioavailability, and rapid degradation. As a result, Spanlastics have the potential to be a game changer in the nano vesicular drug delivery system. These vesicular devices can be used to deliver

lipophilic and hydrophilic medicines with precise site-specificity. This technique is now being used to administer medications to the ocular, oral, topical, trans-ungual, nasal, and middle ear.

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