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EXPLORING SPANLASTIC: AN ADVANCED VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT
In recent years, Vesicles have become the choice of drug delivery. Vesicular drug delivery systems are valuable in evading drawbacks that are associated with conventional dosage forms. Hence Novel drug delivery system such as liposomes, nanoparticles, nanoemulsion, nanosuspension, are been designed to achieve better delivery of drug. In 2011, Spanlastic is evolved as one of the better vesicular drug delivery system. These are the elastic vesicular nanocarrier that entraps the drug in the core cavity in the form of bilayer. They are made up of surfactants that are surrounded by aqueous solution. Spanlastics are chemically stable when compared with other vesicular nanocarriers. These offers targeted delivery and regulated release of medicinal substance and improves drug availability at the site of action. The current review summarizes the structure, advantages, composition, mechanism of drug penetration, method of preparation, evaluation and applications of Spanlastics in drug delivery and targeting.

KEYWORDS: Spanlastics, Vesicular drug delivery, Nanocarrier, Thin film Hydration, Modified Spray technique.

INTRODUCTION
In the past few decades substantial attention has been made on the development of new drug delivery systems.[1] Novel vesicular drug delivery systems have made notable progress in the field of nanotechnology. As these systems have ability to carry a variety of drugs and have been widely used for various purposes, like drug targeting, sustained release, and permeation enhancement of drug.

Conventional drug delivery for all types of treatment is not effective due to limitation in permeation of drugs into cells. To improve bioavailability at the site of diseases by reducing the harmful side effects of conventional drug delivery systems and to overcome the problem of degradation of drug and drug loss, vesicular system are emphasized recently.[2]

Spanlastics, an elastic, deformable surfactant-based vesicles that are used has vehicles have the potential to delivery the drug in wide array. Lately, numerous research papers have been published exploring the potential of spanlastics to act as drug delivery system for wide variety of drugs as they offer targeted delivery of drugs.[3] The Spanlastic (Span + Elastic) was first termed in 2011.

These are very elastic and flexible carriers that resemble transferosomes. The permeability of these deformable vesicular carrier systems is greater than that of drug solutions. The substance is enclosed in a nonionic surfactant-formed vesicle. Spanlastics are microscopic and small. These unique vesicles are designed to overcome the limitations of liposomes, like chemical instability. Due to their tendency for oxidative breakdown and varying phospholipid purity, liposomes are chemically unstable. Edge activators give these vesicles their elasticity. A distinct type of vesicular carrier termed spanlastics delivers ocular, oral, topical, nasal, and trans ungual medication site-specifically.

Salient Characteristics of Spanlastics
1. Spanlastics materials traps stable solutes.
2. They are osmotically active
3. They utilize their bilayer, which supports the release of enclosed drugs, to release the drug in a controlled manner
4. They have malleable structural characteristics, allowing them to be modify as their specific requirements.
5. By shielding it from a biological environment, spanlastics improve the availability of the drug at the target site.[4]

ADVANTAGES[5]

1. The spanlastics system aids the penetration of hydrophilic or lipophilic medicines through biological membranes, including the cornea.
2. Spanlastics do not provoke an immune response.
3. They are biodegradable.
4. They have increased bioavailability in contrast to traditional one.
5. They are osmotically active and stable, which contributes to the enhancement of the medicine's stability once it has been encapsulated**.**
6. During the process of prolonged drug administration, they delay drug molecule clearance from the systemic circulation.
7. They protect the medication from the hostile conditions of the biological environment by enclosing it in a lipid bilayer structure.
8. Oral, parenteral, ocular, and even topical administration are all viable options for delivering them to the site of action
9. Surfactants are not subject to any particular conditions when being handled or stored.

DISADVANTAGES

1. It has a poor water solubility**.**
2. It is easily degraded in an environment similar to that of the stomach, which is acidic. This makes it susceptible to first-pass metabolism in the liver**.**
3. Extrusion and sonication are the most common methods for preparing Multi-lamellar Vesicles (MLV), both take a significant amount of time and necessary of using specialist machinery.

CLASSIFICATION[6]

Multi-Lamellar Vesicles (MLVs): are defined by their arrangement of multiple concentric bilayer membranes. These vesicles have a nested spherical shape. The size of MLVs ranges from 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): These are ranged from 20 nm to 50 µm. MLVs are produced by sonication method.

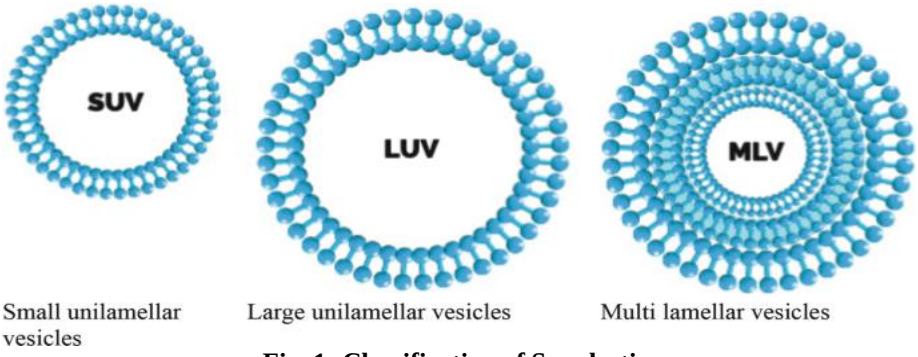

Fig. 1: Classification of Spanlastic.

STRUCTURE AND COMPOSITION[7,8,9]

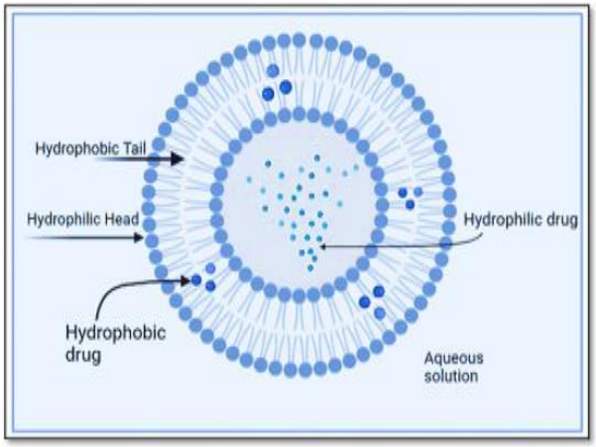

Fig. 2: Structure of Spanlastic.

Spanlastics systems are spherical structures that are made up of molecules that are amphiphilic molecules and consist of concentric bilayers. These Spanlastics are of different types depending on the size of vesicles, these can be Small unilamellar or Large unilamellar. These exhibit remarkable properties of bioencapsulating the matrix. Nonionic surfactant and Edge activator are the vital components of Spanlastics.

Non-ionic Surfactant

Non-ionic surfactants are also known as Surface active substance. They have amphiphilic nature with a nonpolar tail and a hydrophilic head. Non-ionic do not have any charge, making them more biocompatible and less toxic. Non-ionic surfactants can be employed as emulsifiers and wetting agents in order to enhance solubility and permeability of bilayers with higher stability. The non-ionic surfactants class is composed of sorbitan alkyl esters (Spans) which forms the concentric bilayers of spanlastics. The polyoxyethylene sorbitan component of the molecule, known as the span, are of various types, including Span 80 (monooleate), Span 60 (monostearate), Span 40 (monopalmitate), and Span 20 (monolaurate). Span 80 and Span 40 based vesicles exhibit significant disruption, aggregation, and instability. In contrast, the inclusion of saturated alkyl chains in Span 60 increases its sustainability.

Edge Activator (EA)

These surfactants possess a distinctive characteristic of exhibiting elevated hydrophilicity, as indicated by their high hydrophilic-lipophilic balance (HLB) value and these surfactants only have one chain. Edge activators are components that soften the bilayer, such as biocompatible surfactants, to which an amphiphilic substance is added to increase the permeability and flexibility of the lipid bilayer which increases the deformability of the bilayer by lowering the interfacial tension between them. Hence, Edge Activator is also known as "Bilayer softening Component". EAs have a tendency to produce larger spherical vesicles, which results in smaller particle sizes. Tween 80 is an edge activator that gives elasticity to vesicles. Any vesicle larger than the pore size of the biological membrane can easily transfer from the outside to the inside which results in tween-80's temporary increase in pore size. This promotes greater drug penetration and transfer of larger amounts of drugs inside the vesicle. These hydrophilic surfactants, destabilizes the vesicular membranes which yields in increased deformability.

Ethanol

The characteristics of these nano vesicular carriers are improved by ethanol. Its capacity to condense membranes makes it useful. It facilitates in enhancing drug entrapment and partitioning within the vesicles. The vesicular membrane's thickness is reduced, and the spanlastic system's ability to entrap drugs is enhanced. Additionally, by changing the system's net charge toward a negative zeta potential, it stabilizes the steric effect to some extent.

MECHANISM OF ACTION OF SPANLASTICS[10]

Edge activators (EAs) enhance the deformability of vesicles by inducing reduction in the stability of lipid bilayers, hence enhancing the deformability of vesicles. These vesicle's surfactant induces holes in membranes and other lipid structures, and also promotes lysis at greater concentrations. As a result, elastic vesicles can squeeze through intercellular spaces because of the membrane's variable bending energy in the presence of water gradient.

There involve two mechanisms for drug penetration:

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

Following factors contribute towards successful passage of these carriers:

- ✧ The highly stress-dependent elasticity of the vesicle bilayers
- ✧ The existence of an osmotic gradient
- ✧ The surfactant provokes a solubilization (lysis) in the higher concentration range.

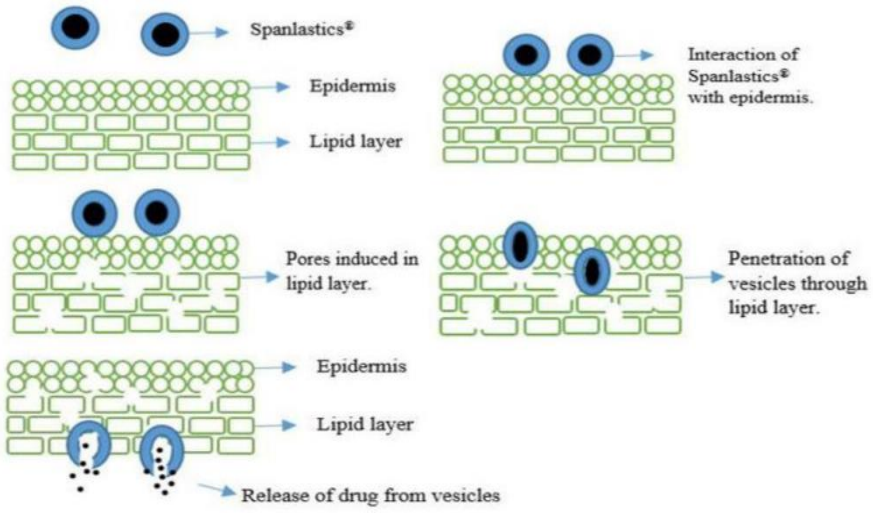

Fig. 3: Mechanism of Action of Spanlastic.

METHOD OF PREPARATION

1. Ether Injection Method[11]

In this method the surfactant is slowly injected into 20ml of ether using a 14- gauze needle at a rate of 25 ml per minute into a 4 ml aqueous phase that has been heated to 60^{o}C. Using a rotary evaporator, the ether solution will be evaporated. Once the organic solvent has evaporated, it will produce single-layered vesicles.

2. Ethanol Injection Method[12]

Specified amount of Span and drug is dissolved ethanol. Then the ethanolic solution is slowly injected into the aqueous solution containing Edge activator and water at temperature 65^{0}C. This mixture was agitated at 1000 rpm for 45mins. Then the volume is adjusted and then the dispersion will be formed and will be subjected to ultracentrifugation.

3. Thin Film Hydration Method[13]

Span 60 is accurately weighed and is added into a round bottom flask and dissolved in chloroform. The organic solvent is evaporated at 55°C under vacuum, using the rotary evaporator at 90 rpm which results in a thin film around the flask. Specified amount of drug is dissolved in the aqueous phase containing the selected edge Activator and cosolvent. This aqueous phase will be added to the deposited thin film. The flask will be again attached to the evaporator for rotation at 90 rpm and a temperature of 60°C under normal pressure for 30 min until all the lipid film are removed from the walls of the flask. After standing for an additional 2hrs at room temperature to hydrate entirely, the resulting distribution will be kept at a temperature of 4^0C overnight.

4. Modified Spraying Technique[14]

Spanlastics can be prepared by dissolving Span in ethanol to form organic phase which will be then transferred to a spray device. The aqueous phase is prepared of sucrose solution (9% w/v in double-distilled water) and heated to 60 °C in a closed system. The organic phase is then sprayed on the aqueous medium at a rate of 250 µL each 5 s while stirring at 1500 rpm and 60 °C. Finally, the resulted formulated nano dispersions will be subjected to freeze–thaw cycles.

EVALUATION OF SPANLASTICS

1. Morphological Examination[15]

The transmission electron microscope is used for morphological analysis to identify the lamellarity, size, shape, and physical stability properties of spanlastics.

2. Entrapment Efficiency[16]

The entrapment efficiency of Spanlastic formulation is studied using ultracentrifugation method. Prepared suspension is centrifuged at 2000 rpm for 20 mins. This leads to the separation of undissolved drug (appearing as supernatant) from drug loaded vesicles (settled at bottom). The Supernatant and sediment will be separated and their volume is measured. The supernatant is taken and diluted with suitable solvent. The amount of drug present in the supernatant will be determined by ultraviolet (UV) spectrophotometrically. All the prepared formulations are characterized for percent entrapment efficiency (%EE), using the formula

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

3. Particle Size and Polydispersibility Index[17]

The Particle size (PS) and Polydispersibility index (PDI) is determined using Zeta Sizer. Spanlastics is diluted with Deionized water and the analyzed at 25^0C.

4. Zeta Potential[18]

Zeta Potential of Spanlastic formulation is determined using Zeta Sizer which helps to observe the electrophoretic mobility of charged vesicles. All measurements is done at 25°C in triplicate after dilution of the formulations. The suspension of particles is said to be stable when it has a zeta potential of approximately ±30 mV.

5. Number of vesicles per cubic millimetre[19]

This is measure by using Haemocytometer which is used to count the number of vesicles per cubic millimeter. The vesicles are diluted with water and vesicles in 80 tiny squares will be counted.

6. Drug Content[20]

To evaluate the total drug content, which is encapsulated, 0.2 mL of a spanlastic dispersion is dissolved in 25 mL of methanol and stirred on a magnetic stirrer to disrupt the vesicle and drug content is measured spectrophotometrically.

7. *In Vitro* Release[21]

The *In vitro* release of Spanlastic is performed using Dialysis Bag Diffusion Method. The Dialysis bag will be soaked in Phosphate buffer solution for overnight. Then the Spanlastic dispersion is placed inside the dialysis bag. The bag is tied on both the sides and they are immersed in the container containing Phosphate buffer solution maintained at 37± 0.1^0C in water bath and stirring at 100rpm. Specified aliquots of sample is withdrawn at different time intervals and replaced with fresh solution. The Samples are analyzed using UV spectrophotometer.

8. Differential Scanning Calorimetry (DSC)[22]

Thermal analysis of prepared spanlastics formulation, and the physical mixture of drug and other spanlastics ingredients is accomplished by a previously calibrated differential scanning calorimeter. Each prepared Spanlastic samples will be placed in a standard aluminum pan and heated in a temperature range of 10–300 ◦C at a heating rate of 10 ◦C/min with continuous purging of nitrogen (25 mL/min).

9. Elasticity measurement[23]

Elasticity is measured by extruding vesicles through the polycarbonate filter of 100 nm pore diameter and measuring the change in size. The time taken for extrusion will be also recorded. Elasticity of vesicle membrane evaluated by deformation index will be calculated from the following equation:

$$D = j/\ t\ (r_v / r_p)^2$$

Where D is the deformability index (mL/s),
j is the amount of extruded suspension (mL),
t is the time of extrusion (s),
r_v is the size of vesicles after extrusion (nm),
r_p is the pore size of the barrier (nm)

10. Corneal Permeability Study[24]

Ex vivo corneal permeability studies will be performed using a jacketed side-by-side diffusion cell device maintained at a constant temperature (35 ± 1 °C) with circulating water. The device consists of two diffusion pools and a diffusional area. Freshly excised rabbit cornea is placed between the donor pool and receptor

pool with the epidermis of the cornea faces the donor pool. Specified amount of formulation is placed in the donor pool and the receptor medium that contains Phosphate buffer. Keeping the device under magnetic stirring and a mixture of O_2 /CO_2 (95:5) bubbled throughout the experiment. Taking specified aliquots of receptor medium after fix time and equal quantify of fresh medium will be replaced to maintain a constant volume and determined spectrophotometrically.

Apparent permeability coefficient (Papp) is calculated using:

$$P_{app} = \frac{\Delta Q}{\Delta t} \times \frac{1}{(A \times C^0 \times 60)}$$

11. Stability Study[25]

The stability of the Spanlastic dispersion is evaluated by storing at two different temperatures (− 4◦C in a refrigerator and 25 ± 2 ◦C) for 3 months. Samples is collected at intervals of 1, 2, and 3 months and evaluated for any physical changes in color or odor, PS, PDI, ZP, and % EE.[25]

FACTORS AFFECTING PHYSICO-CHEMICAL PROPERTIES OF SPANLASTICS[26]

1. Membrane Additives

Addition of Surfactant, medication and other ingredients to the formulation results in improved stability of Spanlastics. Numerous additives affect the membrane stability, shape, and permeability of vesicles; tweens can increase the flexibility of the produced vesicles, allowing them to easily pass into the targeted location.

2. Hydration temperature

Hydration temperature has an impact on both shape and size. The impact of how the vesicles are assembled depends on the temperature fluctuation. Polyhedral vesicles composed of a mixture of C16G2 and solulan C24 (in a ratio of 91:9) undergo formation at a temperature of 25 °C. The vesicles undergo a transition into a spherical shape when exposed to a temperature of 45 °C. Additionally, a decrease in temperature from 55 to 49 °C leads to the aggregation of smaller spherical nano-vesicles into a cluster.

3. Drug characteristics

Drug entrapment effectiveness can be affected by the molecular weight, chemical make-up, hydrophilicity, lipophilicity, and hydrophilic-lipophilic balance (HLB) value of the drug. Drug entrapment may cause to grow the vesicle size. The vesicle size is raised even more by the surfactant bilayer pushing away the drug particle. This is most likely because the drug particle interacts with the surfactant head group, which raises the charge on the polymer and makes it charge higher.

4. Content and Surfactant Type

The HLB value of surfactants like span 85 (HLB 1.8) to span 20 (HLB 8.6) rises along with the mean size of the vesicles. It could be due to the surfactant's surface free energy drops as its hydrophilicity rises. Alkyl chains are existing in a well-ordered form in a gel state, but the bilayer structure is disorganized in a liquid state. The temperature of the gel-liquid phase transition (TC) is used to describe lipids and surfactants. For instance, spans with a higher TC have a greater entrapment efficiency because phase transition plays a role in this process. The HLB value affects the spanlastics' trapping efficiency. For instance, the entrapment efficiency is great at an HLB value of 8.6. However, formulations with HLB values of 14 to 17 are not advised.

5. Surfactant structure

The Critical packing parameter also affects the geometry of the vesicles (CPP). The geometry of vesicle may be predicted using CPP. The CPP value may be calculated using this equation.

CPP = V/ IC*A

CPP: The critical packing parameter
V: Hydrophobic group volume,
IC: The critical hydrophobic group length,
A: The area of the hydrophilic head group.

The following ways in which CPP is useful for predicting vesicle structure include:
1. Spherical micelles generated if CPP equal ½.
2. If CPP between½ and 1, bilayer micelles are generated.
3. If CPP > 1, inverted micelles develop.

6. Osmotic Stress Resistance

Reduction in vesicle diameter is observed, when the hypertonic salt solution is used in the formulation of spanlastics. In hypotonic salt, the spanlastics vesicles release slowly and grow little due to fluid elution obstruction, then rapidly due to osmotic stress releasing their structural parts.

7. Preparation Method

Spanlastics preparation techniques like handshaking, ether injection, and sonication significantly reduce the quality of the final formulation. For instance, vesicles created with ether injection are smaller than vesicles created through the handshaking approach. The vesicles produced by the hand-shaken approach can be reduced by hydrating the mixture above and then vortexing.

8. *In vivo* Spanlastics' actions

Nano-vesicles and *in vivo* spanlastics have been determined to be equivalent, and their dispersion patterns are similar to those of colloidal drug delivery systems. Because of the natural vectoring process, these elements have a noticeably high level of disposition in life. The pattern of drug disposal from circulation changes when bigger vesicles are retained in the alveolar region of the lungs due to retention or maybe phagocytic activity. Smaller vesicles may enter the spleen more readily and pass through the sinusoidal epithelium.

APPLICATIONS

Vesicular drug delivery system, initially used in cosmetics, are now one of the popular medication delivery methods. Spanlastic is an effective method of drug delivery because it can entrap both hydrophilic (lipophilic) and hydrophobic (lipophobic) molecules. The vesicle system has already been developed for numerous pharmaceuticals, including doxorubicin, vaccines, insulin, and siRNA, among others. They are conveniently delivered in a number of different ways, including transdermally, ocular, orally, and intravenously. Some applications of this vesicular medication delivery technology include the following

1. Ocular delivery[27]

Delivery of drug to the ocular segments is challenging due to the various anatomical and physiological barriers. Therefore, the eye segments require targeted drug delivery. Spanlastics, is a special class of vesicular drug delivery which serves as site specific drug delivery system for targeting drugs to eye segments that constitutes corneal membrane and aqueous humor as well as to the posterior eye segment that includes vitreous cavity, retinal pigment, epithelium and choroid. Both lipophilic and hydrophilic drugs can be delivered to ocular tissues.

2. Oral Delivery[28]

The oral route is the most used route for the delivery of drug, although oral drug have problems with bioavailability for a variety of reasons, including low solubility, frequent dosing, drug interactions, unpredictable absorption, first-pass metabolism, and systemic side effects. To evade the drawbacks of oral drug delivery, a unique surfactant-based vesicular system was introduced. Spanlastics are amphiphilic nature which traps the drug in core cavity and results in bilayer form. They are chemically stable, and they possess elasticity and deformability characteristics because of the incorporation of an edge activator. In addition, they have advantage of being biodegradable, non-immunogenic, target-specific, and enhances the bioavailability and stability of entrapped drugs.

3. Nasal Delivery[29]

Intranasal route is one of the most effective routes for directly delivering drugs to the brain via olfactory neuron and trigeminal pathway with avoiding hepatic metabolism and bypassing the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier which could result in dose reduction when compared to oral delivery. Thus, intranasal route is important for drugs used in crisis management such as pain relievers as well as for centrally acting drugs, where the direct pathway from nose to the brain may provide a faster and more specific therapeutic effect. Spanlastic is one of the vehicle of choice to deliver the drug to Brain.

4. Topical Delivery[30]

Administration of drugs through Conventional routes are associated with several drawbacks such as gastrointestinal intolerance, frequent dosing, first pass metabolism, patient incompliance etc. Dermal application of therapeutic agents aids in overcoming the above-mentioned drawbacks. Stratum corneum makes difficult to penetration of drugs through skin. Hence, only limited preparations can be delivered via dermal route. Spanlastic can play a major role in altering the biological membranes and in transporting and targeting the active agents and can easily penetrate through the skin independent of concentration.

5. Ungual Delivery[31]

Human Nail apparatus (finger/toe) is exposed to attacks by fungal species (mostly *Trichophyton rubrum*) leading to a type of infection called as onchomycosis. Various treatment options have been deduced for onchomycosis. Nail is the main barrier to the entry of any foreign material. It therefore, forbids the permeation of antifungal agents via topical formulation. The delivery of antimicrobial agents via nail plate to achieve desired therapeutic action is quite a challenging task for research scientists and pharmacologists. In order to achieve the desired action, the antifungal agent should reach the target site. This highlights the need of developing a novel topical formulation for effectively delivering the drug via trans-ungual route to eliminate the infection.

CONCLUSION

The development of Spanlastics, vesicles composed of surfactants, presents a non-invasive approach to drug delivery that eliminates the need for repeated medication at desired site. The foregoing issues being tackled encompass the challenges pertaining to the insolubility, low bioavailability, instability, and rapid degradation of pharmaceutical compounds. Spanlastics have the potential to serve as a significant advancement in the field of nanovesicular drug delivery systems. Both lipophilic and hydrophilic drugs can achieve site-specific action by utilizing these vesicular systems. These elastic carrier systems have found applications in delivering drugs to ocular, oral, topical, trans-ungual, and nasal and to the middle ear.

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