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(REVIEW ARTICLE)

Review of Proliposomal Gel for Transdermal drug delivery system

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Abstract

Proliposomes are an innovative kind of carrier-mediated drug delivery that offers numerous advantages over traditional liposomes. The conventional liposomes are susceptible to oxidation or hydrolysis, as well as sedimentation, aggregation, or fusion with other substances. While, proliposomes are far more stable than liposomes, making them better suited for the delivery of pharmaceuticals. They are a dry, free-flowing, granular substance that, when it comes in touch with water or a biological fluid inside the body, instantly transforms into a liposomal dispersion. Future systems for delivering medications could be proliposomes. They have achieved a considerable improvement in resolving the stability, bioavailability, and solubility of poorly soluble medicines difficulties associated with liposomes with their non-invasive drug administration into or across the skin. They are a better alternative to the liposomal vesicular system because of their increased physical and chemical stability and potential for scalability for commercial viability. Because they are in dry powder form, they can be manufactured into unit dose forms like tablets, capsules, and beads, among other things. Because of all these advantages, proliposomes have been used for a variety of medical applications.

Keywords: Proliposomes; Liposomes; Skin; Drug delivery; Applications

1. Introduction

The sphere-shaped vesicles known as liposomes are made up of one or more phospholipid bilayers. Both hydrophobic and hydrophilic molecules can be captured by liposomes, which can also prevent the combination's decomposition and release the trapped substances at specific destinations. The liposome can be employed as a delivery system for pharmaceuticals and nutrients. The utilisation of liposome encapsulation to develop delivery methods that can entrap unstable substances (such as antioxidants, antimicrobials, flavours, and bioactive components) and safeguard their activity has also been thoroughly researched by the food and farming industries. Liposomes are promising drug delivery systems because of their size, hydrophobic and hydrophilic nature, and biocompatibility[1]. While having many uses and benefits, liposomes are susceptible to oxidation or hydrolysis, as well as sedimentation, aggregation, or fusion with other substances.

The use of suitable lipid compositions, polymer coating, the addition of stabilising lipids to liposomal structures, the preparation of double liposomes and proliposomes, as well as some other cutting-edge techniques like lyophilizing liposomal solution to stabilise and reconstitute just before use, have all been suggested as ways to increase the stability of liposomes. The proliposome strategy is the most promising of all these methods.Proliposomes are a new type of carriers that facilitate drug delivery and have a number of benefits over traditional liposomes. There have been numerous attempts over a long period of time to increase liposomal stability. To prevent the physicochemical instability that can occur in various liposome solutions, such as aggregation, fusion, hydrolysis, and oxidation [2,3].

As a straightforward, repeatable, and dependable manufacturing method for mass-producing liposome dispersions, the proliposome approach was created. The method is based on hydrated membrane lipids' unique ability to form vesicles

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when in contact with water. Dry powders are created by stacking the phospholipids over a particulate support that has been finely split. Phospholipids on the solid substrate quickly disperse when the dry powders are hydrated with an aqueous solution and then gently mixed to produce a liposomal suspension in an aqueous solution. An appropriate hydration fluid can be used to create liposomes in vitro prior to delivery or in vivo under the influence of physiological fluids. The liposomes that are created during reconstitution are more homogeneous in size and similar to traditional liposomes.

Many site-specific drug delivery strategies have been developed using proliposomes as their foundation. Certain poorly soluble medications may become more soluble and more bioavailable thanks to proliposomal preparations. They are more convenient to transport, distribute, store, process, package, provide maximum flexibility, unit dose as a capsule, and are stable during sterilisation because they are available as dry powder. They are a strong candidate for industrial manufacturing because of all these benefits. These adaptable delivery methods have the potential to be utilised as carriers for many different active substances.

2. Properties of Proliposome

Proliposomes are an innovative kind of carrier-mediated drug delivery that offers numerous advantages over traditional liposomes. The conventional liposomes are susceptible to oxidation or hydrolysis, as well as sedimentation, aggregation, or fusion with other substances. While, proliposomes are far more stable than liposomes, making them better suited for the delivery of pharmaceuticals. They are a dry, free-flowing, granular substance that, when it comes in touch with water or a biological fluid inside the body, instantly transforms into a liposomal dispersion. Figure 1 shows the comparison between the conventional liposomes and proliposomes[4].

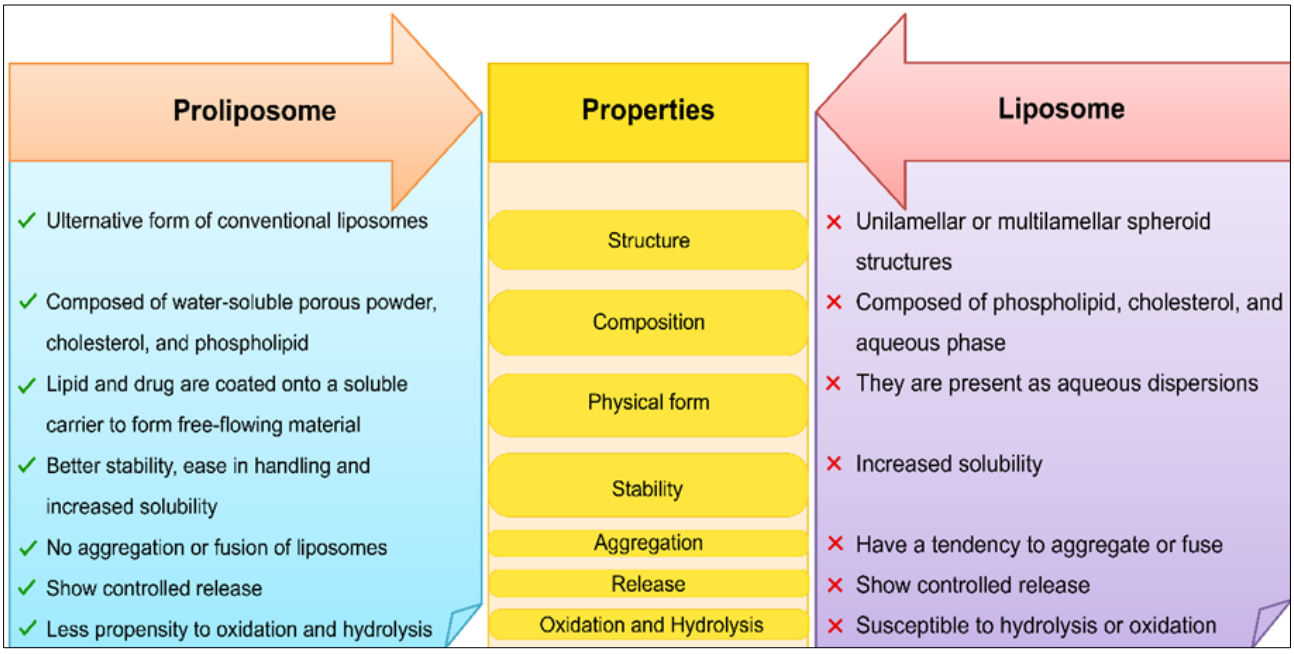

Figure 1 Properties of Proliposome and Liposome

3. Proliposome Formulation Components

The formation of proliposomes can be done using a variety of phospholipids, steroids, solvents and some water-soluble transporters. The detailed information of these components is tabulated in Table 1. The mechanism of proliposome formulation in shown in Figure 2.

Table 1 Cataloguing ofcomponents important for proliposome formulations and their significance

No.	Component	Significance	Reference
1.	Phospholipids	The most often utilised phospholipids are phosphatidylcholines (PC). Lecithin, another name for PCs, can be obtained from both natural and artificial sources. When compared to micellar structures, they form bilayer sheets, which is different from other amphipathic molecules. Egg yolk, soy beans, and very infrequently the heart and spinal cord of cattle, are the most frequently used natural PC sources. Due to their generally inexpensive cost, absence of net charge, and chemical inertness, they are frequently utilised as the main component in proliposomes. In addition to PC, sphingomyelin makes up the neutral lipid bilayers (SM). Various fatty acid chains, including oleic, lauryl, myristic, palmitic, and stearic acid, combined with polar head groups, such as phosphatidylglycerol (PG), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylserine (PS), and phosphatidylcholines (PC), provide a variety of phospholipid structures. Despite the large range of phospholipids that are available, the creation of proliposomes is frequently restricted to the PC and PG families, mostly due to toxicological considerations, purity, stability, and cost.	[1] Akbarzadeh et al., 2013; Parmar et al., 2015; Muneer et al., 2017
2.	Steroids	The liposomal membrane frequently contains cholesterol and its derivatives. Three impacts of their incorporation in liposomal membranes are known: improving the membrane's fluidity or microviscosity, decreasing its permeability to water-soluble compounds, and stabilising it when in contact with biological fluids like plasma. It significantly alters the properties of phospholipid bilayers after incorporation. Although cholesterol does not naturally form bilayers, it can be incorporated at large amounts into phospholipid membranes. By making the bilayers more rigid and decreasing permeability, it improves the retention of hydrophilic pharmaceuticals; however, for hydrophobic medications, it only enhances encapsulation if the drug input is lower than the liposome's capacity for encapsulation.	[17] Rong et al., 2008; Singh et al., 2019
3.	Water-soluble transporters	In order to conveniently modify the amount of carrier needed to support the lipids, the carriers selected should have high surface area and porosity. Moreover, it permits the synthesis of proliposomes with a high surfactant to carrier mass ratio. Due to their water solubility, they enable the hydration-induced quick conversion of liposomal dispersion, and by carefully regulating the size of the porous powder, a very small range of reconstituted liposomes can be produced. Maltodextrin, mannitol, sorbitol, microcrystalline cellulose, magnesium aluminium silicates, etc. are a few of the carriers employed.	[1] Akbarzadeh et al., 2013; Parmar et al., 2015
4.	Solvents	They are employed to give the vesicle membrane suppleness. Ethanol, methanol, ether, and chloroform are the most frequently utilised volatile organic solvents.	[5] Gupta et al., 2008

4. Approaches for Proliposome Preparations

Proliposomes can be made using a variety of techniques. Since different parameters, including vesicle size, size distribution, encapsulation capabilities, and retention of contents are impacted by the production technique, careful selection of an appropriate procedure for a given formulation is crucial.The drug's physicochemical properties, the required phospholipid type, the intended range of particle sizes, and ease of preparation all play a role in the method's choice[5]. An ideal preparation technique would use a small amount of organic solvent, prevent prolonged mechanical stress, use low temperatures and pressure, be repeatable and affordable, produce a high drug/lipid ratio, and be flexible enough to be used in large-scale manufacturing[19].Depending on such parameters some of the methods are discussed here in brief used for preparations of proliposomes.

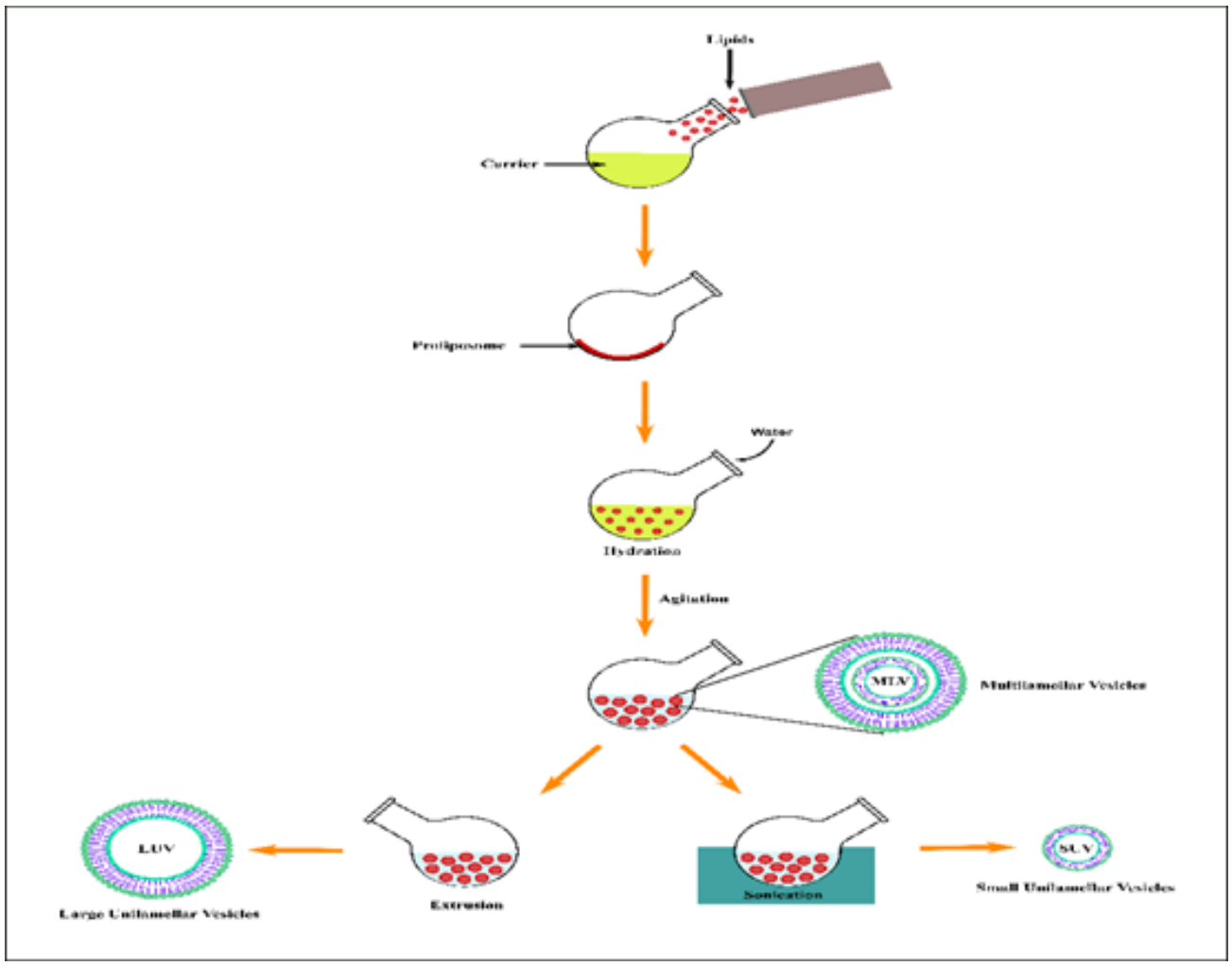

Figure 2 Mechanism of proliposome formulation

4.1. Fluidized bed

Proliposomes are produced on a large scale using the fluidized bed process. The foundation of this technique is particle coating technology. Here, the carrier material can be anything from nonpareil beads to crystalline powder. When non-pareil beads are utilised as the carrier material, the pareil beads are first coated with a seal coating to obtain a smooth surface that can aid in coating the phospholipids and also ensure thin uniform coating development of phospholipids around the core and tiny sized liposomes upon hydration. Drug and organic solvent solutions are sprayed onto carrier material using a nozzle. Vacuum is also used to remove organic solvent from the fluid bed at the same time. When dried overnight under hoover, the traces of remaining solvent are eliminated from the resulting lipid-coated powder/beads[18].

4.2. Film adsorption on a carrier

This process creates lipid-coated solid particles by first combining a lipid with a solid substrate (a water-soluble carrier). When a solid substrate is hydrated, it dissolves and the lipids organise to form liposomes. In this method, a core of a carrier substance is carried in a vessel of a rotary flash evaporator while a drug and phospholipid solution are added drop by drop through a feed tube. When a free-flowing powder matrix is obtained, the matrix's over wetting is avoided at any given time, and a subsequent aliquot of organic mixture is supplied gently[20].

The chosen carriers should have a large surface area and permeability to control the amount of carrier that is required to help the lipids. This also enables the creation of pro-liposomes to have a high surfactant to carrier mass proportion. They may quickly produce liposomal dispersion upon hydration due to their water solubility, and by manipulating the size of the pervious powder, a relatively small variation of reconstituted liposomes can be produced. Sorbitol, maltodextrin, magnesium aluminium silicates, microcrystalline cellulose, mannitol, and other substances are the most often utilised carriers[19].

4.3. Spray drying

This technology may be quickly scaled up in a cost-effective manner and is suited for large-scale manufacturing of proliposomes. It is mostly employed when particles of consistent size and shape are required. The capacity of the spray drying method to combine particle creation and drying into a single, continuous operation, allowing for improved particle control, makes it special. Spray drying is not just applicable to aqueous solutions; it may also be used to prepare particles in non-aqueous systems. The process begins with the preparation of liquid dispersions containing pure lipid or lipids and carriers in an organic combination, which are then poured into a dry cell. Dispersions are atomized using a spray nozzle in the drying cell and desiccated in a concurrent air flow before being collected in a tank[2].

4.4. Supercritical anti-solvent

Proliposomes are made using the supercritical anti-solvent method and supercritical carbon dioxide ($SCCO_2$). When carbon dioxide is kept at or above its critical temperature and pressure, it is in the fluid state, or $SCCO_2$. The equipment used to make proliposomes consists a CO_2 syringe pump, circular cooling lines for the CO_2 pump head and CO_2 that came from a storage tank (-7°C), and a reaction vessel with a magnetic stirrer, pressure gauge, and temperature gauge[23]. First, a clear and uniform mixture of phospholipids, cholesterol, and medication is made. After that, the reaction vessel is sealed with the drug-lipid solution and carrier material. Using a syringe pump, supercritical CO_2 was delivered to the vessel. After roughly 30 minutes of equilibrium-state stirring, more supercritical CO_2 was introduced and flowed into the vessel for another 30 minutes to wash out any leftover solvents. The vessel is then gradually depressurized to atmospheric pressure, and a thin film of the drug-phospholipid mixture is formed on the surface of the carrier particles. The SCF-mediated pro-liposomes are then gathered and kept at 4°C for later use[18].

5. Characterization of Proliposome

Morphology,rate of hydration, angle of repose, penetration, and permeation studies are used to characterise proliposomes. The important parameters and techniques for characterization of proliposomes are show in Table 2.

Table 2 Characterization of proliposomes

Parameters	Properties	Measurement and Techniques	References
Particle size	A crucial characteristic of proliposomes is their particle size. The illegibility of the carrier material's image during the creation of proliposomes is evidence that phospholipid has been deposited on the substance.	Scanning electron microscopy can be used to examine the size distribution and surface morphology (smoothness, roundness, and aggregate formation) of particles (SEM).	[21] Song et al., 2002
Hydration study and Vesicle formation	Understanding the liposomal vesicle formation after in vitro hydration of the proliposomal formulation is crucial.	Optical microscopy can verify the vesicle formation caused by the specific process.	[19] Shruthi et al., 2014; Singh et al., 2019

		It is necessary to spread the liposome suspension over a glass slide and let it dry at room temperature before checking to see if any vesicles have formed on the dry, thin layer of dried liposome suspension.	
Zeta potential measurement	Zeta potential is a further property of proliposomes that is of great interest. The zeta potential makes sense as a measure of particle stability. A proliposomal formulation that is only physically stable due to electrostatic repulsion will have a minimum zeta potential of about 30 mV, and this stability aids in preventing aggregation.	It serves as a gauge for particle charge, with surface charge increasing linearly with zeta potential absolute value.	[12] Leigh et al., 2003
Separation of unentrapped drug	To create a liposomal solution free of unentrapped medication, the resulting pellets are first cleaned and then re-suspended. Another technique is gel filtration, which separates unentrapped medication from liposomal dispersion using a Sephadex-G-50 column, eluted with the appropriate mobile phase, and analysed with the appropriate analytical techniques.	By centrifuging the liposomal suspension, the pellets and supernatant can be separated from the free or unentrapped drug. Gel filtration using a Sephadex-G-50 column.	[22]Vyas and Khar 2006; Singh et al., 2019
Differential Scanning Calorimetry and Powder X-ray Diffractometry	When a medication is formulated into proliposomes, changing from crystalline to amorphous. This is crucial when employing proliposomal formulation to increase the drug's solubility.	Its solid-state properties can be assessed using differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD).	[16] Potluri and Betageri, 2006
Flow Properties	Flow qualities essentially explain content homogeneity and managing processing processes and also ease filling. As the formulation is based on a solid powder, it is crucial to analyse the flow characteristics in order to convert them into practical dosage forms like tablets or capsules.	By taking measurements of the variable’s bulk density, tapped density, angle of repose, Carr's compressibility index, and Hausner's ratio, flow characteristics can be evaluated.	[3] Bobbala and Veerareddy, 2012
Determination of entrapment (entrapped) efficiency	By hydrating the proliposomes to create liposome dispersion, separating the unentrapped drug, and calculating the amount of drug entrapped, the efficiency of drug entrapment is carried out.	One can separate untrapped or free drugs using any of the methods mentioned above.	[20] Singh et al., 2019
In vitro drug release from proliposomes	Numerous methods, including the USP dissolution apparatus Type I, Franz diffusion cell, dialysis tubing, reverse dialysis, cellophane dialyzing membrane, Keshary-Chien diffusion cell, and spectrapormolecular porous membrane tubing, can be used to conduct in vitro drug release studies for proliposomes.	Flap skin, dorsal skin, female albino rat (Sprague-Dawley strain), Wistar rat skin, and albino rabbit skin can all be used for in vitro skin permeation investigations (7–9 weeks old).	[13] Muller et al., 2002; Singh et al., 2019

Stability studies	The stability tests can be carried out by storing the samples for a period of 1-3 months at various temperatures, such as freezing temperature (2-8oC), room temperature (250.5oC), and higher temperature (450.5oC). Drug content and variations in the average vesicle diameter can be seen sometimes. In accordance with international climatic conditions and zones, dry proliposome powder intended for re-formulation should be taken into account for accelerated stability at relative humidity 75%/40°C. On the basis of the countries' climate zones, investigations of long-term stability must be done. Zones I and II must maintain a temperature of 25°C and relative humidity of 60% and III and IV must maintain a temperature of 30°C and 65%, respectively.	Examining the product's appearance, surface properties, medication content, colour change, pH, particle matter, assay, preservative content, pyrogenicity, and sterility is recommended.	[24] Yadav et al., 2011; Singh et al., 2019

6. Applications of Proliposome in Transdermal Delivery

Proliposomes have been investigated for use in oral, transdermal, mucosal, nasal, ophthalmic, pulmonary, and parenteral administration methods. Liposomes generated from proliposomes have benefits as drug carriers, including reduced cost and toxicity, simple handling and storage, and greater stability.

Because they make up the majority of the liposomal system, phospholipids will easily bind to the lipids in the skin and preserve the correct levels of moisture to improve medication absorption. When proliposomes are placed to the mucosal membrane, it is anticipated that they will transform upon coming into contact with mucosal fluids, creating liposomes that serve as sustained release dosage forms for medications that are loaded.Diffusion across the skin can be modified by liposomes that develop after hydration[6]. The viability of proliposomes as a sustained transdermal dose form has been studied in various studies. According to Shruthi et al. (2014)[19], transdermal metformin hydrochloride proliposomal gel permits medication distribution through the skin while significantly lowering blood glucose levels. Repaglinide was produced as a proliposomal gel system by Kumara et al. (2016)[10] to deliver the medication for the treatment of type 2 diabetes mellitus over an extended length of time.

Findings showed that proliposomes were a superior option for topical medication administration of drugs with controlled release. For topical use, a proliposomal gel was created containing the non-steroidal anti-inflammatory drug Piroxicam. The proliposomal gel form of piroxicam demonstrated sustained release and improved anti-inflammatory efficacy[12], [7] proposed that ketoconazole can remain in the body for a long time when it is administered via a proliposomal drug delivery system.Prednisolone proliposomal gel was suggested, and it demonstrated sustained release along with improved anti-inflammatory action, suggesting that it may be useful for topical medication for the management of rheumatoid arthritis[11].

7. Conclusion and Future Perspective

Proliposomes are potential medication delivery systems in the future. With their non-invasive drug administration into or across the skin, they have made a significant advancement in resolving the stability, bioavailability, and solubility of poorly soluble medicines problems related with liposomes. Due to their improved physical and chemical stability and potential for scalability for commercial viability, they are a better option to the liposomal vesicular system. They can be prepared into unit dosage forms, such as tablets, capsules, and beads, etc., because they are in dry powder form. Proliposomes have been used for a wide range of medicinal applications as a result of all these benefits. Proliposomes are employed as effective gene delivery vehicles and are administered orally, parenterally, topically, and in cosmetic and hair products, sustained release formulations, and diagnostic applications. Proliposomes are developing into a valuable medication delivery method. In order to create scale-up batches for pharmaceutical and natural products, further study should be conducted.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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