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Proniosome: A Promising Approach for management of various Formulation design: A review

Piya Mandal[1], Sukriti Mondal[2], Nikhil Biswas[3] , Asha Das[4]
[134] *Department of Pharmaceutics, Girijananda Chowdhury University, Azara,, Guwahati, Assam-781017, India*
[2]*Bachelor's in Pharmacy, JIS University, Agarpara, Kolkata, West Bengal-700109, India*

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ABSTRACT: Proniosomes are water-soluble carrier particles covered with surfactant in a dry formulation. They immediately before use, upon agitation in hot aqueous media, rehydrate to produce niosomal dispersion. Proniosomes are physically stable while being transported and stored. Drugs that are encased in the vesicular structure of proniosomes have a longer shelf life in the bloodstream, have better tissue penetration, and are less toxic. Technically speaking, niosomes are potential drug delivery systems because they are more chemically stable and lack many of the drawbacks of liposomes, such as their expensive cost and inconsistent phospholipid purity. The focus of the current review is on proniosomes' general techniques of synthesis, characterisation, and usefulness in targeted therapeutic action. Proniosomes are solid colloidal particles that can be quickly hydrated before use to make aqueous niosome dispersions that are comparable to those made using more laborious traditional procedures. The proniosomes reduce the issues with niosomes' physical stability, including aggregation, fusion, and leakage. Additionally, they make transportation, distribution, storage, and dosage more convenient. The shape, particle size, particle size distribution, and drug release of the proniosome-derived niosomes are superior to those of traditional niosomes. Proniosomes were frequently produced by the slurry method with maltodextrin serving as the carrier. By using this straightforward procedure, proniosome production takes only a short amount of time and doesn't appear to require any special equipment. .

KEYWORD: Proniosome, Niosome, vesicular carrier, non-ionic surfactant, liposomes.

I. INTRODUCTION:

Since the 1980s, non-ionic surfactant vesicles (niosomes) have been demonstrated to have distinct benefits over conventional dosage forms and play an ever-increasing role in drug delivery [1]. Nonionic surfactants produce more stable, manageable, and reasonably priced vesicles as compared to phospholipids. Niosomes, a type of non-ionic surfactant vesicle, have been found to offer different advantages over traditional dosage forms and are becoming a more significant component of drug administration. Nonionic surfactants generate vesicles that are more stable, manageable, and less expensive to produce than phospholipids. Niosomes that are produced from provesicular (proniosomal) cells have drawn a lot of attention recently as an oral dosage form with the potential to boost therapeutic action, lessen side effects, and increase medication stability to chemical degradation or transformation. Because to their low integrity at the point of absorption, physicochemical instability to hydrolysis, drug separation, and propensity to silt and clump, niosomes themselves have limitations for oral delivery [2].

A proniosomal formulation is a dry version of a liquid-crystalline niosomal hybrid that becomes niosomes when hydrated with aqueous media. It provides a versatile way of drug delivery that not only has the ability to encapsulate pharmaceuticals but also lessens drug degradation after injection, prevents unpleasant side effects, and increases medication bioavailability [3, 4]. Additionally, it is less susceptible to the high cost and inconsistent purity issues of phospholipids based formulations [5] and simple to transport, distribute, and store. Proniosomes, also known as "dry niosomes," are thus a potential and profitable product for the market [6].

A novel drug delivery system that delivers drugs at a preset rate set as per the need, pharmacologic aspects, drug profile, physiological conditions of the body, etc. In current times, no single drug delivery system meets all the standards; however, efforts are created through novel approaches.The delivery of drugs using colloidal particulate carriers such as proniosomes is dry and free-flowing preparation coated with a surfactant.

International Journal of Pharmaceutical research and Applications
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To form a multi-lamellar noisome, proniosomes are rehydrated directly within minutes by transient agitation. Niosome suspension is appropriate for giving medication by different routes. They are promising candidates for industrial applications as they can transport, distribute, store, and process easily. Therefore, proniosomes can be another alternative to liposomal and other vesicular drug delivery systems for the entrapment of both polar and non-polar medications [7]. Proniosomes improve effectivity, scale back or eliminate adverse effects and enhance therapeutic actions of medicine. They are accustomed to avoid the gastrointestinal tract incompatibility, pre-systemic metabolism, and unwanted adverse effects related to oral delivery. Additionally, they maintain therapeutic levels of drug for an extended time, decrease the frequency of administration and improve patient compliance [8, 9, 10]. This article in brief reviews the types, fabrication, characterization, and pharmaceutical applications of proniosomes.

II. STRUCTURE OF PRONIOSOME:

Proniosomes are microscopic lamellar structures, hexangular structures, and blackish structures, where their location is clear, semi-transparent, and semi-solid gel-like structures. Consistent with their methodology of preparation, proniosomes are unilamellar or multi-lamellar. They even have bilayer in their structure having hydrophilic ends that are exposed on the surface and hydrophobic chains that face one another within the bilayer inside the vesicles. Bilayer consists of non-ionic surface-active agents. To create a bilayer surfactant molecule, offers direction in such a way that hydrophilic ends of the nonionic surfactant are arranged toward the outside, whereas the hydrophobic ends exist in the opposite direction. Hydrophilic drugs are placed at intervals in the area encircled within the vesicle and the hydrophobic medication is implanted within the bilayer. For association, in liquid media, proniosomes attach to cholesterol with different categories of non-ionic surfactant like alkyl radical or dialkyl polyglycerol ether [11].

III. COMPONENTS OF PRONIOSOME:

A. Non-ionic surfactant

Surfactants, especially non-ionic surfactants are the key structural components in the preparation of proniosomes. These surfactants do not have any charge as they possess a polar head and non-polar tail. So, their stability, toxicity and compatibility is higher than other surfactants. The non-ionic surfactants have wet and emulsifying effects by which they improve the solubility and permeability of drugs. The hydrophilic-lipophilic balance (HLB) value is critical for selecting surfactants and HLB value between 4 and 8 is compatible with vesicle formation by proniosomes. It is difficult for hydrophilic surfactants to achieve a high concentration because of the high liquid solubility of hydrophilic surfactants. Therefore, aggregation and conglutination to form a proniosomal lamellar structure would be absent [12]. Nonionic surface-active agents, which consist of a polar head and a nonpolar tail, serve as the fundamental components in the preparation of niosomes. These agents exhibit amphiphilic properties, meaning they have both hydrophilic (polar) and hydrophobic (nonpolar) regions. The polar head of the nonionic surfactant interacts with water or other polar solvents, while the nonpolar tail avoids contact with the aqueous environment. This amphiphilic nature allows nonionic surfactants to form the essential bilayer structure of niosomes by arranging themselves in a way that the polar heads face the aqueous phase while the nonpolar tails remain shielded within the bilayer core [13]. Nonionic surfactants used in niosome preparation offer several advantages over anionic, cationic, and amphoteric surfactants. These nonionic surfactants do not carry an electrical charge, making them more stable, compatible, and less toxic. Compared to other types of surfactants, nonionic surfactants exhibit reduced hemolysis and irritation on cellular surfaces. Nonionic surfactants have various applications, including enhancing permeability, improving solubility, serving as wetting agents, and acting as emulsifiers. Their ability to enhance permeability can be beneficial for drug delivery, as it allows drugs to penetrate biological barriers more efficiently. Moreover, nonionic surfactants possess the property of inhibiting p-glycoprotein, a protein that pumps drugs out of cells, thus potentially increasing the absorption and targeted delivery of anticancer drugs [14, 15]. Hydrophilic lipophilic balance and Critical packaging parameters are the important parameters before the selection of surfactants. It plays an important role in obtaining controlled entrapement efficiency. Until date, a variety of non-ionic surfactants with different HLB values have been utilised depending on the delivery of niosomes, including polyglycerol alkylethers, glucosyl dialkyl ethers, crown ethers, polyoxyethylene ethers, and esters like the Brij, Span, and Tween series [16]. Another significant

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aspect that may have an impact on the entrapment efficiency is the temperature of the phase transition. For instance, the high entrapment efficiency of span 60 may be related to its high transition temperature [17, 18]. Iodides, mercury salt, salicylates, sulfonamides, and tannins, phenolic compounds are not utilised with surfactants with gel transition temperatures less than 10 °C because they can induce oxidation [19]. The area of the polar head group, as well as the volume and length of the non-polar group, may be used to determine a surfactant's CPP value. The type of vesicle that will develop may be predicted using CPP values.

B. **Cholesterol**

Cholesterol can interact with non-ionic surfactants and regulates the physical and structural properties of proniosomes [20]. It improves the stability and rigidity of the proniosomal membrane and controls drug permeation through the membrane. Depending on the HLB value of the surfactants, the amount of cholesterol required for the preparation of proniosomes is determined. When the HLB value is above 10, the amount of cholesterol to be increased to cover the larger groups [21]. But entrapment efficiency (EE) of the prepared formulation is decreased [22] above a certain level of cholesterol, possibly due to a decrease in volume diameter [23].

C. **Lecithin**

Lecithin is a phospholipid that acts as a membrane stabilizer in the formulation of proniosomes. The most common lecithins that are used in the formulation are soya and egg lecithin and it has been reported that hydrogenated-type lecithins have advantages over not hydrogenated lecithins, give increased rigidity of the cholesterol and help in the formation of tight vesicles [24]. Double bonds in non-hydrogenated lecithin allow the molecular chains to bend (conformational rotation), which prevents tight contact with the adjacent molecules on forming the niosomal membrane. This results in low rigidity and high permeability of the membrane.

D. **Hydration medium**

Generally, the hydration medium used in proniosomes is phosphate buffer. Depending on the solubility of the encapsulated drug, the pH of the buffer is selected [25]. Ruckmani and Sankar [26] ascertained that drug leakage increased with the increase in the volume of hydration medium but simultaneously, EE increases, when the hydration time was increased from 20 to 45 min.

F. **Organic solvent**

The solvent can act as a penetration enhancer. It also greatly affects the size of the vesicles formed. The sizes of the vesicle and permeation rate of the drug in a proniosomal formulation are influenced by the type of alcohol. Different sized vesicles are formed using different alcohols as they have the order: >> isopropanol < butanol < propanol < ethanol > choloroform [27].

G. Carrier material

Carrier materials accommodate the drug in the proniosomal formulations. Carriers should have safe, non-toxicity, free-flowing properties. They should possess low solubility in the solution of loaded, but good solubility in water for ease of hydration. They increase the surface area and impart flexibility to the proniosomes. The frequently used carrier materials are sorbitol, mannitol, maltodextrin, glucose monohydrate, spray-dried lactose, sucrose stearate, and lactose monohydrate [28].

IV. PREPARATION METHODS OF PRONIOSOME:

A drug that has poor aqueous solubility, low bioavailability and dissolution, poor membrane permeability, low absorption profile, excessive metabolism, variable plasma concentration, and poor patient efficiency is suitable to encapsulate into proniosomes [29]. Three methods are available for proniosomal drug formulation.

A. **Slurry method**

In this method, a single or a mixture of organic solvent is used in the preparation of a stock solution of surfactant and membrane stabilizer. The drug and carrier are dissolved in a membrane stabilizer solution and all the components are mixed until a slurry is formed. With the help of a rotary evaporator at specified conditions (e.g. 50-60 rpm, 45 ± 2°C temperature, and 600 mm of Hg pressure), the slurry is dried, and the freeflowing product is obtained. The obtained free-flowing dried material is further dried with the help of a desiccator at room temperature under vacuum to get proniosomes [30].

B. **Slow spray coating method**

The slow spray-coating method is carried out by spraying organic solution, surfactant,

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cholesterol, and drug onto the carrier and then removing the solvent using a rotary evaporator under controlled conditions at 65-70°C for 15-20 min. Until the desired surfactant loading has been achieved, the process is continued and repeated. The vaporization should be carried on until the powder becomes completely dry [31, 32].

C. Coacervation phase separation method

Most of the proniosomal gel (PNG) is prepared by this method. In this method, exactly measured amounts of drugs, surfactants, and cholesterol are placed in a clean and dry glass vial having a wide opening. Then, the solvent is added and warmed in a water bath at 60-70°C until the surfactant and cholesterol is fully dissolved. To prevent the evaporation of the solvent, the open end of the vial should be covered with a lid. Followed by the addition of an aqueous phase in the vial, the mixture was warmed in the water bath to get a clear solution. It is then cooled at room temperature, between this time PNG is produced from the dispersion [33].

V. CHARACTERIZATION OF PRONIOSOME OR EVALUATION OF PRONIOSOME:

Characterizing proniosomes is crucial for understanding their behavior, quality, and potential for future clinical studies. Several characteristics of proniosomes, such as size, size distribution, zeta potential, morphology, entrapment efficiency (EE), and in vitro release, significantly impact the vesicle's rigidity and its performance in vivo. Size, EE, and in vitro drug release are among the most important parameters to consider. The size of the proniosomes affects their rigidity, and a reasonable vesicle size is desirable for optimal performance. EE refers to the amount of the loaded drug effectively trapped within the proniosomes, and it depends on factors such as cholesterol content, properties of the membrane components, and the specific drug being loaded. The method employed to load the drug into the proniosomes structure also affects the EE rate. Generally, larger vesicles tend to have higher entrapment efficiency as they provide more space to accommodate the active agent. These characterization parameters provide crucial insights into the stability, performance, and efficacy of proniosomes. They help determine the suitability of proniosomes as drug delivery systems and guide further optimization in their formulation and preparation. By understanding the characteristics of proniosomes, researchers can make informed decisions and design proniosomal formulations that possess the desired properties for effective drug delivery.

A. Particle size and polydispersive index

Particle size is a crucial component of proniosome structure since it provides information on the stability and physical characteristics of the particles. The proniosome particle sizes range from around 10 nm to 50 nm. There are several ways to measure proniosome size, including light scattering methods (DLS) and light microscopy [34]. DLS needs to be transformed into PCS (photon correlation spectroscopy) [35]. Only a little concentration of particle samples are needed for this efficient and non-destructive approach. DLS offers information on particle size dispersion inaddition to cumulative data on average particle size [36]. There are also other methods employed, including freeze-fracture replication-electron microscopy (FF-TEM), TEM, and electron microscopic analysis (SEM). proniosome size and the number of bilayers may both be determined using electron microscopic methods [37]. It should be noted that microscopy methods produce artefacts in general. As a result, it is advised to use a variety of techniques to get accurate findings.

B. Angle of repose measurement

The angle of repose of dried proniosomes prepared using the slurry and spray coating method is measured by the funnel and cylinder technique.

C. Zeta potential (ZP)

The stability of the particle can be ensured with the value of ZP. This is ascribed to the electrostatic repulsion between particles with the same electric charge that causes the segregation of the particles. A high ZP value leads to increased repulsive interactions in charged particles and prevents the agglomerate formation between the particles. This ensured uniform size distribution in proniosomes. A proniosomal formulation having ZP value minimum ± 30 mV is considered a physically stable formulation. So, aggregation of particles can be avoided [38, 39].

D. Osmotic shock

An osmotic shock study helps in the determination of vesicle size changes. For this, the proniosomal formulations are incubated in different types of solution like hypertonic, isotonic, and hypotonic solutions for 3 h. Changes in vesicle size are detected by an optical microscope [40].

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***E*. Entrapement efficiency**

Entrapment effectiveness is the most important aspect for the therapeutic usage of niosomes [41]. Centrifugation, gel chromatography, dialysis, or filtering should be used to remove unloaded pharmaceuticals (free drug) from the whole process before to EE measurement. Using 50% n-propanol or 0.1% Triton X-100 at around 1 hour of incubation, the drug trapped in the niosomes is assessed with full removal of the free drug [42]. The concentration of loaded medication in the vesicular structure, also known as entrapment efficiency, may be calculated using the following equation.

$$EE\% = \frac{Total\ entrapped\ drug}{Total\ amount\ of\ drug\ added} \times 100$$

The amount of drug that is trapped in the vesicles makes up the concentration of entrapped drug. The entire dose is equal to the total ratio of the main drug [43].

***F*. Drug content**

The calibration curve is used to calculate drug content. For this, proniosomes are lysed with methanol in a volumetric flask by shaking for 15 min. Then, the stock solution is prepared with methanol. With the help of phosphate buffer, 10% solution is prepared from the stock solution. Aliquots are withdrawn and absorbance is measured followed by a drawing of calibration curve [44].

***G*. Rate of spontaneity**

The rate of spontaneity is the measure of the number of niosomes formed following hydration of proniosomes. To determine the rate of spontaneity, PNG is transferred and spread uniformly along the walls of the small stoppered glass tube container. Then, NaCl (0.154 M) was added with caution and placed to one side without any turbulence. With the help of Neubauer's chamber, the number of niosomes eluted from proniosomes is calculated [45].

***H*. Stability study of proniosome**

To ensure the stability of the prepared proniosomes, they are placed at a various temperatures, freezing temperature (2-8°C), normal temperature (25 ± 0.5°C) and elevated temperature (45 ± 0.5°C) for 1-3 months and the change in drug content and mean vesicle diameter is observed at a different time interval. The International Conference on harmonization (ICH) guidelines propose dry proniosomes powder should be studied for the accelerated stability at 75% relative humidity and 40°C as per international geographical zones and geographical conditions [46].

***I*. In-vitro dynamics study**

One of the key aspects of niosome characterization is the evaluation of in vitro drug release, which is influenced by several factors such as the hydration temperature, drug concentration, and membrane properties. Dialysis membrane is commonly used to study the release rate of active agents (drug molecules). The process involves washing and soaking a clean dialysis bag in distilled water, followed by filling it with the niosome-drug mixture and sealing it. The sealed vesicle bag is then placed in a 200-ml glass of phosphate-buffered saline (PBS) at a constant temperature (usually 37 °C) and stirred using a magnetic stirrer. At predetermined time intervals, samples are collected and replaced with an equal volume of freshly prepared medium. These samples are analyzed using suitable methods to determine the amount of drug released over time, such as UV spectroscopy or high-performance liquid chromatography (HPLC) [47, 48]. Another method used for in vitro drug release studies is the Franz diffusion cell. In this method, proniosomes are placed in a Franz diffusion cell equipped with a cellophane membrane. A suitable release buffer is selected, and the proniosomes are then subjected to dialysis at room temperature. At specific time points, the samples are withdrawn from the solution, and effective analysis is performed to measure the drug content. Common analytical methods include UV spectroscopy and HPLC. These techniques allow for the assessment of drug release kinetics and the determination of drug release profiles from niosomal formulations [49].

VI. PRONIOSOMAL DRUG DELIVERY THROUGH DIFFERENT ROUTES

***A*. Oral routes**

The oral route of drug administration is the most preferred route for drug delivery. But bioavailability of the orally administered drug is sometimes affected by first-pass metabolism, instability in the gastric environment, low permeability through the intestinal epithelium. In some cases, absorption of the drug may be altered due to the presence of food. Thus, to improve the bioavailability of the oral drug, different nanocarriers are engaged. Oral proniosomes are

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one them that can solve the limitations of the conventional oral dosage form [50]. In vitro release kinetics of oral vinpocetine (VP) prepared using the slurry method indicated a faster release rate of reconstituted niosomes in contrast to VP suspension at pH 6.8 or 7.2 phosphate-buffered saline. In vivo pharmacokinetic study data also showed a better correlation with the in vitro data [51]. Oral acemetacin also prepared using the slurry method in proniosomal powder and tablet formulations, displayed better pharmacokinetic properties [52]. Lornoxicam is a widely used analgesic drug that belongs to the non-steroidal anti-inflammatory group. Proniosomal form of lornoxicam showed significantly higher ($p<0.05$) transmucosal flux across the oral mucosa than lornoxicam containing carbopol gel and the diffusion of lornoxicam was higher (more than two folds) in proniosomal formulation [53]. Proniosomal telmisartan tablets prepared with surfactants having different HLB values (span 40 and brij 35), cholesterol (20-50%), and phospholipids (egg yolk and soybean). In vitro as well in vivo comparative study showed extended drug release with a higher Cmax. The Cmax was increased 1.5 fold while AUC0-∞ also increased significantly 3 fold compared with the commercial tablet. The sustained release pattern of telmisartan was indicated by tmax, which was increased 3 fold in contrast to conventional tablets. The relative bioavailability was also increased by 3.2 fold [54].

B. Pulmonary routes

With the aid of the pulmonary route, one can easily treat respiratory diseases than other delivery methods. Through this route, drugs can be directly applied within the lungs. Drugloaded particles like liposomes dispensed through aerosol can easily distribute to the bronchi and lungs and prolong the release of the drug. Liposomal delivery also has minimum systemic side effects due to localized action to the lungs. But liposomes may be degraded by oxidation or hydrolysis. So, the proniosome can be an option to overcome the limitations of the liposome [55]. For pulmonary drug delivery, the air-jet nebulizer is known very well. Proniosome-derived niosomes of cromolyn sodium were prepared by Abd-Elbary et al. They used sucrose stearates in the formulation. The results exhibited a controlled release of drugs from the proniosome-derived niosomes compared to standard drug solution. Furthermore, high nebulization efficiency and physical stability were also achieved. Likewise, aerosol properties of beclometasone dipropionate (BDP) niosomes using Aeroneb Pro and Omron Micro Air vibrating mesh nebulizers and Pari LC Sprint air-jet nebulizer were investigated by Elhissi et al [56] The study demonstrated that the satisfactory EE of BDP in proniosome-derived niosomes and the value was higher than that in conventional thin filmmade niosomes [57].

C. Vaginal routes

Vaginal drug delivery is one of the favorable routes to target the disease associated with female health issues. It offers both the local and systemic delivery of drugs. Usually, different categories of drugs like antibiotics, antifungal, antiprotozoal, antiviral, labor-inducing agents, spermicidal agents, steroids, etc. are delivered through the vaginal route [58] PNG has excellent mucoadhesive properties and provides a constant release pattern, which is very useful for vaginal drug delivery. Tenofovir disoproxil fumarate (TDF) is an antiretroviral drug (a nucleotide analog) that works through the inhibition of viral reverse transcriptase. PNG of TDF was prepared with the help of cholesterol, surfactants (span 20, 40, 60, 80, tween 20 and 80), lecithin by coacervation phase separation method. A comparative in vivo dissolution study was conducted between proniosomes suppository, drug suppository and PNG formulations for 24 h using cellophane membrane, our results indicated the proniosomal suppository. Another result revealed a controlled and sustained release rate compared to the other two formulations [59]. Terconazole, an antifungal drug, PNGs were developed on the basis of span 60 and brij 76 in different molar ratios (1:1, 1:1.5, and 1:2) relative to cholesterol. The results displayed that increased concentration of cholesterol relative to the surfactant affected both EE and vesicle size of niosomes prepared by incorporating into 1% carbopol gel. Drug release profiles from different prepared PNG formulations in simulated vaginal fluid studied in comparison with the commercial product of terconazole for 24 h. Depending on the high EE % and in vitro release profile, selected formulation was further evaluated for stability, mucoadhesion to the vaginal mucosa and inhibition of candida growth. Results indicated that the selected formula was in good stability and provided higher mucoadhesion and retention time than the commercial product, which resulted in more efficient in vitro inhibition of Candida albicans [60].

International Journal of Pharmaceutical research and Applications
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***D.* Parental routes**

In parenteral drug delivery, targeted and sustained drug release at a predetermined rate can be achieved due to remarkable advancement in pharmaceutical technology. Flurbiprofen [61] and letrozole [62] are prepared by the slurry method. Both drugs showed sustained activity and reduced dosing frequency.

***F*. Dermal and transdermal rotes**

The dermal route is employed for local action only to treat different types of skin disease. This route can avoid systemic effects and therefore offers fewer side effects. However, through transdermal delivery, we can deliver drugs for systemic action. But in both the dermal and transdermal drug delivery, the skin prevents the penetration of drugs. Vesicular drug delivery can be used to overcome this problem. Non-steroidal anti-inflammatory drugs (NSAIDs) such as piroxicam, [63] ketoprofen, meloxicam, celecoxib, and tenoxicam30 are planned to avoid gastrointestinal adverse effects. Here, all the NSAIDs except ketoprofen are prepared by the coacervation phase separation method, whereas ketoprofen is prepared by the slurry method. Fluconazole-loaded PNGs were prepared by the coacervation phase separation method using different non-ionic surfactants (spans and tweens). The prepared fluconazole PNGs were evaluated for various parameters such as PS, drug EE %, and in vitro drug release. The experimental results showed that the EE % for the prepared formulae are acceptable (85.14-97.66%) and they are size (19.8-50.1 nm). The planned gel also showed sustained drug release. The formulation, which was prepared from span 60:tween 80 (1:1), and cholesterol showed highest EE % and gave slow release (40.50 ± 1.50% after 6 h), was subjected to ZP test, TEM as well as microbiological study. The results indicated a well-defined spherical vesicle with sharp boundaries and good physical stability of fluconazole within the prepared gel. Moreover, this formulation showed an excellent microbiological activity represented by a greater zone of inhibition (5.3 cm) compared with control gel (fluconazole in 2% hydroxy propyl methyl cellulose gel formula) (4.2 cm) and plain gel with no drug (0 cm) against C. albicans. Fang et al. studied transdermal estradiol gel and the results provided a higher permeation flux of estradiol across the skin. In vitro skin permeation study of dermal boswellic acid gel, was studied for 24 h, and a sustained release pattern was observed (84.83±0.153 mg/cm2). Inhibition of inflammation of the proniosomal patch was also significantly ($p<0.001$) higher compared to the marketed gel at the same dose [64]. In an attempt to modify the anti-hyperlipidemic effect and to reduce statins-induced hepatotoxicity, atorvastatin calcium (ATC) transdermal PNG was developed by a coacervation phase separation method. Different non-ionic surfactants (spans, tweens) were incorporated in the vesicle's lipid bilayer, along with lecithin. PNG gel was characterized for encapsulation EE %, vesicle size, polydispersity index (PDI), and ZP. The results revealed nano-sized (≤350 nm) range vesicles with relatively high ATC EE (70.12-88%). Ex vivo results of the selected formulation demonstrated the permeation superiority of ATC proniosomes over free drugs. The selected PNGs showed significantly high flux ranging from 4.23 to 8.46 µg/cm2 h - 1 with permeability coefficient values (P) (0.004-0.008 cm/h) when compared to free ATC dispersion, which significantly possessed lower flux and permeability coefficient results (2.92 µg/cm2 h - 1 and 0.003 cm/h respectively). The pharmacodynamic study revealed that transdermal administration of ATC-PNG succeeded in retaining the antihyperlipidemic efficacy of orally administered ATC without elevating liver biomarkers. Histological examination signified the role of optimized ATC-PNG in hindering statininduced hepatocellular damage [65]. Transdermal cilostazole (CLZ) proniosomes were prepared by a coacervation phase separation technique. The optimum formula composed of 540mg span 60 and 59.7mg of cholesterol, had the highest EE % of (75.125 ± 0.125%), PS of (300.3 ± 0.2nm), ZP of (-39.35 ± 0.15 mV), the percentage of the drug released after 2 h was (24.32 ± 0.13%) and after 24 h was (81.175 ± 0.325%). The safety of the proniosomes for topical application was confirmed by the histopathological examination. The CLZ-loaded proniosomes showed promising results with high potential to delivery it across the skin. CLZ loaded PNG was prepared by the coacervation phase separation method using span 60, cholesterol, and lecithin. The optimized formulation had the highest EE of 90% and an average PS of approximately 325 nm PDI reflected homogeneity in the formulation. ZP was -59.76 mV, high enough to indicate a stable formulation. The in vitro release studies manifested a sustained release behavior of clozapine from the PNG. The ex vivo permeation demonstrated noteworthy permeation of the drug through stratum corneum with a steady state flux of 18.26 ug/cm2/hr [66].

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Galantamine hydrobromide (HBr) is used for treating Alzheimer's disease and is described as proniosome gel by coacervation phase separation method to overcome the side effects of oral delivery. Microscopical observations of the gels showed vesicles of optimum size from 3.030 - 3.735 mm. The gel also showed an optimum rate of spontaneity in the range 9.60 mm3 x 1000 to 11.80 mm3 x 1000 and EE of vesicles in the range 66.15% to 86.92%. The gels had pH in suitable range of skin (5.92- 6.9). The in vitro drug diffusion studies revealed that the PNG containing tween 80 showed maximum drug diffusion (99.24%), whereas the gel containing span 20 showed minimum drug diffusion (71.74%) [67].

G. Intranasal routes

The nasal drug delivery method has some limitations like mucociliary clearance, degradation of drugs by the enzyme. Vesicular drug delivery systems can circumvent these limitations. Duloxetine (DX) is a new norepinephrine reuptake inhibitor used for treating depression. But it has high firstpass metabolism and low bioavailability (<50%) following oral administration, eventually leading to low cerebrospinal fluid concentrations. Khatoon et al [68] designed mucoadhesive thiolated chitosan (TCS) gel containing proniosomes of DX for intranasal drug delivery to enhance the drug's contact time with nasal mucosa, bypass the first-pass effect and target the brain possibly using the olfactory pathway. Here, soya lecithin, cholesterol, and tween 80 was used in the preparation of the gel. pH of the DX-loaded proniosomal gel (D-MPNG) was 5.67 ± 0.145, indicating the compatibility of formulations within the nasal cavity without producing irritation. Notably, D-MPNG exhibited better control, releasing only 24% DX at pH 7.4 over 24 h compared to 78% release at pH 5.5. The presence of thiol groups of TCS significantly controls water uptake, resulting in moderate swelling and higher viscosity; thus, providing a sustained effect for a longer period [69].

VII. COSMECEUTICALS APPLICATION OF PRONIOSOME

Cosmeceuticals are generally used to refer to skincare products that contain active ingredients that are beneficial for improving the skin's appearance and promoting healthy skin [70]. Antiaging cosmeceuticals are most frequently recommended by physicians, who use them as an integral part of a comprehensive skin rejuvenation program. Moisturizers and serum containing ingredients such as vitamin C, niacinamide, retinol, peptides, growth factors, and botanicals can all be used in this regard. Additionally, patients undergoing cosmetic procedures such as laser resurfacing and chemical peels may be given cosmeceuticals to prime the skin for procedures, encourage healing, and reduce complications after. Cosmeceuticals are also recommended for patients with acne, rosacea, eczema, and other skin conditions, where they are commonly used along with prescription medications. For example, moisturizers containing anti-inflammatory botanical ingredients may be used in conjunction with prescription medications for treating rosacea. Cosmeceuticals containing soy can be used to provide added skin lightening benefits when paired with hydroquinone. Applying therapeutic and cosmetic agents onto or through skin requires a non-toxic, dermatologically acceptable carrier, which not only controls the release of the agent for prolonging action but also enhances the penetration to the skin layer [71]. Proniosome gel meets such criteria, which are useful for the delivery of cosmetics and cosmeceuticals. The therapeutic agents which can be used for incorporation into proniosomal carrier systems include, moisturizing, nutritional, anti-wrinkle, anti-aging, cleansing, sunscreen particles, etc. Proniosome is a potentially scalable method to produce niosomes for the delivery of hydrophobic or amphiphilic drugs [72]. Anti-aging cream containing the methanolic purple glutinous rice extract loaded in niosomes was developed by Manosroi et al [73]. Anthocyanin present in purple glutinous rice extract is responsible for the anti-aging activity. After 6 cycles of heating and cooling test, the formulation with 1% w/v of the purple glutinous rice extract contained 52.28% anthocyanin ofthe initial. For in vivo antiaging activities, a cream containing niosomes loaded with the extract gave significantly decreased melanin index and skin roughness reduction of 14.05 and 9.95% of the initial, respectively. The percentage changes of the increased skin hydration, skin elastic extension, and skin elastic recovery when applied on human volunteers' skin with this formulation were +48.73, 24.51, and +35.98%, respectively Tretinoin (TRT) is a widely used retinoid for the topical treatment of acne, photo-aged skin, psoriasis, and skin cancer. TRT-loaded proniosomes were prepared by the slurry method with the help of span 60 and D-sorbitol, span 40, cholesterol 95% stabilized, and tween 20. prepared hydrated proniosomes were

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characterized by an evaluation of PS, the effect of drug concentration, EE, etc. EE of all hydrated proniosomal dispersions ranged from 76.6±0.001% prepared to use span 40 to 94.15±0.041% prepared using span 60. In vitro drug release was increased till 5th hour. Diferuloylmethane or curcumin is obtained from turmeric, which possesses infiammatory properties blocking the formation of reactive oxygen species. Proniosomes of curcumin were prepared using non-ionic surfactants (tween 80, span 60) either solely or in combination with cholesterol. The highest encapsulation efficiency of curcumin in niosomal formulations was 99.74%. Kinetically, niosomes fitted to the Korsmeyer-Peppas model with non-Fickian transport. The anti-inflammatory activity of curcumin in various formulations was evaluated using a rat hind paw edema method and the percentage of swelling was 17.5% following 24 h in the group treated with curcumin niosomal emulgel. Proniosomal formulations containing the natural antioxidant resveratrol (trans-3,5,4′-trihydroxystilbene, RSV) were prepared by Schlich et al. RSV is a polyphenol compound having anti-inflammatory, neuroprotective, anti-aging, and anticancer effects. Proniosomal powders were prepared by the slurry method and characterized. The hydration and sonication of proniosomes resulted in the formation of lipid nanoparticles with a mean diameter in the range 180-300 nm and a highly negative surface charge.

RSV release from proniosome-derived niosomes was investigated in simulated gastric and intestinal fluid. biocompatibility assay carried out on intestinal cells (Caco2) demonstrated that proniosomes prepared with an HLB of 13.5 were significantly less toxic than their HLB16.7 counterpart. All the tested formulations could be employed safely at the doses commonly administered by the oral route.

Canthaxanthin (CTX) is a xanthophyll (a subclass of carotenoids) with widespread applications in pharmaceutical and cosmetic industries. It is a superior antioxidant and scavenger of free radicals compared with carotenoids such as β-carotene [74].

CTX was encapsulated in proniosome powders, which were were prepared with an equimolar ratio of span 60/cholesterol and four different carriers, namely, maltodextrin, mannitol, lactose, and pullulan [75]. The study showed that the niosomes produced by hydration and sonication of the proniosomes were small (≤200 nm) and quite homogeneously dispersed (PDI ≤0.3). The encapsulation efficiency of CTX in formulations varied between 55.3 ± 1.8% and 74.1 ± 2.7% after hydration and sonication. Although light and high temperatures affected the stability of CTX drastically, encapsulation in proniosomes retarded its degradation. This formulation can provide convenient, nontoxic, and inexpensive vehicles for dissolving and stabilizing CTX in functional food products. O-padimate is a UV-B filter widely used as a sunscreen agent. A study investigated the combined influence of 3 independent variables in the preparation of O-padimate proniosomes, which were prepared by the slurry method with span: Brij, surfactant. The developed gels were characterized for vesicle size, morphology and EE, skin permeation studies, rheological properties, and sun protection factor (SPF). Results reveal that optimized O-padimate proniosomal formulations showed high SPF and low transepidermal water loss [76].

Rutin (Rut) is a natural flavonol that has various therapeutic properties including antioxidant and antitumor activities. Rut PNG for cutaneous applications was designed to improve the poor aqueous solubility of Rut. The gel was prepared by the coacervation phase-separation method and complies with the standard requirements in terms of PS (140.5 ± 2.56 nm), ZP (-27.33 ± 0.09 mV), encapsulation capacity (>50%), pH (7.002 ± 0.18), and rheological properties. The results showed high biocompatibility of the gel on the 3D reconstructed human epidermis model characterized by increased viability of the cells and lack of irritant and phototoxic potential. The values on 2D cells confirmed the preferential cytotoxic effect of Rut on melanoma cells (IC50 value: 8.601 µM, nuclear fragmentation) compared with normal keratinocytes. Our data suggest that the PNG is a promising drug carrier for Rut in the management and prevention of skin disorders [77].

VIII. CONCLUSION:

Future vesicular drug delivery techniques utilising proniosomes may be promising. They are one of the drug carriers used in vesicular drug delivery systems, which are an improved substitute. To liposomal drug delivery because of its controlled and prolonged action, greater physical and chemical stability, and potential for scaling for commercial viability. They provide excellent potential for enhanced drug administration through a variety of routes, including oral, parenteral, dermal, transdermal, ophthalmic, vaginal, pulmonary, and nasal. The dry form of

proniosomes can be used to make a variety of unit dose forms, including tablets, capsules, and beads. Proniosomes are being extensively researched as medication carriers due to their adaptability. There is a lot of scope to investigate new carrier materials for the preparation of proniosomes and their potential remains to be investigated to the full extent.

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