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Proniosomal Gel: A Provesicular Approach for Dermal Drug Delivery

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ABSTRACT

Pronisomal gels are emerging vesicular drug delivery systems suitable for many hydrophilic and hydrophobic drugs. They are composed of non-ionic surfactants, which turn into a liquid crystalline semisolid gel upon dissolving a minimal amount of adequate solvent and an aqueous phase. Upon application to the skin especially under occlusive conditions, they turn into niosomes due to hydration by skin moisture. Thus they are combining all the permeation-enhancing properties of niosomes but with the superior stability of semisolid formulations. They are also considered structurally similar to liposomes. Yet the preparation procedure and composition make them much more stable compared to liposomes. They can enclose both water-soluble and fat-soluble drugs and offer a lot of advantages in transportation, storage, and cost of production. The current review provides an overview of the different types of vesicular systems including niosomes with special emphasis on proniosomal gels and their applications mainly for dermal and transdermal routes using various categories of drugs.

1. INTRODUCTION:

The skin serves as a promising platform for drug delivery. It becomes one of the most advantageous routes of administration for different drugs either dermal or transdermal applications. Although, the stratum corneum (SC) remains the main barrier for the penetration of the drug molecules through the skin. During the past years, many techniques were developed to modify this barrier; therefore, the skin conveys a specified quantity of the molecules drug at a definitive rate to the dermal microcirculation. Vesicular carriers have gained notable attention towards improved dermal drug delivery. The role of the vesicles as drug delivery systems can be adjusted to produce variable effects either local or transdermal. So, the action of these vesicles can be described as controlled release drug carriers. They have distinct advantages over conventional drug delivery mainly related to being able to serve as drug-containing reservoirs. Also, the alteration of the particle composition can regulate the release rate to the target site and enhance the permeation rate or increase the stability of the drug molecules [1][2][3][4][5].

In the field of nanotechnology, there were numerous trials to develop various vesicular drug delivery systems. Prototypes of the vesicular systems are the liposomes and the niosomes. They can encapsulate both water-soluble and fat-soluble drugs. Liposomes are simply produced through the self-association of phospholipids in the aqueous phase to form a bilayer which might be spherical unilamellar or multilamellar vesicles. They were well-chosen to be an effective carrier to transdermal drug delivery because they can ease in the loosening of the stratum corneum and therefore this can help in increasing the permeation of active molecules. Although, liposomes offered several advantages as vesicular delivery systems, still have major problems. Liposomes may have some issues as chemical instability like oxidation of phospholipids, degradation by hydrolysis in aqueous solution, sedimentation, and aggregation on storage. The associated issues paved the way for the exploration of the non-ionic surfactant vesicles which are known as niosomes. Although niosomes are structurally similar to liposomes in having a bilayer, they are more stable, and therefore, they can present several benefits over liposomes. In niosomes, non-ionic surfactants are used to act as penetration enhancers, and thereby, they overcome the barrier properties of the skin and allow efficient drug delivery. However, the niosomes overthrown the complications associated with the chemical stability of phospholipids on storage, they still have few physical issues like

aggregation, fusion, and leaking of drug molecules from the vesicles or hydrolysis of the drug on storage [2][3] [6].

A more stable version of niosomes is the proniosomes, which are dry powders that form niosomal dispersion on brief agitation in hot aqueous media. This dry, free-flowing output is more suitable for long-term storage and sterilization. Proniosomes were considered as substitutes to liposomes and other vesicular systems for entrapping hydrophobic and hydrophilic drugs. They showed superiority over the other vesicular carriers, such as cost productivity, chemical, and physical stability in comparison to liposomes, low toxicity owing to non-ionic nature, and easy formulation, which made them a promising industrial product[7].

2. Types of vesicular drug carriers:

2.1. Liposomes

They are considered to be colloidal, vesicular systems that are composed of one or more phospholipidic bilayers with an aqueous core where diversity of materials and medications can be encapsulated. They are one of the most common vesicular delivery systems used to deliver the medication molecules to specific tissues. They can also be considered as an advanced technology tool that can be useful in many displacing as physics, chemistry, colloid systems, and biochemistry [2][8][9][10]. They have different shapes and sizes; either unilamellar (small unilamellar vesicles[SUV]with a size range of 0.02–0.05 um, large unilamellar vesicles [LUV] with size range around 0.06 um, or the multi-lamellar vesicles[MLV] whose size range is 0.1–5.0 um. Liposomes are amphipathic molecules, in which, the medication molecules can either be enclosed in an aqueous space or embedded into the lipid bilayer. Liposomes can be constuited from natural phospholipids and derived phospholipids with mixed lipid chains like egg phosphatidylethanolamine or of pure components like(dioleolylphosphatidylethanolamine) [11]. Liposomes are also considered to be advanced drug delivery systems. Due to the structural simarliarty between the lipid bilayer and cell membrane, they can deliver drug molecules more efficiently than the free drug. They increase the solubility of fat-soluble and amphibolic medication molecules. They can utilize the passive targetting technique for the cells of the immune system. They can produce sustained release effect . They help in the reduction for the exposure of the senstive tissuses to toxic drugs . They are biodegradabe, biocompitable, non immunogenic and can be coupled

with specific ligands to achieve active targetting [11][9]. However, they have many physicochemical instability issues such as sedimentation, aggregation, fusion, phospholipid hydrolysis, and drug leakage. Also, their production cost is very high. These mentioned instability issues led to the evolution of new vesicular systems such as proliposmes, niosomes, and proniosmes [10] [2][11].

2.2. Proliposomes:

Proliposomes can be a suitable substitute for liposomes. They are constuited from hydrophilic porous powder as a carrier, phospholipids, and medications that are dissolved in an organic solvent. The lipid and the medication molecules are mixed together covering the surface of a soluble carrier to form free-flowing granular material. This result showed controlled release, better stability, and increased solubility [12]. They opened new areas of liposome application where they can either be constuited *in-vivo* under the impact of biological fluids or in vitro before administration using revalent hydrating fluid. The physical stability of liposomes could also be enhanced without affecting their authentic features owing to their solid nature. They can be a potent carrier to make the oral absorption of hydrophobic medications more efficient. The proliposomes can be administrated through oral, parental, and the topical route. They can be a very good candidate as suitable carriers in gene delivery and are the suitable carrier for targeting anti-cancer drugs to tumor sites. They can be utilized for controlling drug release rates through manipulating the phospholipid composition of bi-layers [2][10][13][14] [15] [16].

2.3. Niosomes:

Niosomes are vesicles that are consisted of nonionic surfactants and cholesterol. The vesicle is constuited from a bilayer of non-ionic surface-active agents and thereby, they are named niosomes [17][18].

Nonionic surfactants in niosomes tend to orient themselves in such a way that the water-soluble end faces outward (toward the aqueous phase), whereas the fat-soluble end faces inward to each other to form a closed bilayer structure, which encloses solutes in an aqueous solution. Correspondingly, the closed bilayer structure of niosomes has hydrophilic inner and outer surfaces, with a sandwiched lipophilic area in between. Niosomes can be categorized into groups based on their vesicle size, namely, small unilamellar vesicles (0.025–0.05 μm), multilamellar vesicles (>0.05 μm), and large unilamellar vesicles (>0.10 μm) [19] [18].

Niosomes have been developed showing superior benefits over liposomes. Where, they showed improved efficacy, lesser side effects, and increased chemical and physical stability. They can provide higher drug entrapment efficiency comparing to liposomes as niosomes are formed from uncharged single-chain surfactant and cholesterols, in contrary to liposomes, they are formed from neutral or charged double chain phospholipids and the concentration of cholesterol is higher in liposomes than in niosomes. They are cost-effective for industrialized fabrication and they do not need specialized storage conditions contrary to liposomes. They prolong the circulation of the encapsulated medications and boost their metabolic stability in an emulsified form is contrary to liposomes. The niosomal vesicles can act as a depot system providing a better release for the medications in a controlled manner and a late clearance of the medication molecules from the circulation. They also can encapsulate the water-soluble drug by partitioning these molecules into their hydrophobic structure [17] [18]. On the other side, the most common issues associated with niosomes are physical stability problems such as aggregation, fusion, and leakage. Preparation of proniosomes may overthrow the issues discussed before because proniosomes can be hydrated instantly before use toresult in an aqueous niosomal dispersion [18].

2.4. Proniosomes

Proniosomes can be defined as dry formulations that are constuited from hydrophilic nonionic surfactant coated carrier system which can instantly be converted to niosomes upon hydration [17][20].

Proniosomes are produced from the combination of non-ionic surfactant and cholesterol, then this can be followed by hydration in the aqueous media. Where the surfactant molecules direct themselves in a way that the hydrophilic ends of the non-ionic surfactant are oriented outward and hydrophobic ends are oriented towards the opposite direction to form the bilayer. So, in other words, these systems can be defined as being liquid crystalline compact niosomes hybrids in which upon hydration, they can be transferred to niosomes [19][21].

Proniosomes can enclose both water-soluble and fat-soluble medications. The proportion between the nonionic surfactant and cholesterol could influence both the release characteristics and the entrapment efficiency of the integrated medications. They provide better entrapment of the drug molecules inside the vesicles increasing the therapeutic efficacy. The entrapment of the medications in the proniosomal vesicular structure preserves

their systemic circulation, provides controlled release, improves the permeation in the targeted areas, and minimizes the undesirable effects. They produce targeted and sustained drug delivery and decreased drug toxicity. They overcome chemical instability issues like hydrolysis of incorporated medications which minimizes the shelf life of the dispersion. The shape, the size, and the fluidity of the niosomes can be controlled upon required. Proniosomes are also termed as 'dry niosomes'.They present extra satisfaction for transportation; distribution, storage, and dosing that make them an adequate delivery system with the potential for use with a broad spectrum of medications. The permeation enhancing the impact of the added surfactants and the capability of these systems to be spontaneously formulated into transdermal patches makes proniosomes an attractive drug delivery system to be applied transdermally [3] [2][17][22][23][24][25][26].

2.4.1. Proniosomal gels:

Proniosomal gel preparations can be defined as semisolid liquid crystal products of non-ionic surfactants. Besides, they contain cholesterol and lecithin in lower concentrations. They can be formulated by dissolving the surfactant in a minimum amount of an organic solvent such as ethanol and aqueous phase as water. These structures are considered to be liquid crystalline compact niosomes hybrids that can be transformed into niosomes in situ after hydration. Based on the limited concentration of the added solvent, the formed proniosomes can be a blend of phases of liquid crystals which are characterized by being lamellar or hexagonal or cubic structures. The lamellar phase showed sheets of surfactant arranged in the bilayer, the hexagonal phase showed the cylindrical compact structure arranged in a hexagonal fashion, and the cubic phase consists of a curved continuous lipid bilayer extending to three dimensions. While formulating this gel, in the beginning, a less viscous composition is formed in some cases. On the other hand, by adding water, considerable interaction occurs between the surfactant polar groups leading to swelling of the bilayers. By adding more solvent, multilamellar multi-vesicular spherical structures are formed. Finally, the niosomal suspension can be formed after complete hydration of the vesicles. [3][27].

The semisolid consistency of the proniosomal gel makes it easy to be applied directly to the skin. Proniosomal gels are considered to be a selective vesicular system optimum for the delivery of many medications through the transdermal route due to the penetration enhancing effect of the added surfactants. [21][28][2] [26][17] [29].

By applying the proniosomal gel to the skin, they become hydrated and easily transformed into niosomal vesicles. When these vesicles approach the stratum corneum, they get aggregated and stick to the surface of the skin. This kind of interaction can lead eventually to producing high thermodynamic activity of the medication at the surface of the vesicle and on the stratum corneum contributing to augmented permeation of the lipophilic drug molecules into the skin layers [21]. Another proposed mechanism for permeation of proniosomal gel through the skin; the proniosomal gel can change the structure of the stratum corneum layer leading to structural modifications in the intercellular lipid layer. In brief, the presence of the phospholipids and cholesterol present in proniosomes can cause an increase in the permeation of active molecules in the skin tissues [30]. These gels avoid the problems caused by either liposomes or niosomes as hydrolysis or oxidation and this may increase the half-life of the incorporated drugs. They can perfectly encapsulate both water-soluble and lipid-soluble drugs. They show controlled and sustainable release of drugs. The formulations can be collectively described as being biodegradable, biocompatible, and non-immunogenic for the body [21].

Five main constituents are contributing to the formulation of the proteasomal gel, namely; nonionic surfactants either sorbitans or polysorbates, phosphatidylcholine (lecithin) soya or egg lecithin, alcohol (ethanol, isopropanol or butanol), cholesterol and finally the aqueous phase.

A. Nonionic Surfactants:

Concerning the used surfactants in the preparation of the proniosomal gel, they are divided into two main classes; sorbitan esters (Spans) and polyethylene sorbitan fatty acid esters (Tweens) which are described in Table 1 [31].

Table No. 1: The two main classes of surfactants (Sorbitan esters and Polyethylene sorbitan fatty acid esters [31][32]**.**

Surfactant	**Sorbitan esters (Spans)**	**Polyethylene sorbitan fatty acid esters (Tweens)**
Chemical nature	They are chains of partial esters and its mono/dianhydrides mixed with fatty acids. Spans can be described as sorbitan mono-esters. They can be produced easily through the dehydration of sorbitol. By increasing the degree of esterification, the HLB value (hydrophilic-lipophilic balance) can be highly decreased, leading to high increase in the degree of solubility for the fat-soluble entities.	They are chains of partial esters and its mono/dianhydrides mixed with fatty acids, ethylene oxide and sorbitol. The resultant product is non uniform and it consists of a blend of molecules of variable sizes. By increasing the degree of ethoxylation, the solubility of tweens in aqueous solutions is highly increased.
Examples	Span 20/span 40/span 60/span80	Tween 20/ tween 40/ tween 60/tween 80
Characteristics	Although sorbitan monolauarte (span 80) has the longest chain length, it shows lower entrapment efficiency than others. This could be explained on the basis of the presence of unsaturation or the presence of tilting in the carbon chain leading to decreasing the compactness of the bilayer and increasing the leakage of the vesicles. By adding moderate quantities of cholesterol, span surfactants can be ordered in an ascending way as follows: span 80, span 20, span 40, and span 60.	They were known to produce relatively low entrapment efficiency due to their hydrophilic nature. This can be compensated by adding a relatively high amount of cholesterol.

The ability of the surfactant to form a bilayer as well as the pattern of niosomes formation depends mainly on three main factors;

a. The hydrophilic-lipophilic balance (HLB) of the surfactant.

b. The phase transition temperature.

c. The critical packing parameter (CPP).

a. The HLB value:

The choice of surfactants must be dependent on the HLB value, which is a true indication of its capability to form the vesicles uniformly. Also, the HLB value has a major role in governing the drug entrapment efficiency of the resultant vesicles. It was proved that the HLB value between 4 and 8 is suitable for uniform vesicle formation. Nonionic surfactants with stearyl (C18) chains produce higher entrapment efficiency if compared to those with lauryl (C12) chains. The longer alkyl chain for the tween series of surfactants associated with the hydrophilic structure can result in high entrapment efficiency for the hydrophilic drugs. Surfactants with an HLB value in the range (14–17) were found to be not able to produce noisomes. On the other hand, the ones with an HLB value of 8.6 can produce niosomes with the highest encapsulation efficiency. As the HLB value decreases from 8.6 to 1.7, the entrapment efficiency decreases. Cholesterol could be added to enhance the stability of the formed vesicles, allows the hydrophobic surfactants to form vesicles, minimizes their tendency to aggregate, and contributes to more stability to the lipid bilayer through catalyzing the gel-liquid transition temperature of the vesicles [33] [25][34] [30] [3][28].

b. Phase transition temperature:

Phase transition temperature has a pivotal role in the degree of encapsulation of the drug into niosomes. As the transition temperature of surfactants increases, the permeability decrease, and the entrapment efficiency increases. Spans that owe the highest phase transition temperatures contribute to owing to the highest encapsulation efficiency and vice versa. It was found that the entrapment efficiency of tween-based vesicles is relatively low in comparison to that of span based ones. The hydrophilic surfactants exhibit high aqueous solubility on hydration, but, they do not reach a condition of being concentrated systems to permit free hydrated units to have aggregates and lamellar structures are produced. The role of lecithin is highly dedicated to augmenting the permeation of the medication molecules into the skin, enhancing the encapsulation efficiency of the drug owing to possessing high phase transition temperature. Span 40 and span 60 produce vesicles of larger size with higher entrapment of drug due to their high phase transition temperature and low permeability [33] [25][34] [30] [3].

c. The critical packing parameter (CPP):

The category of the vesicles formed can be predicted depending on the critical packing parameter (CPP) of a surfactant. The method of calculating CPP is based on the volume of the hydrophobic group, area of the hydrophilic head group, and length of the lipophilic alkyl chains of the surfactant. After calculating CPP, if, the value of CPP is between 0.5 and 1, it indicates that the surfactant is likely to form vesicles. On the other side, a CPP value below 0.5 indicates a large contribution from the hydrophilic head group area and it is meant to form spherical micelles. Finally, CPP value above 1 indicates a large contribution from the hydrophobic group volume and it must form inverted micelles [33] [25][34] [30] [3].

B. Phospholipids:

Phospholipids are the main constituents for biological membranes which can be obtained from variable sources such as egg yolk or soybeans where they are usually named after the source extracted from such as egg lecithin and soya lecithin. Lecithin is the major phospholipid type used in the preparation of proniosomal gel. It is a complex mixture of acetone insoluble phosphatides such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, combined with triglycerides and fatty acids. The composition of lecithin differs greatly based on the origin of the lecithin and extent of purification. In which, egg lecithin contains 69% phosphatidylcholine and 24% phosphatidylethanolamine, while soybean lecithin contains 21% phosphatidylcholine, 22% phosphatidylethanolamine and 19% phosphatidylinositol along with other constituents.

Lecithin has an important function in the vesicular system such as:

• It can act as a penetration enhancer, egg lecithin contains saturated fatty acid while soya lecithin contains unsaturated fatty acids, oleic acid, and linoleic acid, therefore, soya lecithin has good permeation over egg lecithin.

• It aids in improving drug encapsulation due to its high phase transition temperature that augments the compactness of the bilayers with minimum leakage of the medication molecules from the vesicles.

• Lecithin provides stability, but to a lesser degree in comparison to cholesterol [25] [30] [31][28].

C. Alcohols:

Alcohols used in proniosomal gel formulation have a considerable impact on the particle size of the vesicles and penetration capabilities of the drug molecules. The vesicles formed from the use of variable alcohols are of variable particle size. In which, they obey the following sequence according to the produced particle size: Ethanol > Propanol > Butanol > Isopropanol. The smallest size of vesicles produced through the use of isopropanol is attributed to its higher branching while the highest size of vesicles produced with ethanol is due to its higher water solubility [35].

D. Cholesterol:

The main membrane stabilizers incorporated in the proniosomal gel are cholesterol and lecithin. Cholesterol is a natural steroid that is believed to be one of the vital components of the cell membrane which has a significant role in the stability, fluidity, and permeability of the membrane bilayer. It is a vital component used in the design of proniosomes to improve stability and penetrability to the vesicles. Entrapment efficiency (EE) also depends to large extent on the concentration of cholesterol used. The entrapment efficiency can be in a direct proportion to cholesterol concentration to a definite extent. After exceeding a certain limit, it could be an inverse relationship. The increased entrapment efficiency may be attributed to many causes in which, the assembly of the cholesterol molecules into the vesicular bilayer leads to augment the rigidity and the stability of the vesicles, increase and the gel-liquid transition temperature of the vesicles. On the other side, by exceeding a definite limit, the decreased entrapment efficiency can be attributed to the competition present between the cholesterol and medication molecules leading to the leakage and the disruption of the lipid bilayer. The quantity of cholesterol can be added based on the HLB value of the surfactant. As the HLB value of the surfactant increases above 10, it is needed to utilize more than the minimum amount of cholesterol to make a substitution for the large head groups present [36] [34] [35] [37].

Cholesterol may reinforce bilayer assembly and avoids the aggregation by the incorporation of molecules that stabilize the system against the formation of an aggregate by repulsive steric or electrostatic effects [37].

E. The hydration medium (the aqueous phase):

There are three main examples frequently used in the preparation of proniosomal gels including hot water, 0.1% glycerol, and phosphate buffer. The encapsulation efficiency of various drugs can be readily affected by the pH of the aqueous hydration phase. Therefore, phosphate buffer with different pH's is most commonly used for the formulation of proniosomes. The choice of the hydration medium is based on the solubility of the drug [38] [35][30].

The Coacervation phase separation method is the most popular utilized technique for formulating proniosomal gels. Weighed quantities of the lipid, the drug, cholesterol, and the added surfactants are taken in a wide-mouthed glass beaker, and then the organic solvent (a minimal quantity of alcohol) is added. All the ingredients are mixed well with a glass rod and warmed over a water bath at 60-70°C until accomplishing complete mixing and the surfactant mixture was dissolved altogether. The bottle should be covered with a lid to bypass the evaporation of the solvent. Finally, the aqueous phase (glycerol, isotonic phosphate buffer, or distilled water) is added to the mixture in small quantities to assure that only the gel is formed and not the dispersion. Again, it is heated further for 2 min to produce a clear dispersion in which upon cooling to room temperature gives a proniosomal gel. In this formulation, water addition results in swelling of the bilayer due to the interaction of water and polar groups of surfactant [21][39] [30][40].

3. Dermal applications of proniosomal gels:

The use of proniosomal gels is considered to be very advantageous for transdermal delivery of various drugs. This is because; the system provides the ease of fabrication of the transdermal patch without the need for the dispersion of vesicles into a polymer matrix. This provides controlled systemic transdermal drug delivery. This was successfully implemented on the diuretic drug furosemide. Proniosomal gel formulation can be considered as a promising topical substitute able to maintain the medication level in the blood constant [41].

In the following section, a review of all classes of drugs fabricated as proniosomal gels will be presented as follows:

3.1. Anti-inflammatory agents:

To produce higher skin permeation, proniosomal hydrocortisone gels were successfully formulated by a coacervation-phase separation method utilizing versatile mixtures of non-ionic surfactants along with cholesterol and lecithin. The optimized prepartions were selected with the following composition (Span 20: Span 40, Span 20: Span 60, and Span 20: Span 80 mixtures) as they showed superior encapsulation efficiency in comparison to the other mixtures. In vivo studies revealed that the proniosomal 1% hydrocortisone was superior in comparison to commercial 1% hydrocortisone cream. This can be attruibuted to due to its prolonged action and improved efficacy [42].

Ketorolac tromethamine shows several side effects such as bleeding in the GIT and causing peptic ulcers making the oral route an unfavorable route of administration. Also, the short half-life of the drug (3.8 to 6 hours) embraces the need for a prolonged action or sustained-release formulations. Proniosomal suspensions were prepared to utilize handshaking technique and proposed for the transdermal administration of the drug. They were prepared by adding 1%w/v carbopol 940 containing a mixture of selected surfactant (sodium cholate) plus penetration enhancer (dimethyl sulfoxide), glycerin, methylparaben added to the prepared proniosomal suspension. The formulation showed high drug release data over 17 hours in comparison to the corresponding marketed product with acceptable skin tolerability [43]. Mefenamic acid proniosomal gel significantly has enhanced skin permeation and therapeutic efficiency presenting a superior inhibition of rat paw edema in comparison to the control group [44]. Meloxicam proniosomal gels were prepared similarly and presented better pharmacological activity in comparison to the standard meloxicam gel [45]. Other researchers successfully prepared proniosomal gel loaded with ursolic acid through incorporating the medication in a mixture of span 60, cholesterol, and alcohol utilizing coacervation phase separation technique to bypass the bioavailability problem of this potential biologically active compound. Entrapment efficiency of the formulated gel was found to be above 90% and the total percent of cumulative release of ursolic acid was found to be 60.8% after 24 h indicating the prolonged action. In vivo evaluation revealed that the developed formulation exhibited significant anti-inflammatory value in carrageenan-induced rat paw edema model and was found quite comparable with the standard diclofenac gel [46]. Proniosomal gel loaded with naproxen was developed to treat the inflammatory and degenerative disorders of the mucoskelatal systems. The vesicles constructed from (span 40: span 60) with a definite

weighed amount of cholesterol/lecithin /the drug showed high entrapment efficiency and release rate in comparison to the other formulas. This can be ascribed to the high transition temperature of span 40 and span 60 resulting in high entrapment efficiency of the medication molecules[47]. It was proposed that the delivery of α-mangostin utilizing proniosoaml gels improved the skin permeation as it is a highly fat-soluble drug [48]. Also, other anti-inflammatory drugs were successfully prepared as proniosmal gels for transdermal delivery include Lornoxicam [26][49], tenoxicam [50], flurbiprofen[51]and aceclofenac [52].

3.2. Antifungal agents

Tolnaftate proniosomal gels were prepared to avoid the slow release of the drug commonly observed from conventional ointments[53]. The addition of Phospholipid 80 H and Lipoid S45 as penetration enhancers made them more suitable for the effective topical therapy of tinea. Itraconazole proniosomes were incorporated in versatile gel bases in order to formulate proniosomal gels for transdermal drug delivery[54]. An optimized formulation was prepared with 1:9 molar ratio of cholesterol to lecithin showing very small particle size with high entrapment efficiency of fluconazole. The small particle size and the compatible nature of the vesicles allowed the drug to diffuse into the deeper skin layers and achieve higher drug retention [55]. Span 60, tween 80 (1:1), and cholesterol showed highest encapsulation efficiency and achieved a sustained release thus reducing the need for frequent administration and resulting in enhancing the topical efficacy of fluconazole [56]. A longer contact time between the antifungal agent teraconazole and vaginal mucosa was achieved using proniosomal gels [57]. Proniosomal gel loaded with miconazole nitrate for its antifungal activity against trichophyton rubrum was prepared utilizing coacervation phase separation technique. The in vitro antifungal activity of the prepared vesicles was executed using agar disc diffusion method. The results showed that the proniosomal formulation had better permeation of miconazole nitrate and there was a constant increase in the zone of inhibition with an increase in drug concentration [58]. Clotrimazole proniosomal gel permeation through the skin was significantly enhanced in comparison to the drug solution. Also, the anticandidal activity showed a significantly improved activity if compared to the marketed product and the carbopol gel [59]. No clear erythema, edema, or inflammation was detected on the rabbit's skin after one week of application of clotrimazole proniosomal gels[60].

3.3. Dopamine agonist (Parkinson's disease):

The low oral bioavailability and the need for multidose antiparkinson's therapy make the transdermal route a perfect candidate for drug delivery of antiparkinson agents. Ropinirole formulation integrated with span 60 was selected as being the optimized formulation as it showed good polydispersitivity with relatively small particle size and it can also accomplish the desirable release of ropinirole HCL along one day [61]. Bromocriptine proniosomal gel was found to exhibit high encapsulation, constant release pattern of the medication, and high permeation capabilities. The formulations were found to be quite stable, nonirritant to the skin over three months [62].

3.4. Antihypertensive drugs:

It was proven that enalapril maleate could be a well-chosen active constituent for formulating proniosomal gel for the management of hypertension. The transdermal proniosomal gel had proven to have well-sustained release characteristics. [63]. Lisinopril was also incorporated into proniosomal gels in addition to lecithin, cholesterol, surfactants, and other permeation enhancers [64]. To avoid the extensive first-pass metabolism of the medication lacidipine if administrated orally and to improve its permeation through the skin, proniosomal gel loaded with lacidipine was prepared [65].

Valsartan proniosomal gel preparations formulated with 9:2:9 molar ratios of span 60 to cholesterol to lecithin proved to have the highest encapsulation efficiency of the drug[66]. Similarly, metoprolol [67], atenolol [68], and ondansetron [69] were successfully explored for transdermal sustained delivery using proniosomal gels.

3.5. Skin diseases

Proniosomal gels were utilized as a new approach that localizes methotrexate in the skin to enhance the delivery of different medications through the skin. This becomes beneficial for the dermal cure of psoriasis or similar skin conditions [70]. Higher skin localization is also achieved using proniosomal gel loaded with tretinoin, which could produce enhanced efficiency for treating acne, lesser side effects as irritation of the skin, and higher stability of the product leading to increased patient compliance [71]. Another study aimed to formulate a modified proniosomal gel (HMPG) of hydroxyzine hydrochloride. HMPG formulations were prepared using coacervation phase separation technique with a versatile mixture of non-ionic

surfactants (Tweens and Spans) with phospholipids such as phospholipon 80H and 90H. Taguchi design of experiments was utilized to optimize different formulation variables. Tween 60: Span 40 with Phospholipon 90 H formulation showed the highest encapsulation efficiency of 94.8%. In vitro drug release was found to be as low as 1.33%, ex vivo drug permeation into the skin showed only 1.18 % and drug deposition in the stratum corenum was found to be 88.24% at the end of 24 hr. These findings revealed that modified proniosomal formulations of hydroxyzine hydrochloride were revalent for topical drug delivery system for the treatment of localized urticarial [72].

3.6. Antipsychotic drugs:

Proniosomal gel loaded with risperidone was proposed for efficient treatment of schizophrenia. They are utilized for transdermal delivery to overcome some disadvantages as the short duration and limited bioavailability of orally administered risperidone. The data gathered in this study proposes that the encapsulation efficiency for spans was higher in comparison to tweens. Proniosomes with span 60 showed no signs of erythema or edema with the highest flux across the rat skin. The relative bioavailability was above 90 % after transdermal administration of proniosomes [73].

3.7. Analgesic agents:

Oral therapy of tramadol, an opiate analgesic, undergoes extensive hepatic metabolism and needs regular administration. Transdermal therapy by virtue can avoid these issues and can enhance the efficacy and minimize the abuse liability of tramadol. Through formulating proniosomal gel, the possibility of transdermal delivery of tramadol and evaluating its therapeutic potential in vivo was examined lately. The vesicles exhibited optimal characteristics including spherical shape, good entrapment efficiency, adequate zeta potential, higher stability, and greater transdermal flux. The amorphization and dispersion of tramadol in the aqueous core of proniosomal vesicles were confirmed by differential scanning calorimeter. Release profile showed steady and prolonged tramadol release by Fickian diffusion. Transdermal therapy showed prominent reduction of induced twitches ($P < 0.005$) in mice and edema ($P < 0 .05$) in rats in comparison to oral tramadol. In conclusion, the highly noticed enhancement in the antinociceptive and anti-inflammatory effects from proniosome carriers implies its possibility to be a revalent substituent to the oral therapy of tramadol with greater efficacy[74].

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