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Review Article

BICELLE: A LIPID NANOSTRUCTURE FOR TRANSDERMAL DELIVERY

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ABSTRACT

The transdermal delivery is challenging route for drug delivery and henceforth has a narrow range of drug. The effective skin treatments require products able to penetrate the skin gently, remaining there and delivering its benefits in target layers. The permeability is the main barrier for the transdermal delivery system. However, due to certain advantages of the transdermal route, there are numerous transdermal delivery systems available which are managed to penetrate by enhancing skin penetration. Few studies have widened the transdermal approach for hydrophilic, macromolecules and conventional drug for new therapeutic indications. The present review summarizes a new lipoidal nanostructure formulation for the transdermal delivery of drug or cosmetic. Bicelles are formed by a long and a short-chain phospholipid dispersed in aqueous solution. Bicelle provides appropriate size, high stability, and biocompatibility of formulation which makes it a versatile platform that can be applied in different skin disorder. The limitation of Bicelles is in environments with high water content which modify their morphology. A new nanostructure that overcomes its limitations is known as: Bicelle encapsulated liposome, Bicosomes. The specific characteristics of bicelles and their high versatility, the use of these nanostructured lipid systems as a colloidal carrier should be considered. The review presents the method for preparation and evaluation. Bicelles and its modified formulation have a great potential in biomedicine, cosmetics, and term pharmacy.

Keywords: Transdermal delivery, Bicelles, Cosmetics, Bilayer vesicles, Nanostructure

INTRODUCTION

The transdermal delivery of drugs is a challenging area in pharmaceutical research. There are pros and cons of this route. Recently lot of advances in the technologies are resulting in a larger number of drugs being delivered transdermally including conventional hydrophobic small molecules, hydrophilic and macromolecules. Transdermal delivery is a desirable form of drug delivery to the target area via the human skin.[1]The skin is one of the most extensive and readily accessible organs of the human body. The skin of an average adult body covers a surface area of approximately 2 $m^2$and receives about one-third of the blood circulating through the body [2]. The Transdermal delivery system that has been developed over the years has been classified into different generation by Prausnitz *et al.*

According to the classification, the first generation dealt mostly with small, lipophilic and uncharged molecules that can be delivered in the therapeutic range by passive diffusion alone. Most of the TDS that are currently on the market belong to this generation. But with the advancement, the use of chemical enhancers and techniques such as ultrasound and iontophoresis increased for the delivery of drug molecules that cannot undergo passive diffusion. These belong to the second generation of transdermal products that target reversible disruption of the skin's outer layer, the stratum corneum or use an additional driving force for drug delivery [3]. The third generation of delivery systems is currently under development employing techniques such as microneedles and electroporation for delivery of macromolecules. These systems target its effect towards the stratum corneum, rather than modification of the drug molecule itself. The fourth generation comprises of vesicles drug delivery systems [4]. A various transdermal formulation such as microparticles, microspheres nanoparticle, and liposomes show enhance skin penetration dependent on its size [5]. It has a certain obvious advantage over other delivery systems [4, 6].

Advantages

1. Transdermal delivery system provides pain-free and convenient self-administration for patients in comparison with i. v. routes

2. It eliminates the frequent dosing administration and plasma level peaks and valleys which are associated with oral and injections. Thus maintaining constant drug plasma concentration

3. It is beneficial to the drug with short half-life

4. Because of more patient compliance, it is an approachable delivery system in long-term therapy such as chronic pain treatment or smoking cessation therapy.

5. It is good for drugs which are poorly bioavailable in GI tract and which are used for skin disorders.

6. It eliminates the Hepatic first pass metabolism which allows the amount of drug to be administered to be lowered.

7. It is suited best for hepato-compromised patients.

8. There are certain advances in formulations of conventional patch dosage form due to which the release rate of the drug can be controlled in desired pattern, on-demand or variable release rate.

However, skin is main permeability barrier for transdermal delivery [7]. It is elastic, rugged and under the normal physiological condition, self-regenerating. With a thickness of only a few millimeters (2.97±0.28 mm), the skin separates the underlying blood circulation network and viable organs from the outside environment.[2] It serves as a barrier against physical and chemical attacks and shields the body from invasion by the microorganism. The main challenges faced for transdermal delivery are described below.

Challenges

Anatomy and physiology of skin

Microscopically the skin is a multilayered organ composed of, anatomically, many histological layers, but it is generally described in terms of three tissue layers: the epidermis, the dermis, and the subcutaneous fat tissue as shown in fig. 1. The epidermal layer composed of squamous epithelial cells, show two main parts: the stratum corneum and stratum germinativum [2].

The stratum corneum forms the outermost layer of the epidermis and consists of many layers of compacted, flattened, dehydrated, keratinized cells in stratified layers. The latter layer of the epidermis is a regenerative layer. Studies have shown that the stratum corneum is replenished about every 2 w in a mature adult. In normal stratum corneum, the cells have water content of only approximately 20 % compared to the normal physiological level of

70%. The stratum corneum requires a minimum moisture content of 10% (w/w) to maintain flexibility and softness. It becomes rough and brittle [8]. The dermis is made up of a network of robust collagen fibers of fairly uniform thickness with regularly spaced cross-striations. This network may, however, be an artifact of histological fixation since examination of unfixed dermis suggests that it is a gel structure responsible for the elastic properties of the skin. Beneath the dermis, the fibrous tissues open out and merge with the fat-containing subcutaneous tissue. On the other hand, the upper portion of the dermis is formed into ridges (or papillae) projecting into the epidermis, which contains blood vessels, lymphatics, and nerve endings. This is a sheet of fat-containing areolar tissue, known as the superficial fascia, attaching the dermis to underlying structures [9].

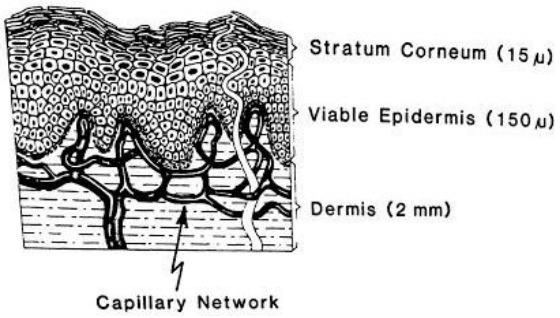

Fig. 1: The skin

Skin irritation

The delivery of drugs by these routes adds the potential for side effects in the form of skin irritation at the delivery site. The pH of the skin's surface has been reported to be in the range of 5.4-5.9 and is important in the maintenance of skin barrier function and defense against infection and disease. The skin also has an excellent buffering capacity against large changes in pH.[10] However applying the drugs and cosmetics on the surface of the skin can raise its surface pH and likewise induce skin irritation. For example, alkaline solutions of pH 9 and above applied to the skin have been reported to cause skin irritation. In the same study, an aqueous solution of pH 5 and 7 did not cause irritation when applied to the skin. A solution at pH 10 when applied to the skin, compared with pH of 4 or 6.5, increased the transition temperature of stratum corneum lipids.[11] Observed adverse effects were swelling of the stratum corneum and disruption of the skin barrier function, as indicated by an increase in transepidermal water loss.[12] To avoid skin irritation it is very important to buffer formulations applied to the skin as close to skin's surface pH as possible.

Skin permeation

The composite structure of the permeation skin barrier in humans is represented by three distinct layers: the stratum corneum (15 *u*m thick), the viable epidermis (150 *u*m thick), and the papillary layer of the dermis (100-200 *u*m in thickness). This composite structure is pierced in various places by two types of potential diffusion shunts: 40-70 hair follicles and 200-250 sweat glands on every square centimeter of skin area [1]. These skin appendages, however, actually occupy, grossly, only one-tenth of 1% of the total human skin surface. Even though foreign agents, especially water-soluble substances, may be able to penetrate into the skin via these skin appendages at a rate faster than that through the intact area of the stratum corneum, this trans appendageal route of Percutaneous absorption has provided a very limited contribution to the overall kinetic profile of skin permeation. Therefore, the skin permeation of most neutral molecules at steady state can thus be considered a process of passive diffusion primarily through the intact stratum corneum in the interfollicular region.[13] Thus, for studying the fundamentals of skin permeation and the mechanism of transdermal drug delivery, the organization of the skin can be represented by a simplified four-layer model as shown in fig. 2.

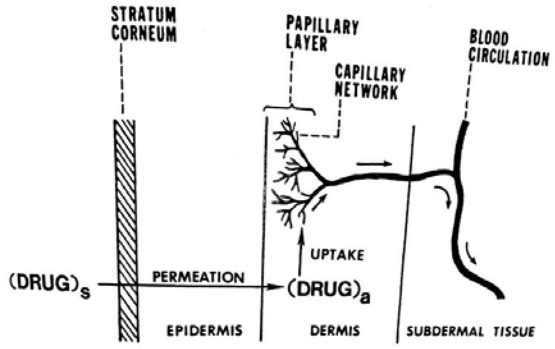

Fig. 2: A multilayer skin model is showing the sequence of Transdermal penetration of drug [Courtesy: Y. W. Chien; Novel Drug Delivery System, 2nd Edition vol 50 chapter 7]

The phenomenon of percutaneous absorption can be visualized as consisting of a series of steps in sequence: sorption of a penetrant molecule onto the surface layers of stratum corneum, diffusion through it and the viable epidermis, and finally, at the papillary layer of dermis, the molecule is taken up into microcirculation for subsequent systemic distribution. Here the diffusion through the stratum corneum is often a rate-limiting step.[7] The rate limiting stratum corneum is composed of dead, keratinized, metabolically inactive horny cells. A typical horny cell is made up of an amorphous matrix of mainly lipid and nonfibrous protein, within which keratin filaments (60-80 A ° in diameter) are distributed.[14] Moreover, hydration apparently increases the thickness of stratum corneum by several fold [15]. When compared the water diffusivity through stratum corneum and another biological membrane, the diffusional resistance of the stratum corneum towards the permeation of water molecules is approximately five orders of magnitude greater than that for erythrocyte membrane [14, 15].

The best evidence that the stratum corneum is essentially a uniformly good permeation barrier came from the studies using isotopic tracers. Thus, it suggests that the outer layers of the skin greatly impede permeation. Owing to the selective nature of the skin barrier, only a small pool of drugs can be delivered systemically at therapeutically relevant rates. Besides great potency, the physiochemical drug characteristics often evoked as favorable for percutaneous delivery include moderate lipophilicity and low-molecular-weight [16]. Thus, there rises a need of lipophilic vesicle for transdermal delivery of hydrophilic, polar drugs. These types of vesicles are of appropriate size, high stability, and biocompatibility. In order to replace the subcutaneous lipids or to provide drugs and other substances needed to restore skin functionality, several systems have been designed as skin. Micelles and liposome are perhaps some of the most used systems for these purposes. This review paper proposes a new delivery system called as Bicelle.

Bicelles

Bicelles have emerged as promising membrane models, due to their attractive combination of lipid composition and physicochemical characteristics. Bicelles are discoidal phospholipid nanostructures at high lipid concentrations. It contains a phospholipid with a long hydrocarbon chain situated in a bilaminar, flat center with a short-chained phospholipid located at edges. Usually, long-chained phospholipids namely dimyristoyl-phosphatidylcholine (DMPC) or dipalmitoylphosphatidylcholine (DPPC) forms a flat bilayers and a short-chain phospholipid, normally dihexanoyl-phosphatidylcholine (DHPC), stabilizes the rim of the structure as shown in fig. 3 [17].

The lipid bilayered structure of this system, with diameters in the range of 10-30 nm and thickness about 5-7 nm [18], presents optimal conditions as potential platforms for applications related to skin research. This is because of the structural resemblance of bicelle and lipid layers of the skin stratum corneum (SC), the absence of surfactants in the composition of Bicelles and the possibility of encapsulating different molecules in their structures.

The Bicelles are able to mimic the particular types of cell membranes [19]. Bicelles exhibit an intermediate morphology between lipid vesicles and the classical mixed micelles, combining some of the attractive properties of both of these model membrane systems. Like micelles, bicelles are non-compartmentalized, optically transparent, and effectively mono-disperse. On the other hand, bicelles, in contrast with the classical mixed micelles, have not surfactants in their structure and maintain some key bilayer properties that are absent in the latter systems [20].

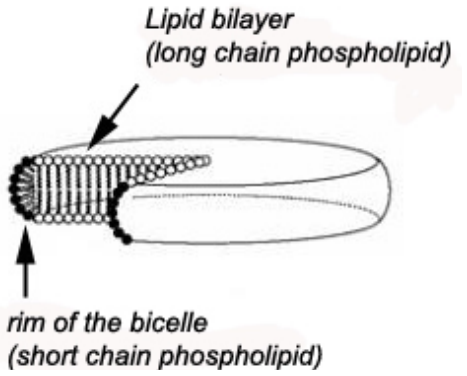

Fig. 3: Ideal bicelle model

Bicelles are able to modify biophysical skin parameters and modulate the skin's barrier function, acting to enhance drug penetration. Because of their nanostructure assemblies, bicelles have the ability to penetrate through the narrow intercellular spaces of the stratum corneum of the skin to reinforce its lipid lamellae. The bicelle structure also allows for the incorporation of different molecules that can be carried through the skin layers. Bicelles should be considered as promising carriers for dermal applications [17].

Formulation and characterization of bicelles

1. DMPC/DHPC bicellar systems

The classical description of bicelles as discoidal objects formed by a DMPC bilayer closed in the edges by DHPC molecules has been well accepted for samples below their main phase transition temperature (*T*m) [18]. In the last years, diverse studies have shown the morphology and phase diagram of DMPC/DHPC bicelles to be very complex [21].

At temperatures below the Tm, of the DMPC, the resulting bicelles were shaped disks [9]. As the temperature rose from the gel to liquid crystalline phase in the presence of Ln3+the bicelles fused together in an end-to-end manner to form lamellar sheets with perforated holes that were lined with DHPC. Further temperature increase caused phase separation with the formation of DHPC-rich mixed micelles and DMPC-rich-oriented lamellae, and the DHPC-rich mixed micelles became incorporated into the oriented bilayers at even higher temperatures [22] In the absence of Ln3+, bicelles were. disk-shaped in the gel phase, and chiral nematic in the liquid crystalline phase, which was described as wormlike micelles, and at higher temperatures were multilamellar vesicles [21]. Additionally, recent studies have demonstrated that inclusion of the small amount of charged lipids eliminated the appearance of the worm-like or ribbon phase [23].

2. DPPC/DHPC bicellar systems

The increase of only two carbons the long-chained lipid (from 14 to 16) there is a difference in the *T*m values (24.1 °C for DMPC and 41.5 °C for DPPC [24, 25] this fact results in significantly different polarities above and below their *T*m. Furthermore, in these systems, the q ratio has also been adjusted to 3.5 in order to diminish the concentration of DHPC and total lipid concentration (CL) was adjusted to 20%. On the other hand, thinking in the application of bicellar systems as colloidal carriers the preservation of the shape and size of bicelles would be a requirement. Hence, it is necessary that Tm of lipids building bicelles exhibit higher values than the experimental temperature (for *in vivo* application about 37 °C). The increase in the q value to3.5 (diminution in the relative proportion of DHPC) was chosen in order to diminish the surfactant character of the lipid mixture thus making the model more appropriate for *in vivo* studies. In the present section, we revised the dimensions and morphology of DPPC/DHPC bicelles and the bicelle-vesicle transition that takes place by the effect of dilution. A dilution of the systems would be desirable for purposes of the use of bicelles as colloidal delivery systems. The physicochemical characteristics of this new bicellar system have been characterized using 31PNMR, SAXS, DLS, and FFEM techniques.

Dimensions and morphology of the bicellar systems

The characterization of the bicelles is in general performed following the same methodology and techniques as those used to characterize the bicelles. Applying the form factor squared of the simplified Gaussian model to SAXS a bilayer thickness value (dB = 5.4 nm) was obtained. The size distribution curve obtained by DLS shows a HD value of 11.3 nm and a PI of 0.072. Fig. 10 shows a cryo-SEM image at 37 °C, in which small discoidal aggregates of about 15 nm in diameter were observed.[26] As a consequence, this result shows quite good agreement with the DLS data despite the different resolution of each technique. Morphological transformations of specific bicellar systems due to the changes in the composition, temperature and time after preparation. Two bicellar systems have been revised; a classic one formed by dimyristoyl phosphatidylcholine (DMPC) and di hexanoyl phosphatidylcholine (DHPC) and another formed by DPPC dipalmitoyl phosphatidylcholine and also by the DHPC.

Bicellar formulations for transdermal applications

Rubio L *et al.*, have proposed a bilayered disc-shaped nano aggregates for delivery of the anti-inflammatory flufenamic acid and Diclofenac diethylamine to the skin. They reported an increase in penetration of the drug loaded bicellar system as compared to drug ethanolic solution. Moreover in their extended work, they found that possible microstructural and organizational changes that were induced in the stratum corneum (SC) lipids and the collagen of the skin. Thus, the repair of the skin microstructure should be prioritized in anti-inflammatory formulations [27].

Ujawal R, *et al.* worked on a new method for crystallizing membrane proteins in Bicelles. When mixed with protein in a ratio of 1:4 (bicelle: protein) an optimal bicelle concentration range supported the crystal growth. They formulated the solution comprising of DMPC: CHAPSO (2.8:1) and tried to crystallize the Bacteriorhodopsin [28].

Barbosa-Barros and coworkers studied bicelles on skin treatment formed by DMPC/DHPC at q ¼ 2 and CL ¼ 20%. These bicelles can increase skin permeation, elastic parameters, and decreased skin hydration without affecting SC lipid microstructure and without promoting erythema or visual signs of irritation. This increase in the permeability could be related with an alteration in the phase behavior of SC lipids by the effect of phospholipids in the bicelles. the inclusion of ceramides in bicelles was also studied. It has been proven that bicelles support an inclusion of 10% mol ceramides without affecting their structural integrity [29].

The structural characterization of Amphotericin B DODAB was conducted in dioctadecyl dimethyl ammonium bromide (DODAB) bicelles. A new optical parameter is proposed for the estimation of the relative amount of amphiphile-bound monomeric AmB. With theoretical simulations of the spectra of spin labels incorporated in DODAB bicelles, it was possible to prove that monomeric AmB binds preferentially to lipids located at the edges of DODAB bicelles, rigidifying them, and decreasing the polarity of the region [30].

Lorieau J. L. and his co-workers demonstrated that alignment of a structured peptide or small protein solubilized in bicelles can be altered by either changing the phospholipid aggregate shape, charge, or both together. For the hemagglutinin fusion peptide solubilized in bicelles, they show that bicelle shape and charge do not change its helical hairpin structure but impact its alignment relative to the alignment medium, both in charged compressed acrylamide gel and in liquid crystalline d (GpG) [31].

Results of diacylglycerol kinase (DAGK) activity in various large bicelle systems (q=2.5) by L. Czerski *et al.* have shown that the enzyme activity was comparable to those found in the

mixed micelles and vesicle [32]. Jennifer A. *et al.* Indicated that small isotropic bicelles (q ¼ 0.5) provide an excellent substrate for phospholipase A2, a lipolytic enzyme. The aligned phase can be used to determine the orientation of the enzyme at the surface. The isotropic phase can be used to analyze the structure of the enzyme and to measure the enzyme activity. Small bicelles can offer nanoscale standardized membrane mimics for spectroscopic characterization of weak encounter complexes formed between ganglioside clusters and amyloidogenic proteins [33]

PEG-stabilized bilayer disks are flat bilayer disks prepared by a carefully optimized mixture of 1,2-istearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and 1,2-distearoyl-snglycero-3-phosphoethanolamine-N-[methoxy(polyethy-eneglycol)-5000][PEG-DSPE (5000)]. The bilayer disks are stabilized by inclusion of lipids with PEG tails, which assemble preferentially along the edge of the disks. The structure of the disks are open bilayer structures, with a hydrophobic discoid center built by DSPC and cholesterol and a hydrophilic PEG edge covering the hydrophobic rim by PEG-substituted lipids, without an aqueous inside.[33]The disks have the potential to generate more accurate partition values compared to liposomes with excellent long term stability. The size of the disks can be conveniently regulated by the amount of PEG-substituted lipids included in the lipid mixture. The disks show excellent long-term stability and the size of the disks can be conveniently regulated by the amount of PEG-substituted lipids included in the lipid mixture [34,35]. In order to obtain disk form, the PEG-lipid concentration needs to be above that at which the lipid bilayer becomes saturated with PEG lipid. In the case of PEG-lipids containing PEG 2000, and PEG 5000, disk formation typically begins at PEG-lipid concentrations corresponding to about 5 mol%, and PEG-lipid concentrations in the range of 15-20 mol% are required to produce pure disk preparations [34, 36]. The PEG-lipids accumulate at the highly curved rim of the disks while the phospholipids and cholesterol reside in the bulk of the bilayered aggregates.

Estibalitz Fernandez et al., worked to study the in-vitro effectiveness against free radical formation in the porcine skin. β-carotene antioxidant was incorporated in two different lipid nano aggregates, bicelles and bicosomes. Bicelles are discoidal nanostructures formed by self-assembly of phospholipids dispersed in aqueous solution. Bicosomes emerge as a strategy to stabilize and protect bicelles encapsulating these nanostructures in liposomes. Results from Dynamic Light Scattering (DLS) and cryo Transmission Electron Microscopy (cryo-TEM) demonstrated a slight modification in the size of both systems when β-carotene was incorporated. EPR revealed that after skin irradiation both systems presented free radical scavenging activity. This activity was statistically significant for bicosomes containing β-carotene. Considering these results, bicelles and bicosomes could be useful lipid systems for future dermo pharmaceuticals applications [37].

Po-Wei Yang *et al.*, studied Disc-shaped bicelles are formed by mixing long-chain lipids with short-chain lipids at suitable molar ratios, and they have a relatively of uniform size, typically around a few tens nanometers. They suggested a novel way of packing the DNA can be developed by using the much smaller disc-like bicelles. The anionic lipid bicelle-ion–DNA (AB–DNA) complexes can be formed with the help of divalent ions. Multi-stacked AB–DNA complexes can be formed with diameters of around 50–100 nm and lengths of around 50–150 nm as revealed by TEM. It was found that the anionic bicelle could not form stable complexes with DNA at low calcium ion concentrations, such as 1 mM. The AB–DNA complexes can be formed in the investigated range of 10 mM to 100 mM calcium ion concentrations. The interaction of DNA with anionic bicelles was investigated by SAXS. It was concluded that more DNA can be packed in the form of AB–DNA complexes at above the critical calcium ion concentration [38].

L. Rubio *et al.*, studied the potential usefulness of bicellar systems to retard the penetration of drugs into the damaged skin. The *vitro* percutaneous absorption of bicellar systems into *in vitro* damaged skin was studied. The active compound used in this study was diclofenac diethylamine (DDEA). A retardation effect for DDEA was detected by *in vitro* percutaneous absorption studies when DDEA was vehiculated in the bicellar systems with respect to an aqueous solution of the drug. It seems that the use of bicellar systems as a vehicle for topical application of DDEA on skin with an impaired barrier function may inhibit the penetration of DDEA to the systemic level. Such systems may consequently repair stratum corneum barrier function to some extent. The use of these systems could be considered a new alternative strategy to treat topically pathological skin with different drugs [39].

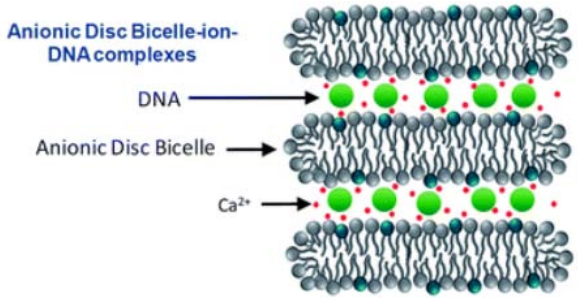

Fig. 4: Bicelle-DNA complexes

Ronald Soong *et al.*, reported that negatively charged bicellar mixtures, doped with dimyristoyl phosphatidylglycerol (DMPG), exhibited SANS profiles consistent with a perforated lamellar morphology for the magnetically alignable phase. Correspondingly, F68 diffusion in this magnetically aligned phase was normal Gaussian, in that the mean square displacements increased linearly with the experimental diffusion time, with a lateral diffusion coefficient of 1.9×10^{-11} m^2 s^{-1} consistent with a lipid bilayer inserted configuration. Neutral bicellar mixtures, that is, lacking DMPG, in contrast, displayed SANS profiles characteristic of ribbons arranged in such a fashion as to produce extended lamellae. Within the lamellae, the ribbons exhibited an in-plane periodicity (inner ribbon) of between 120 and 140 Å. The presence or absence of DMPG, rather than of F68, dictated the ribbon versus lamellar morphology. It is studied to show that bicelles are likely into extended lamellar sheets and eventually, fold into multilamellar vesicles [40].

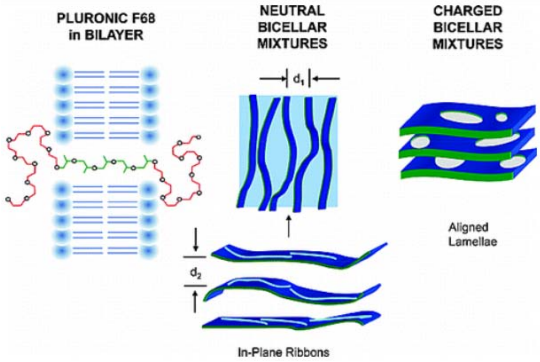

Fig. 5: Lamellar morphology of bicelle

M J Greenall studied mixtures of micelle-forming and lamella-forming amphiphiles in solution can form disk-shaped bilayers, sometimes referred to as bicelles. Using self-consistent field theory (SCFT), we investigate the structure and stability of these aggregates in a blend of two species of PS–PDMS diblock with PDMS homopolymer at 225 °C. The center of each disk is mainly composed of lamella-forming diblocks, while its thicker rim is mostly formed of micelle-forming diblocks. However, this segregation is not perfect, and the concentration of micelle farmers is of the order of 10% on

the central flat surface of the bicelle. The free energy density of the disk has a minimum as a function of the disk radius when both micelle-and lamella-forming diblocks are present, indicating that the bicelles have a preferred, finite radius. However, it decays monotonically when only lamella former is present, indicating that the bicelle structure is always unstable with respect to further aggregation in these systems. It was identified that a concentration range where the bicelle is predicted to have a lower free energy density than the simple spherical, cylindrical, and lamellar aggregates formed with similar amphiphile number fractions [41].

Advantages of bicelles: as smart lipid vesicle nanosystems

Bicelles are replacing lipid-based liposomes and surfactant based micellar systems as models to study membrane proteins. Liposomes are spherical particles constituted of phospholipid bilayers, often including sterols and/or membrane proteins, having an aqueous inside. In contrast to liposomes and micelles, bicelles do not have an aqueous inside. The DPPC/DHPC bicelles were able to penetrate the skin SC *in vitro* and formed vesicles inside the intercellular lipid spaces. *In vivo*, the driving force for the rearrangement of the bicellar lipids would be the hydration gradient across the skin, which varies from 15% to 29% in the SC and reaches 70% in the stratum granulosum. The conversion of bicelles into vesicles inside the SC hinders their migration outside the tissue and allows for a lipid reinforcement effect in the skin. Moreover, the possibility of adapting the aggregates' morphology depending on the specific application makes the bicelles smart nanosystems. These aggregates represent a new skin-compatible carrier for drug delivery, enriching the skin per se [42].

Liposomes can be either unilamellar or multilamellar and whereas the surface lipid leaflet is readily accessible for interactions with solutes, the inner leaflet, and the inner bilayers are initially hidden [43]. Compared with a liposome, the disks are open bilayer structures, with a hydrophobic discoid center built by DSPC and cholesterol and a hydrophilic PEG edge covering the hydrophobic rim by PEG-substituted lipids, without an aqueous inside. The disks have the potential to generate more accurate partition values compared to liposomes with excellent long term stability. The size of the disks can be conveniently regulated by the amount of PEG-substituted lipids included in the lipid mixture [43].

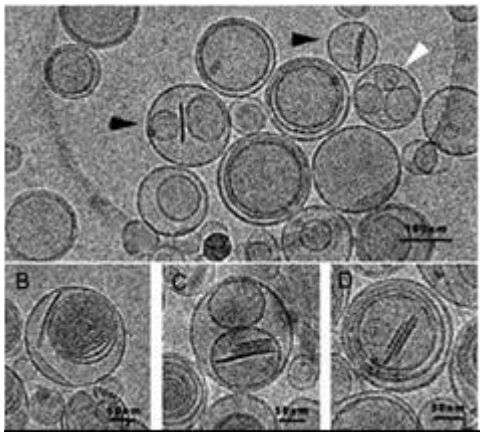

Fig. 6: Cryo-TEM images liposomes with bicelles inside (black arrowheads) and liposomes inside other liposomes (oligolamellar (white arrowheads))

Bicosomes

Under dilute conditions, Bicelles become larger and adopt a variety of morphologies. There is a need to protect bicelles in environments with high water content. Bicelles were formed in concentrated conditions and subsequently encapsulated in liposomes. These new structures are called Bicosomes. This formulation facilitates administration of Bicelles in diluted water solutions in such a way that bicelle morphology is preserved. It enhances the biological membrane permeability. The method of preparation of Bicosomes is described as follows. The liposome composition consisted of 80% Lipoid S-100 and 20% cholesterol. These two components were mixed in chloroform, and afterward, a lipid film was formed by removing the chloroform by rotary evaporation. The film was hydrated with the previously formed bicellar solution. These solutions were extruded three times through 800-nm polycarbonate membranes. The liposome solution was centrifuged to collect Bicosomes.[44] Characterization of systems before and after dilution by dynamic light-scattering spectroscopy and cryo-transmission electron microscopy showed that free bicelles changed in size and morphology, whereas encapsulated bicelles remained unaltered by the effect of dilution as shown in fig. 4.[44] Due to their characteristics, bicosomes can be useful as carriers and as permeater of either drug for systemic application, diagnostic marker molecules or cosmetic compounds increasing their capacity to repair damaged tissues.

Future scope

The effective treatment of the skin is still a challenge, and a number of skin diseases are considered chronic. Bicosome Technology is a versatile platform that can be applied in different skin disorders. The capacity for these systems to regenerate skin barrier function and to target specific skin layers is its usefulness in the dermatology field. The strategy of treatment based on bicosomes, in which actives are directed to specific skin layers and remain there exerting their action for days, is unique. No other technology on the market offers these effects. Different drugs such as antibiotics, anti-inflammatories, antifungals, vitamins, and peptides have been incorporated in the bicosome platform. The efficacy of the molecules is increased when they are carried in bicosomes. Our main target is the skin, but this delivery system can also be applied on other different tissues like mucosa. The way to market for Bicosome health care products is through partnering with larger pharmaceutical companies. Additionally, bicelles are able to modulate the biophysical parameters and barrier function of the skin. Given these properties, these nanostructures appear to be smart nanosystems with great potential in biomedicine and dermopharmacy.

CONFLICT OF INTERESTS

Declared none

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