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LIPOSOMAL COSMECEUTICALS: NEW ERA OF ANTI-AGEING FORMULATIONS.

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ABSTRACT

Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits. Some cosmeceuticals can act effectively when reaching their target sites in the deeper layers of the skin. However, the barrier nature of skin causes significant difficulties for compounds to be delivered through. Therefore, scientists are investigating various strategies to overcome these barrier properties. Liposomes have been claimed to improve the topical delivery of compounds. This review deals with the potential of liposomes as a skin delivery system for cosmeceuticals, with a focus on the clinical application of liposomes. The topical application of liposomes offers a wide range of advantages including increased moisturization, restoring action, biodegradability, biocompatibility and extended and slow dermal release. The incorporation of cosmeceuticals using suitable delivery systems is important in the management of cosmetic disorders.

KEYWORDS: cosmeceuticals, dermatology, drug carrier, liposomes, topical delivery.

1. INTRODUCTION

The human skin consists of three distinct layers: the epidermis, dermis, and subcutaneous layers. Among these, the epidermis is composed of stratum germinativum and stratum corneum (SC) and forms a protective barrier against the loss of moisture and electrolytes from the body and thus maintains normal skin physiology.[1] In the SC, the corneocytes produced from a proliferating keratinocyte are surrounded by the lamellar bodies of lipids, including ceramides, cholesterol, and fatty acids. Natural moisturizing factor (NMF), which is exclusively observed in the corneocytes of the SC, is a group of naturally occurring hydrophilic components including free amino acids, pyrrolidone carboxylic acid, lactate,

sugars, urea and minerals.[2] Hygroscopic NMF components are able to bind water molecules from the atmosphere and combine it with their own water content, thus allowing the stratum corneum to stay hydrated. Damage to the skin from causes such as atopic dermatitis, especially to the SC, lead to decreased levels of amino acids among the various NMF components in the SC.[3]

Liposomes are starting to be widely applied in dermatology. Topically applied lipid vesicles can be considered as one type of the so-called "percutaneous penetration enhancer"[4] Phospholipid vesicles enhance the penetration of compounds incorporated and/or encapsulated in them. It was demonstrated that conventional liposomes do not penetrate intact through the horny layer of the human skin.[5] They are deposited at the skin surface and disintegrate into multi-lamellar layers. Individual molecules of liposomal lipids seem to penetrate deeper. How- ever, an interaction of external lipids (fusion and/or mixing) with the stratum corneum lipids of the multi-lamellar intercellular lipid layers is evident.[4] Liposomes used in the topical application are often incorporated into a vehicle to achieve suitable viscosity and application properties.[6] The other parameter influencing the properties of topical liposomal dosage form is the size of liposomes. The importance of vesicle size distribution on the deposition of liposomal drugs into the strata of the skin was studied by du Plessis et al.[7] It was shown that the intermediate particle size of 300 nm resulted in both the highest reservoir in the deeper skin strata as well as the highest drug concentration in the reservoir, confirming that topical drug delivery is influenced by the size of liposomes.[8] The word “cosmeceutical” is used to define a product that fits the niche between a drug and cosmetics.[9] It is used in the professional skin care arena to describe a product that has measurable biological action in the skin, like a drug, but is regulated as a cosmetic since it claims to affect appearance.[10] Cosmeceuticals are not categorized by the FDA, but this term is used by skin scientists, physicians, and skin care professionals, to encourage the consumers to continue buying cosmetic products especially antiaging and sunscreen products, marketed by many manufacturers with scientific claims and natural positioning as a way to emphasize that using these products is not only necessary but also natural. Cosmeceuticals are the fastest growing segment of the personal care industry.[11] Cosmeceutical formulations now have expanded from skin to body to hair and a number of topical cosmeceutical treatments for conditions such as photo aging, hyperpigmentation, wrinkles, and hair damage have come into widespread use.[12] Recent researches focusing on cosmeceutical products highlighted strong growth perspectives in the coming years. According to them expanding at a rapid

compound annual growth rate of 7.7%, the global cosmeceutical market will reach $31.84 billion by 2016.[13] The global cosmeceutical market offers huge potential among the Asian countries, such as Japan, China, and India which are set to attract major players in the future. Japan has already made a remarkable position in the global cosmetics market and its position in the cosmeceutical segment is effectively improving. Areport, "Cosmeceuticals market to 2018," forecasted that the global cosmeceutical smarket will reach $42.4billion by 2018.[14]

2. LIPOSOME

The word 'liposome' is derived from the Greek: 'lipo' referring to their fatty constitution and 'soma' referring to their structure. A liposome is a spherical vesicle with a membrane composed of a phospholipid and cholesterol bilayer. Liposomes are simple, microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecule.[15] Kind of structure makes it possible to incorporate lipophilic drug into lipid bilayers as well as hydrophilic drug into the aqueous compartment.[16] To target the active ingredients, the lipid bilayer can merge with the cell membrane, thus delivering the liposome contents.[15] Due to the similar lipids with epidermis, liposomes can also improve dermal drug delivery while reducing systemic absorption.[17] This includes the ability of lipid vesicles, depending on lipid composition, to alter cell membrane fluidity and to fuse with cells. In early studies, liposomes containing stratum corneum lipids have been tested in order to enable better skin penetration.[18] Usually, liposomes are classified into three categories on the basis of their size and lamellarity (number of bilayers): i) small unilamellar vesicles (SUVs) or oligolamellar (OLVs), ii) large unilamellar vesicles (LUVs) and iii) multilamellar vesicles (MLVs).[19] Liposomes are one of the most investigated drug carrier systems due to their unique properties. The first work using liposomes as a drug delivery system for the local treatment of skin diseases was performed by Mezei and Gulasekharam (1980).[20] and appeared in the cosmetic market in 1986.[21] The suggestion was based on drug disposition data of the triamcinolone acetonide-loaded phospholipid liposomes formulated as lotions or gels. Encapsulation of triamcinolone acetonide into liposomes resulted around five times increase in drug skin deposition. The work of Mezei suggested that dermatological application of liposomal formulations compared with conventional ones led to increased drug skin deposition and decreased its systemic biodisposition.[22]

2.1 Advantages of topical liposomes

The major advantages of topical liposomes in dermatology are

i) to reduce serious side effects and incompatibilities that may arise from its drug localizing characteristics and thus avoiding systemic absorption; ii) to increase drug accumulation at the skin due to the mimic epidermis composition, which enables liposome substantivity with biological membranes; iii) nontoxic and biodegradable characteristics of liposomes; iv) easy to scale up for manufacturing[23]; v) washing out may be delayed, which provides waterresistant character[24]; vi) to moisturize and restore action of the constitutive skin lipids membranes; vii) to localize drug depots in the skin, resulting in sustained release of dramatically active compounds, so improving the therapeutic index of the drug at target site while reducing the toxicity profile to its minimum.[15] Besides its unique beneficials, liposomes show some disadvantages such as low stability, low encapsulation efficiency, high cost of manufacturing, degradation by hydrolysis or oxidation, sedimentation, aggregation or fusion of liposomes during storage.[16, 25]

3. INDICATIONS FOR LIPOSOMES AS DRUG CARRIERS IN COSMECEUTICS

3.1 Acne

Acne vulgaris (commonly called acne) is a skin disease that is most common during adolescence, afflicting more than 85% of teenagers.[26] Acne is an inflammation of sebaceous glands and associates with the immune response to various Grampositive bacteria including chiefly Propionibacterium acnes (P. acnes) andStaphylococcus epidermidis that colonizes sebum-rich follicles.[27] Clindamycin hydrochloride liposomes were prepared using either soya lecithin and cholesterol or hostaphate and cholesterol. Clinical treatment of acne vulgaris with a lotion of liposomal drug shows better efficacy than nonliposome lotion (especially of the treatment of pustules where clinical improvement was 77% of initial number). Application of a conventional lotion solution, a nonliposomal emulsion lotion and a liposomal emulsion lotion resulted in decreases of 42.9, 48.3 and 62.8%, respectively, in the total number of lesions after a 4-week treatment. The result supports the possibility of developing products utilizing the liposomal dosage form that are superior to the existing dosage forms for topical therapy.[28] Benzoyl Peroxide is a useful agent for treatment of acne, which acts by inhibition of the P. acnes in the pilosebaceous units. But its disadvantages such as bleaching of dyed clothing and local irritation with burning and erythema may limit patient compliance. A comparative double-blind study in 30 patients after 3 months showed a significant improvement in the therapeutic response (about two times) of treatment with liposomal benzoyl peroxide as compared with a conventional benzoyl peroxide gel, with obvious reduction in unfavorable symptoms and bleaching of clothing.[29] Liposomes were

shown as an interesting carrier for tretinoin in skin disease. Liposomal tretinoin dermal delivery was found to be affected by several factors including vesicle composition, morphology and size of liposomes. In particular, it has been shown that negatively charged liposomes showed strongly improved newborn pig skin hydration and tretinoin retention in the skin.[30] In a comparative clinical evaluation of liposomal gel of benzoyl peroxide and tretinoin for acne, it was concluded that the liposomal tretinoin gel was shown to have better response in the treatment of comedones, whereas the liposomal benzoyl peroxide gel of this investigation showed a predominant response in the treatment of papules and pustules. Hence, concomitant therapy with liposomal tretinoin and liposomal benzoyl peroxide gel is expected to give more effective treatment of acne.[29]

3.2 Hyperpigmentation and melasma

Facial and neck pigmentations are custom and considerable cosmetic problems that are common in middle-aged women, related to endogenous (hormones) and exogenous factors (cosmetics, perfumes, sun exposure), and often represent paramount causes of emotional distress.[31] 4n-Butylresorcinol is a derivative of resorcinol, which inhibits melanin production as well as the activity of both tyrosinase and tyrosinase-related protein-1. A randomized, double-blind, vehicle-controlled and split-face comparison study investigates the hypopigmenting efficacy of 4-n-butylresorcinol at lower concentrations. Liposomal 4-n-butylresorcinol 0.1% cream or vehicle was applied to each side of the face twice daily for 8 weeks of 23 patients with a clinical diagnosis of melasma. The melanin index of the 4-n-butylresorcinoltreated side showed a significant decrease when compared with the vehicle-treated side proved by mexameter measurements. No adverse reactions such as skin irritation were observed throughout the study. Liposomal 4-n-butylresorcinol 0.1% cream was well tolerated and demonstrated significant higher efficacy than vehicle alone in more than 60% of the patients for the treatment of melisma.[32] The whitening effect for hydrogel-containing liposomal linoleic acid was far greater than for free linoleic acid in ethanol or hydrogelcontaining linoleic acid evaluated in the ultraviolet (UV) radiation-stimulated hyperpigmented dorsal skin of brownish guinea pigs and UV-stimulated hyperpigmented human upper arm skin. Liposomes might enhance the incorporation of linoleic acid into melanocytes.[33] It was also shown that the permeation rate of linoleic acid in the liposomal formulation was found to be lower than that in the conventional formulation without liposomes, suggesting the increased retention time of linoleic acid in the skin by the liposomal formulation.[34] The percutaneous permeation experiments of linoleic acid-loaded

ethosomes (ethanolic liposomal) and transfersomes (deformable liposome) through human stratum corneum-epidermidis membranes were studied and showed that both carriers are accumulated in the skin membrane model as a function of their lipid compositions. The results showed that both vesicular carriers could be a potential system for the topical treatment of hyperpigmentation disorders. On the other hand, the permeation of ethosomes through the skin can be the result of the effect of ethanol both on the stratum corneum lipids and the vesicle fluidity, thus contributing to their superior clinical use to transfersomes.[35]

3.3 Classification of liposomes

The liposome size can vary from very small (0.025 μm) to large (2.5 μm) vesicles. Moreover, liposomes may have one or bilayer membranes. The vesicle size is an acute parameter in determining the circulation half-life of liposomes, and both size and number of bilayers affect the amount of drug encapsulation in the liposomes. On the basis of their size and number of bilayers, liposomes can also be classified into one of two categories: (1) multilamellar vesicles (MLV) and (2) unilamellar vesicles. Unilamellar vesicles can also be classified into two categories: (1) large unilamellar vesicles (LUV) and (2) small unilamellar vesicles (SUV).[36] In unilamellar liposomes, the vesicle has a single phospholipid bilayer sphere enclosing the aqueous solution. In multilamellar liposomes, vesicles have an onion structure. Classically, several unilamellar vesicles will form on the inside of the other with smaller size, making a multilamellar structure of concentric phospholipid spheres separated by layers of water.[37]

4. METHODS

4.1Thin-Film Hydration Method

The thin-film hydration procedure is the most common and simple method for preparation of MLV by dissolving the phospholipids in the organic solvents: dichloromethane.[38][54], chloroform[39, 40], ethanol and chloroform-methanol mixture (2:1 v/v; 9:1 v/v; 3:1 v/v). A thin and homogeneous lipid film is formed when solvent is evaporated under vacuum at the temperature: 45-60ºC. Nitrogen gas is involved in order to completely remove the residual solvent. A solution of distilled water, phosphate buffer[41] phosphate saline buffer at pH 7.4 and normal saline buffer are used in hydration step. The time for the hydration process varied from 1 h to 2 h at the temperature 60-70ºC. In order to obtain full lipid hydration, the liposomal suspension is left overnight at 4ºC.[40] The thin-film hydration method can be used

for all different kinds of lipid mixtures. The main drawbacks of the method are related to low encapsulation, difficulty of scaling up and the size distribution is heterogeneous.[40]

4.2 Injection Methods

a. Ether Injection Method

In ether injection method a solution of lipids is dissolved in ether or diethyl ether/methanol mixture which is slowly injected to an aqueous solution of the material to be capsulated. The subsequent removal of the organic solvent under reduced pressure leads to the formation of liposomes.[42, 43] The main disadvantage of the method is heterogeneous population and the exposure of compounds to be encapsulated to organic solvents or high temperature.

b. Ethanol Injection Method

In ethanol injection method the ethanolic lipid solution is rapidly injected to a vast excess of preheated distilled water or TRIS-HCl buffer. The incorporation of the drug in liposomal vesicle depends on its hydrophilic/hydrophobic character. Nimesulide as lipid soluble component incorporates better in liposomes than 5fluorouracil which migrates to external aqueous phase. The main advantage of ethanol injection method is including of non harmful solvent as ethanol, as well as easy scale up of the method. The possibility of formation of azeotrope with water reduces its applicability.

4.3 Sonication Method

The sonication method is based on size transformation and involves the subsequent sonication of MLVs prepared by thin-film hydration method, using sonic energy usually under an inert atmosphere including nitrogen or argon. The sonication method enables homogenous dispersion of small vesicles using bath type or probe type sonicator with a potential for greater tissue penetration. The probe tip sonicator delivers high energy to the lipid suspension. The possibility of overheating of the lipid suspension causes degradation.[44, 45] Sonication tips tend to release titanium particles into the lipid suspension which must be removed by centrifugation prior to use. The bath sonicators are the most widely used instrumentation for preparation of SUV.[46, 47] They are used for large volume of dilute lipids. The oxidation of unsaturated bonds in the fatty acid chains of phospholipids and hydrolysis to lysophospholipids and free fatty acids, as well as denaturation of thermolabile substances and very low encapsulation efficiency of internal volume are the main drawbacks of the method.

4.4 High-Pressure Extrusion Method

MLVs prepared by thin-film hydration method are repeatedly passed through filters polycarbonate membranes reducing the liposome size in high-pressure extrusion method.[48] The liposomes are prepared using thin-film hydration method subsequently using an extruder for ten cycles to obtain extruded liposomes with uniform diameters.

4.5 Reverse-Phase Evaporation Method

The reverse-phase evaporation method is used with the organic solvents such as diethyl ether/isopropyl ether or mixture of diethyl ether and chloroform (1:1 v/v) and a mixture of chloroform: methanol (2:1 v/v) containing phospholipids. The organic phase should be immiscible with aqueous phase, thus an oil/water emulsion is created. Phosphate buffer saline or citric-Na2HPO4 buffer is added to aqueous phase with aim to improve the efficiency of liposome formulations. The formation of liposomes is allowed by continued rotary evaporation of the organic solvents under vacuum. The main advantage of the method is a very high encapsulation rate. The main drawback of the method is the possibility of remaining the solvent in the formulation and it has difficulties to scale up.

4.6 Calcium-Induced Fusion Method

The calcium-induced method is based on adding of calcium to SUV. The formation of multilamellar vesicles is as result of fusion. The addition of ethylenediaminetetraacetic acid (EDTA) to the preparations results in the formation of LUV liposomes.[48] The preparation of LUV liposomes can be obtained only from acidic phospholipids.

4.7 Dehydration-Rehydration Method

The method of dehydration-rehydration is used as method for the preparation of liposomes, also.[49] The small unilamellar vesicles which are composed of phosphatidylcholine, 1, 2-dioleoyl-3- (trimethylammonium) propane, cholesterol and plasmid DNA are prepared by sonication method. The obtained formulation is frozen and left freezedried overnight. The formation of multilamellar dehydration-rehydration vesicles containing DNA in their structure due to the bound of the cationic charges of the inner bilayers is as a result of a controlled rehydration of the dry powders.

4.8 Freeze-Thaw Method

The method of freezing and thawing is introduced for increasing the trapped volume of liposomal preparations. The freeze-thaw method is dependent on the ionic strength of the

medium and the phospholipid concentration. It influences to a physical disruption of lamellar structure leading to formation of unilamellar vesicles. The unilamellar vesicles are rapidly frozen followed by slow thawing, while the freeze and thawing cycles are repeated. The preparation of MLV propranolol liposomes by freeze-thaw method is described in the literature.[49] The liposomal propranolol formulation is prepared by using distearoylphosphatidylcholine and dimyristoylphosphatidylcholine as phospholipids in phosphate buffered saline buffer, followed by six freeze-thaw cycles.

4.9 Microfluidization

A method based on microfluidization i.e. microemulsification is used for the large scale manufacture of liposomes. The preparation of antibiotic liposomes by thin-layer hydration method followed by sonication with a bath-type sonicator and microfluidization in order to achieve partial homogenization was described by Boltič et al.[49] The process of microfluidization is reproducible and yield liposomes with good aqueous phase encapsulation. Supercritical Fluids (SCF) in the Preparation of Liposomes Supercritical fluids are introduced in the preparation of liposomes to overcome existing problems with conventional methods such as requiring a high amount of toxic organic solvents and limited laboratory scale production. The most common used supercritical fluid in the preparation of liposomes in pharmaceutical field is supercritical carbon dioxide. It has several advantages: nontoxicity, non-flammability, recyclable and easy removal from the solvent, operation at moderate temperatures and avoiding degradation of the product in an inert atmosphere. The use of SCF allows controlling of extraction condition by variation of temperature, pressure or adding modifier solvents as cosolvents: acetone, ethanol, methanol, dichloromethane and ethyl acetate. A comparison between thin-film hydration method and SCF method is reported by Karn et al. A mixture of phosphatidylcholine, cholesterol and cyclosporin A is dissolved in ethanol followed by pumping supercritical carbon dioxide to the reaction vesicle in SCF method. Distilled water in hydration step in thin-film hydration method is used.

5. DISCUSSION

The combined results suggest that topically applied liposomal formulations, particularly those prepared from lipid mixtures of composition similar to the stratum corneum, would be an effective delivery system for the treatment of skin diseases. Since these liposomal formulations provide sustained, enhanced levels in deeper strata of the skin, they have the capacity to meter a sufficient quantity of drug into deeper tissue to treat the skin

symptomology. Such metering should also reduce the incidence of undesirable side effects arising from systemic administration, or enhanced systemic absorption of drug after topical administration with vehicles (e.g., alcoholic solution) that disrupt the stratum corneum bilayer structure. Liposomal carriers make a new horizon in dermatology. Liposomes are suggested to be good vehicles for delivery of therapeutics into skin because of associated hydrophobic lipid construction. It should be emphasized that, in general, liposomes not only play an important role as a drug delivery vehicle for skin tissue targeting, but also have a potential role in the transdermal application of cosmetics. In addition to the ability for drug delivery into skin layers, the liposomes are known to enhance skin hydration in dry skin conditions due to the similarity between liposome components and cutaneous lipids, thus making liposomes a novel application in cosmeceuticals and pharmaceuticals.

Liposomes as drug delivery system to and through the skin continue to be an area of research to be further explored for a better understanding.[50] Liposomal formulations provide sustained enhanced drug levels in strata associated with blood and lymph supplies and enable the delivery of sufficient quantities of drug into the skin. Standard lipid vesicles do not penetrate into deep skin regions and the probability of any systemic absorption is very low.[51] application of liposomes in the management of dermatological disorders as our literature review implied. Liposomes seem to be more beneficial for delivery of irritant, unstable and polar ingredients, which make them to be safer, more stable and easier to accumulate in skin, respectively. These advantages cause the concentration of cosmeceutical products formulators on liposomes, which consequently led to emerging the new classes of liposomes. The development of ethosomes and transfersomes recently became a key step toward an effective topical transdermal formulation. Although intensive research should take place to refine these systems, that could provide better efficiency and minimal side effects. Study on liposomes has developed substantially over the last 30 years and, nowadays, a wide range of liposomes varying in size, composition and surface characteristics were fabricated and introduced for required purposes. A number of extensive review articles have been published in this area.[52, 53] But the number of commercialized liposomal systems is far behind the expectations due to the relatively high cost of the products and problems related to physical stability. The methods for scale-up of liposomes, which produces vesicles in micro size, being difficult to reach nano size range if required for industrial production. In spite of these limitations, the development of research in this area will provide in the future the appearance of new products and patents related to liposomes for cosmeceuticals. One of the main aims of

research should be focusing on overcoming to problems against commercialization of liposomes. Exploring how to change or modify fabrication methods from laboratory to industry scale is important issue. Determining and fixing these problems is the challenge and mission for future development of new liposomal cosmeceuticals. Most of the studies cited in this review focused on in vivo applications of liposomes and clinical data, which have verified the enhancing efficiency of liposomes on topical drug delivery. Confirmation of liposomal use in clinical and in vivo systems may extend their applicability. Based on our presented information in this review, our conclusion is that liposomal formulations have been rightly highlighted in the topical dermatological treatments. This will guide the future studies to target other indications and show the benefits of liposomal cosmeceuticals in dermatology.

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