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Insights into the Application of Reverse Micelles in Cosmetic Formulations: A Review

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Synopsis

Reverse micelles are aggregates of amphiphilic molecules in nonpolar solvents. They have polar cores surrounded by surfactant head groups that can solubilize various hydrophilic compounds such as dyes, proteins, and antibiotics. They are frequently studied for extraction of organic and inorganic compounds. Advantages of reverse micelles are ease of production, high encapsulation efficiency, and protection of encapsulated compounds. The cosmetic market has been continuously growing over the years as more innovative cosmetics products are released into the market. Reverse micelles can be used as nano-sized carriers to encapsulate various hydrophilic active ingredients in cosmetic formulations. They can be prepared using safe, biocompatible, nontoxic, and biodegradable materials, thus are suitable to be incorporated into cosmetic products. The viscoelastic property and the skin permeation property can be adjusted. Targeted delivery and sustained release of active ingredients can be achieved through proper formulation. In addition to being directly included in formulations, reverse micelle systems are also used for the preparation of active ingredients and the analysis of cosmetic products for quality control. Therefore, reverse micelles show great potential for application in the cosmetic sector. This paper reviews related works in past two decades and provides some insights for future studies to broaden the implementation of reverse micelle systems in cosmetic products.

INTRODUCTION

Beyond the beauty of the face or attractiveness of the skin is the health of the skin itself. Human beings tend to spend a lot of money on beauty products to improve their individual appearance. In recent decades, skin care has gained increasing attention of people of all ages. This leads to the rise of the cosmetic market around the world. The cosmetic market in Asian countries is one of the fastest growing markets (1). The sum value of global

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cosmetics and toiletry products sold in the year 2004 was $230 billion and continues to grow (2). Several online market researches anticipate the global cosmetic market to exceed $400 billion by the year 2027. In 2013, $407 million was spent on cosmetic and toiletry products imported into Malaysia, indicating that the demand for these products is mainly met by imports (3). This reflects both the undersupply and low consumer awareness of local cosmetic products. A study revealed that Malaysians are not aware of the cosmetic products made in Malaysia (4).

Various active ingredients are included in cosmetic formulations for different functions, such as antioxidant activity, antimicrobial activity, antiaging properties, and UV filtering. However, not all active compounds are readily soluble in the solvents used in cosmetic formulations. Many techniques have been used to enhance solubilization of active ingredients in cosmetic formulations. These techniques include liposome, micelle, reverse micelle, solid lipid nanoparticle, noisome, nanocapsule, and others. Chemical stabilities, biocompatibility, and skin permeability of active ingredients can be increased with advance encapsulation technologies available for topical cosmetic application (5). The encapsulation technologies used in cosmetic formulations must also be non-irritating to the skin and nontoxic. Currently, in order to adhere to stricter regulations and consider an increasing public awareness of the environment, these techniques should also be sustainable and environmentally friendly.

Amphiphilic molecules or surfactants can self-assemble into micelles (oil-in-water microemulsions) or reverse micelles (water-in-oil microemulsions) at appropriate compositions. They have unique structures that can be used to solubilize hydrophilic and lipophilic compounds. Aqueous solubility of hydrophobic compounds is greatly enhanced by encapsulation inside micelles, while oil solubility of hydrophilic compounds is greatly enhanced through encapsulation in reverse micelles. This characteristic is very useful for blending various active compounds in cosmetic formulations. Micelles are commonly used in cosmetic formulations due to many advantages, including ease of production, high encapsulation efficiency, protection of active ingredients, adjustable rheological properties, good skin-permeation properties, targeted delivery of active ingredients, and sustained release of active ingredients. However, there are fewer reports on the incorporation of reverse micelle in cosmetic products.

This paper reviews the application of reverse micelles in cosmetics reported in the past two decades. The fundamentals of reverse micelle formation and the reports of reverse micelle for cosmetic applications are discussed in following sections. The authors' intention is to gather as much knowledge as possible and provide insights on the topic. Reverse micelles have the advantages of normal micelles. However, due to the formulations of cosmetic products currently available, direct utilization of reverse micelles in the formulations is rare compared to normal micelles. Instead, most reports utilized reverse micelles for the extraction and purification of active compounds such as proteins and plant extracts for cosmetic formulations. More research on the use of reverse micelles for cosmetic applications is needed.

ABBREVIATIONS:

AOT Sodium bis(2-ethylhexyl) sulfosuccinate

CMC Critical micelle concentration

CTAB Cetyltrimethylammonium bromide

HA	Hyaluronic acid
HLB	Hydrophilic lipophilic balance
IL	Ionic liquid
IPM	Isopropyl myristate
ML	Methyl laurate
MO	Monoolein
PC	Phosphatidylcholine
SC	Stratum corneum

SURFACTANT

Surfactants are one of the main components present in the mixture system aimed to form micelles. Surfactants are amphiphilic molecules that consist of both a hydrophobic tail and a hydrophilic head. The hydrophobic tail repels water or polar solvents while the hydrophilic head attracts them. The hydrophobic tail is made up of linear or branched alkyl chain lengths with 6 to 30 carbon atoms (6, 7). In general, surfactant molecules in a solvent will align themselves near the surface, or interfacial area, and reduce the surface or interfacial tension. The addition of surfactants into an oil and water mixture decreases the surface tension between the oil and water phases (8). Reduction of surface or interfacial tension then leads to micellization (9). This characteristic is exploited to greatly enhance the solubility of various molecules in aqueous or organic solvents.

Surfactants can be classified as anionic, cationic, non-ionic, and zwitterionic according to the charge of their hydrophilic head groups (7). The charge on the surfactant head group determines the net charge of the micelles formed. It also affects the type and strength of interactions between the surfactant molecules and the solutes. In general, attractive electrostatic interactions are the main driving forces for the encapsulation of active compounds into reverse micelles. Nonetheless, hydrophobic interactions and hydrogen bonds also contribute to the encapsulation of active compounds. Some of the surfactants commonly used to form reverse micelles are anionic AOT and cationic CTAB. Zwitterionic surfactants may have a net positive, negative, or neutral charge depending on surrounding pH value, although they generally have a neutral charge. Lecithin is a commonly used zwitterionic surfactant in cosmetic formulations. Non-ionic surfactants are rarely used alone in reverse micellar systems due to their low encapsulation efficiency. However, their weaker interactions are beneficial in providing a milder environment for the better protection of the active ingredients. They are usually used together with ionic surfactants to form mixed reverse micelles. Some commonly used non-ionic surfactants are the Span series and Tween series.

Surfactants have significant effects on the skin, such as altering the skin structure and allowing for the penetration of active ingredients. In order to maintain healthy skin or to avoid any clinical skin conditions, it is important to maintain the nature of the skin structure (10). Therefore, selection of suitable surfactants for the use in cosmetic formulations is crucial. The surfactants selected must not be skin sensitizers, irritants, or cause skin allergies. Sugar-based surfactants are recently applied in cosmetic products (11). These surfactants are milder to the skin while having good surfactant properties. Surface active ionic liquid (IL) has also gained increasing interest in cosmetic formulations. An

advantage of using surface active IL is that they can be designed to form micellar systems with the desired properties. In an effort to find more sustainable and environmentally friendly surfactants, researchers have studied the micellization of several biosurfactants. These biosurfactants are obtained from various natural sources such as microorganisms and plants. Some biosurfactants that can form reverse micelles are sophorolipids and rhamnolipids.

HYDROPHILIC AND LIPOPHILIC BALANCE (HLB)

HLB is an important parameter that determines the tendency of a surfactant to form normal micelle or reverse micelle (12). HLB of a surfactant depends on the hydrophobicity and hydrophilicity of the surfactant (13). It is described by a numerical scale ranging from 0 to 20, and relates to the ratio between the molecular weight of hydrophilic part of surfactant molecule to its total molecular weight. For non-ionic surfactants, HLB value of 0 means nonpolar and 20 means polar soluble. The HLB can be applied to ionic surfactants with a scale up to 50. The HLB of surfactants aimed to form reverse micelles or water-in-oil microemulsion has a value between 3 and 6. On the other hand, HLB of surfactants for the formation of micelles or oil-in-water microemulsion has a value between 8 and 18 (14).

CRITICAL MICELLE CONCENTRATION (CMC)

At low concentration, surfactant molecules exist as monomers in a solution. When the surfactant concentration in a solution is increased to a certain value, micelles or reverse micelles start to form spontaneously. This concentration is known as CMC. Reverse micelles formed above CMC are thermodynamically stable (15). Surface tension and conductivity measurement are common techniques used to determine the CMC of a surfactant solution. The procedures involve measuring the surface tension or the conductivity of a solution containing an increasing amount of surfactant and making a plot of the measured value. CMC of the system can be identified at the points where abrupt change in the measured values is observed. Another method utilizing solubilization of 7, 7, 8, 8-tetracyanoquinodimethane is also used to determine the CMC of a surfactant solution where rapid change in the color of dye occurs when CMC is reached (16, 17). CMC value depends on several factors such as the type of surfactant, temperature, pH, and ionic strength (7, 16). Typical CMC of commonly used surfactants are between 10^{-4} mol/L and 10^{-2} mol/L (11).

SELF-ASSEMBLY

When surfactant concentration in a solvent reaches their CMC value, the isolated surfactant molecules will spontaneously arrange themselves into ordered structures. The interactions involved during the self-assembly process are Coulomb interaction, hydrophobic interaction, hydrogen bonds, and coordination bonds (18). The self-assembly process is simple and requires only low energy input, such as stirring. Thus, micellar systems have gained interest as carriers for active compounds because of its ease of production and economical advantage (8). Surfactant concentration above their CMC should be used to ensure the formation of functional micelles or reverse micelles.

TABLE I
Morphology of Surfactant Aggregates at Different Packing Parameters

Packing parameter, p	Morphology of aggregates
<1/3	Spherical micelle
1/3–1/2	Cylindrical micelle
1/2–1	Vesicle
Around 1	Planar bilayer
>1	Reverse micelle

Several factors must be considered to obtain the desired micellar systems. Molecular structures of surfactant molecules, mobility of surfactant in the solvent, and reversibility or adjustability during the self-assembly process must be considered. Micellization conditions such as solution pH, ionic strength, and temperature may also cause different aggregates to form. Morphology of surfactant aggregates can be predicted by using a packing parameter as shown in following equation:

$$p = \frac{V_{bc}}{a_0 l_c}$$

Where p = packing parameter, V_{bc} = the volume of hydrophobic chain, a_0 = mean cross-sectional area of the head group in the aggregate, and l_c = length of the fully extended chain. The various morphologies that formed at different values of the packing parameter are given in Table I. The equation shows that morphology of micelles depends mainly on the hydrocarbon chain length and the dimension of the head group. Reverse micelles are formed at a p value larger than 1. The shape of reverse micelles can be spherical or cylindrical depending on the compositions of the micellar systems.

Understanding the micellization behavior of a surfactant system is helpful in determining its potential applications. Some commonly used methods to investigate the micellization process are transmission electron microscopy, dynamic light scattering, small angle neutron scattering, and fluorescence quenching. Simulation techniques like dissipative particle dynamics methods and molecular dynamics are also used to study the micellization process. Models can be developed based on free energy change during micelle formation to predict the properties of micelles (19). These experimental and simulation techniques can provide data to deduce the interactions between surfactant molecules, surfactant-solute interactions, and the solubilization site of the solute. Rheological changes such as micellar shape and viscosity of the system at different temperatures, ionic strength, pH, and presence of additives or impurities can be studied through those techniques. In mixed surfactant systems, the balance between molecular interactions, such as electrostatic interactions and hydrophobic interactions, also affects the micellization behavior. It is important to design cosmetic formulations with most suitable surfactants, optimized compositions, desired properties, and lower production costs.

NORMAL MICELLE

Normal micelles form when surfactant concentration in an aqueous solution reaches its CMC. Hydrophobic interactions are the main driving force of micellization (20). The

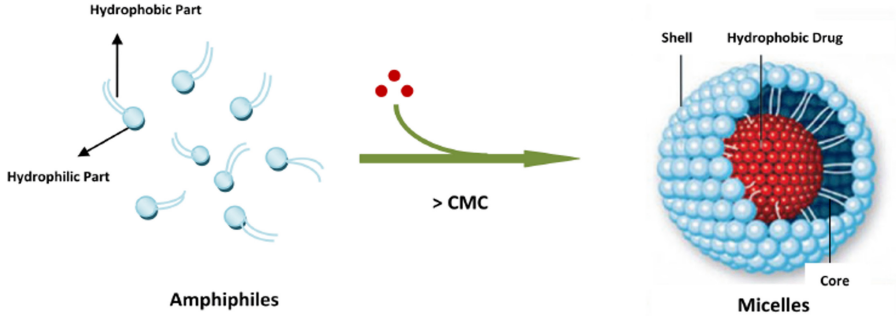

Figure 1. Structure of a spherical micelle encapsulating hydrophobic molecules (7).

structure of normal micelles resembles core-shell structures where the core is composed of oil phase or hydrophobic solvent. Surfactant molecules align themselves so that their hydrophobic tails point toward the micellar core and their hydrophilic head groups at the micellar surface. The shape of micelle can be spherical or cylindrical depending on their *p*. The hydrophobic core can encapsulate hydrophobic molecules, thus significantly increasing their solubility in aqueous solutions. More hydrophobic molecules are generally located deeper inside the micellar core during encapsulation. Fewer hydrophobic molecules may solubilize near the oil-surfactant interface or in the palisade layer of the micelle. The structure of a spherical micelle encapsulating hydrophobic molecules is shown in Figure 1.

The micellization process largely depends on the concentration of surfactant in the system (8). The number of micelles formed generally increases with surfactant concentration. High surfactant concentration may lead to micellar growth. The micelles formed are generally classified as spherical with their average diameter about double the diameter of the amphiphile surfactant molecule (6). Formation of three-dimensional, cubic micellar structures was reported when a high surfactant concentration is used (7). Temperature is another important factor affecting micellization and the structural morphology the micelles formed (16). This is related to the variation in the strength of the interactions between the surfactant molecules at different temperatures. Other factors such as surrounding pH, salt concentration, and the presence of additives may also influence the properties of the micellar system.

Micelles can act as nano-sized carriers to transport active ingredients across skin. Hydrophobic active compounds can be delivered to a targeted spot by encapsulation within the micelles. The controlled release of active ingredients from the micelles can be achieved through proper formulation design (8). This allows delivery of active ingredients that are normally unable to penetrate the skin. In cosmetic applications, the size of the micelle is an important factor because only micelles with a smaller diameter than the pores of the Stratum corneum (SC) can penetrate the skin barrier, while larger micelles are obstructed from penetrating the skin (21). However, micelles do not necessarily need to penetrate the skin to deliver the active compounds. Micelles may disintegrate on the skin surface and in the hair follicles to release their contents into deeper skin layers. In cosmetic formulations, essential oils and hydrophobic active ingredients are added to skin care products, such as toner, through solubilization in micelles (9). Functions of the active ingredients in micelles are preserved and their stability can be improved, allowing the products to be stored for longer duration.

REVERSE MICELLE

When surfactant concentration in an oil phase or nonpolar solvent reaches its CMC, reverse micelles are formed. The surfactant head groups gather to form an aqueous core while their hydrophobic tails point toward the bulk solvent phase. The structure of a spherical reverse micelle is shown in Figure 2. Size of reverse micelles are estimated through measuring the water content in the system (22). Karl-Fischer titration is usually conducted for measuring the water content of reverse micelle systems. Generally, the size of reverse micelles is from 1 nm to 10 nm (23). Cylindrical reverse micelles may also form depending on the composition of micellar systems and surrounding conditions. The water-to-surfactant ratio and the surfactant concentration in the bulk phase are important factors that determine the shape and size of reverse micelles formed (19). Regardless of shape, reverse micelles are very useful for the solubilization of polar compounds in nonpolar solvents. Reverse micelle systems usually contain a low amount of water. The water molecules are encapsulated in reverse micelles and dispersed in a nonpolar solvent (24). The polar compounds are encapsulated in the water cores of reverse micelles (17, 25). The suspension and dispersion of polar soluble ingredients in oil phases is made possible by utilizing reverse micelles formation (15).

Reverse micelle systems are often used in the extraction of biological compounds, enhanced oil recovery, and the formation of nanoparticles. Reverse micelles are also used in the investigation of biomaterial due to their resistance to water properties (26). Reverse micelles can be produced at room temperature, thus making it more advantageous compared to other nanoparticle systems (27). Extraction using reverse micelles is usually done in two stages: the forward extraction and the backward extraction (28). Forward extraction involves selective dissolution of bioactive compounds into the reverse micelles, and backward extraction involves the release of encapsulated compounds into the fresh aqueous phase (22). Reverse micelle extraction is particularly effective at extracting charged compounds. The possibility of biodiesel production using diesel-based, reverse micelle was also reported (Nguyen et al., 2010). Reverse micelle systems have potential in formulating innovative cosmetic products. The following sections will focus on discussing the applications of reverse micelles in relation to the cosmetic field.

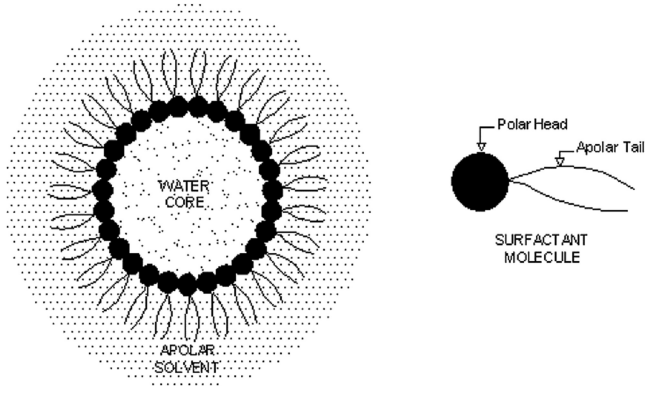

Figure 2. Structure of a reverse micelle (43).

REVERSE MICELLE IN COSMETICS

Reverse micelles can be applied in cosmetic formulations to encapsulate hydrophilic active ingredients. Encapsulation in reverse micelles can protect the active ingredients and preserve their activities. The solubilization and encapsulation of proteins and dyes in reverse micelles show potential improvements in cosmetic formulations (23, 29). Furthermore, the application of reverse micelles in cosmetic skin care products shows the enhanced penetration of active ingredients into the SC and through the epidermal barrier (17). In addition, reverse micelle extraction has been used to extract various active ingredients, such as plant extracts, for use in cosmetic formulations.

DIRECT APPLICATIONS IN COSMETICS

The direct inclusion of reverse micelles in cosmetic formulations is possible yet they are limited in their function. This means that reverse micelle systems may not be suitable for all skin care formulations. Substantial dirt such as sebum and cosmetic residues can be removed from the skin's surface by using cosmetic products formulated with oil-based emulsion or microemulsion (9). Oil-based liquid cleansers have the advantage of retaining the oiliness on skin's surface after cleansing. This is not achievable using typical water-based cleansers as they contain only a small amount of oil. This can be a reason for introducing reverse micelles into the cleansing formulations since the reverse micelles tend to form in nonpolar solvents such as oil (15). The reverse micelles in the formulations can improve the cleansing property through encapsulation. Examples of these cosmetic products are cleaning oils, gels, and lotions. Another cosmetic formulation that can benefit from using reverse micelles is lipstick. Lipsticks in general are made up of oil-based formulations which have a lower moisture content. To increase the moisturizing function of the lipsticks, reverse micelles are employed to encapsulate water-soluble collagen in the oil phase of the lipstick formulations (30).

Reverse micelles allow hydrophilic active ingredients to be included in cosmetic formulations, especially the oil-based ones. The components used must be mild to the skin and nontoxic. Examples of such reverse micelle systems are AOT in orange essential oil (31), AOT in Isopropyl myristate (IPM), and AOT in Methyl laurate (ML) (32). These reverse micelle systems utilize nontoxic solvents and do not include co-surfactants. IL-AOT–based reverse micelle in IPM or ML shows potential in cosmetic applications (33). The advantage of IL is that it can be tailored to have certain properties, it has less toxicity, and it is environmentally friendly. The mixture of lecithin, sophorolipids, and rhamnolipids in IPM or ML is able to form reverse micelles at an appropriate mixture ratio (34). This reverse micelle system shows good tolerance toward changes in temperature and electrolyte concentration, thus is useful for designing more robust formulations. Inclusion of biosurfactants also helps improve the biocompatibility, sustainability, and biodegradability of the formulation. All of the aforementioned reverse micelle systems can be used to encapsulate hydrophilic active ingredients and are suitable to be used in cosmetic formulations.

The encapsulation of various active compounds and drugs in reverse micelles has been reported. A food-grade lecithin reverse micelle system was used to encapsulate gallic acid, p-hydroxybenzoicacid, protocatechuic acid, and tyrosol (34). It was found that the antioxidant activities of the encapsulated active compounds are preserved. AOT/ Phosphatidylcholine (PC) and AOT/ Monoolein (MO) reverse micelles in soybean oil can solubilize ascorbic acid,

TABLE II
Reverse Micelle Systems and Encapsulated Active Compounds or Drugs

Reverse micelle system	Encapsulated compounds	Reference
Lecithin/IPM	Insulin	40
AOT/n-heptane Igepal CO-520/cyclohexane	Ascorbic acid	41
Soybean phospholipid/camelina oil	Quercetin	42
Glyceryl monooleate/IPM/isopropanol	Hyaluronic acid	17
Reverse micelle form by FDA compliance materials	Deferoxamine	43
Polyglyceryl-3-diisostearate/vegetable oils	Polar antioxidants	44
Span 80/glycolipid/olive oil	Diclofenac sodium	45
Food grade lecithin reverse micelle	Gallic acid, p-hydroxybenzoicacid, protocatechuic acid, and tyrosol	35
lecithin/IPM	Lidocaine	46
Tween 80/Span 20/IPM/isobutanol	Sodium levothyroxine	47
AOT/PC/soybean oil	Ascorbic acid, folic acid, and $FeSO_4$	36
AOT/MO/soybean oil	Ascorbic acid, folic acid, and $FeSO_4$	37
AOT reverse micelles Lecithin reverse micelles	Acrylamide	38
AOT/isooctane	C-phycocyanin	39
AOT/IPM	Glyceryl trinitrate	48

folic acid, and $FeSO_4$ (36, 37). PC acts as a zwitterionic co-surfactant, while MO acts as a non-ionic co-surfactant. The study showed that mixed surfactant systems can promote the formation of reverse micelles. The addition of NaCl may also promote the formation of reverse micelles. All components are food grade thus are safe to include in cosmetic formulations. Another study shows the encapsulation of acrylamide in AOT and lecithin reverse micelles. Micellar growth and sphere-to-cylinder transition were observed after the addition of acrylamide (38). Reverse micelle systems have been reported to solubilize various dyes. C-phycocyanin can be solubilized in AOT reverse micelles in isooctane (39). The resulting solution has a nice blue color appearance. This shows the potential to use natural dyes in cosmetic formulations through reverse micelle systems. Examples of reverse micelle systems encapsulating active compounds or drugs are given in Table II.

The formation of cylindrical reverse micelles is triggered by adjusting the compositions of the reverse micelle system. When cylindrical reverse micelles become long enough to entangle each other, organogel is formed. The formation of organogel is mainly driven by hydrogen bonding and hydrophobic forces (49). Organogel still can effectively solubilize hydrophilic compounds in nonpolar solvents, but it has different viscoelastic properties compared to spherical reverse micelle systems. Lecithin is commonly used to form cylindrical reverse micelles. Lecithin alone forms spherical reverse micelles. Certain additives can trigger the sphere-to-cylindrical transition of lecithin reverse micelle and then lecithin organogel may form. A recent study shows that addition of sugar alcohols causes the formation of cylindrical lecithin reverse micelle in n-decane (50). The viscoelastic properties of the system can be controlled by using different sugar alcohols and temperatures. Another study shows that the addition of inorganic salts such as LiCl, LiBr, LiI, NaBr, NaI, and KI leads to the formation of lecithin organogel (51). The organogel was found to form easier when using alkane solvents with longer hydrocarbon chain length. The addition of certain carboxylic acids like citric acid and 1,2,3-propanetricarboxylic acid also caused the formation of lecithin organogel (52). It depends on the number of carboxyl groups in the carboxylic acids. Lecithin organogel has been tested for encapsulation of various active compounds such as methyl nicotinate, fenretinide, curcumin (53), caffeine or caffeine

microparticles (54), and Tamoxifen (55). Lecithin organogel has many advantages including ease of preparation, safety, biocompatiblity, protection of active compounds, enhanced skin permeation, and long-term storage stability. Therefore, it is a promising formulation to be included in various cosmetic products for topical applications.

The SC layer of the skin acts as the first barrier that denies entrance of foreign substances and protects the inner skin layers. Sometimes it is desirable to deliver active compounds into the skin layers to repair the skin's structure and improve the appearance. However, most active ingredients cannot normally enter the skin layers. Reverse micelles can be employed as nano-size carriers to improve the skin penetration of active ingredients into the SC layer (17). Surfactants are known to modify the skin structures. Besides that, reverse micelles can improve the hydration of the SC layers (16). These factors, combined with the small size of reverse micelles, allow the reverse micelles to penetrate skin layers while carrying their contents. Through appropriate formulation, the reverse micelles are able to release their contents at a desired spot, thus achieving targeted and sustained release of active ingredients. Delivery of active compounds through topical administration follows several routes to reach the targeted sites. These penetration routes are shown in Figure 3. The transcellular route involves direct penetration of substances though the corneocyte. The intercellular route involves penetration following gaps between the corneocyte, but not directly across the corneocyte. The trans appendageal route involves delivery via hair follicles (56). Nevertheless, penetration deep into the receptor section and systemic system of the body may not be a desirable property for skin care products. Therefore, cosmetic formulators must optimize their designs to ensure that no side effects will arise after applying the skin care products.

Potential of reverse micelles as carriers for active compounds and drugs has been reported by researchers. Hyaluronic acid (HA) can be encapsulated in glyceryl monooleate reverse micelles and dispersed uniformly in IPM (17). HA is a cosmetic supplement that is used to retain the moisture and elasticity of the skin especially after UV exposure. The study shows that reverse micelles greatly enhance HA permeation in the SC, epidermis, and dermis layers. The SC penetration occurs mainly through the intercellular route. Then, the reverse micelles collapse and release HA into deeper skin layers. The reverse micelle delivery system of deferoxamine was formulated using FDA compliant materials like emulsifiers cetyl alcohol and plurol oleique (43). The formulation enhances permeation and provides sustained release of deferoxamine. The delivery performance of reverse micelle systems are affected by various factors. The addition of glycolipid can reduce the size of reverse micelles and enhance skin permeation (45). Water content and viscosity are found to affect skin permeation and the release of active compounds (40). Another study reported that skin permeation property has a complex relationship with the structure of polyethylene glycol surfactants used to form the reverse micelles (57). Integration of a reverse micelle system on other formulations can improve the delivery performance. Reverse micelle formulation with patches was reported to provide extended release of lidocaine to the skin (58). Inclusion of reverse micelle in film formulation was found to increase skin retention of sodium levothyroxine (47). Various studies showed that a reverse micelle system has the potential to be used as delivery system of hydrophilic active ingredients in cosmetic formulations.

INDIRECT APPLICATIONS IN COSMETICS PRODUCTS

Indirect application here refers to reverse micelle systems that are not included in final cosmetic formulations or products but are used to prepare the ingredients or to analyze

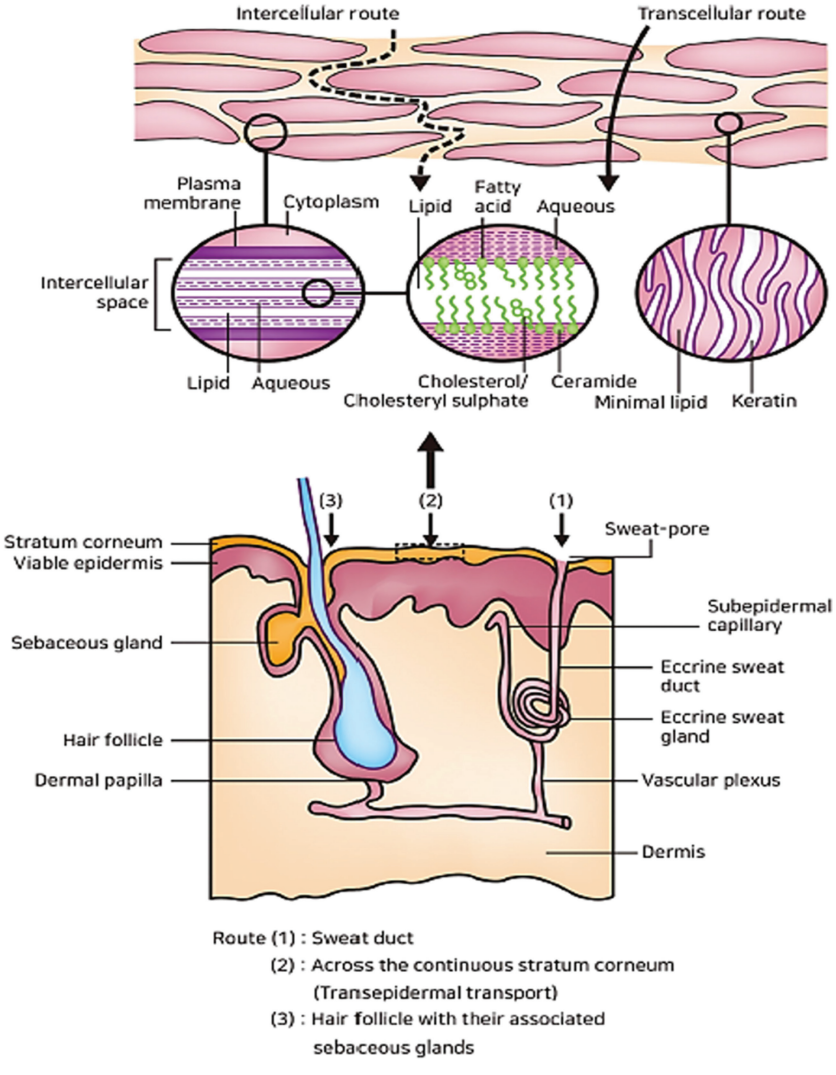

Figure 3. Penetration routes: across SC (upper image), through transcellular route (solid-line arrow), and intercellular route (dotted-line arrow); into epidermis and dermis (lower image) through (1) sweat pores, (2) SC layer and (3) hair follicles (30).

the cosmetic products. Nowadays, cosmetic products often incorporate natural bioactive ingredients such as proteins and plant extracts (59, 60). Reverse micelle extraction can be used to extract and purify these bioactive compounds. Reverse micelle extraction has many advantages compared to conventional liquid-liquid extraction methods. It allows the use of safer organic solvents, avoids formation of stable emulsion during extraction, and protects bioactive compounds from degradation due to direct contact with solvents. It is highly selective, easy to operate, conducted under mild conditions, and is a fast process. It also has the potential for large scale and continuous operation. Several important factors that must be considered during reverse micelle extraction are surfactant concentration, salt concentration, solution pH, and phase volume ratio. In general, these parameters should be

optimized to maximize the interactions between reverse micelles and bioactive compounds during forward extraction. On the other hand, the interactions should be minimized during backward extraction. Reverse micelle had been used for extraction of jacalin from jackfruit (61), bromelain from pineapple peel (62), miraculin from miracle fruit (28), soybean protein (63), tea polysaccharides (64), lignin peroxidase and manganese peroxidase (65), as well as many other biomolecules. Reverse micelles have been used to extract rhodamine B in lipsticks for analytical purposes (66). It is an efficient extraction method that can be used in quality control of cosmetic products.

Besides using for extraction, reverse micelles can be used to form nanoparticles for cosmetic formulations. Gold and silver nanoparticles are attractive active ingredients in cosmetic formulations. They have good antimicrobial activity and wound-healing properties. Reverse micelles can be used to prepare gold nanoparticles (67, 68) and silver nanoparticles (69, 70). Zinc oxide nanoparticles, which are commonly used as UV filters in cosmetic products, can be produced using reverse micelles (71). Other non-metal nanoparticles that are included in cosmetic formulations, such as chitosan nanoparticles, can also be prepared using reverse micelles (72). Therefore, reverse micelles not only have the potential to be included directly in cosmetic formulations, but they are also useful for preparation of various active ingredients used in cosmetic products.

CONCLUSION

Reverse micelle systems are widely used in downstream processing for extraction and the purification of bioactive compounds. Reverse micelle systems have many advantages such as ease of production, high encapsulation efficiency, and the protection of active ingredients. It can be prepared using safe, biocompatible, nontoxic, and environmentally friendly materials. Reverse micelle-based formulations can be designed to achieve specific rheological properties, desired skin permeation properties, targeted delivery of active ingredients, and sustained release of active ingredients. Therefore, reverse micelles have great potential as carriers of active ingredients in cosmetic formulations. To date, few studies have reported direct implementation of reverse micelles in cosmetic formulations. Reverse micelles are also used for preparation of active ingredients and the analysis of cosmetic products.

Reverse micelle technology is promising in the cosmetic sector. More research needs to be conducted to study the interactions between reverse micelles and the active ingredients in cosmetic. This knowledge is important to identify their potential applications and help cosmetic formulators design innovative products based on reverse micelle formulations. Studies on preparation of reverse micelle formulations using natural materials such as essential oils and biosurfactants are needed as the current trend is toward more sustainable and environmentally friendly products. The skin penetration properties and delivery of active ingredients by reverse micelle formulations also need more investigation. This is important to optimize the functions of cosmetic products and to ensure that no negative side effects arise after application of the products.

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