Chapter

14

POLYMERIC MICELLES FOR CUTANEOUS DRUG DELIVERY

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14.1. INTRODUCTION

Polymeric micelles are colloidal carriers which are nano-sized assemblies. They are composed of amphiphilic block polymers and characterised by core-shell morphology formed through self-association of hydrophilic and hydrophobic block copolymers in water. Micelles can increase the aqueous solubility of hydrophobic compounds in their inner cores. They have also other advantageous including improvement of the chemical stability of drugs, and easy scale-up procedure for industrial production. Micelles have therefore been widely investigated for use in the nasal, ocular, and skin delivery of drugs to overcome the natural transport barrier of biological membranes [1-3].

In recent years, different types of nano-sized carriers have been widely investigated for the cutaneous delivery of drugs. Micellar carriers have also been explored for the topical delivery of drugs via skin. The cutaneous delivery of drugs, particularly for the treatment of skin diseases, would be beneficial in terms of improving the bioavailability of hydrophobic drugs, the targeting of drugs into skin layers, controlling the release rate of drugs, decreasing side-effects such as irritation, and protecting the drugs from physicochemical conditions such as light, oxidation, *etc.* Nano-sized polymeric micelles have thus been considered a promising drug carrier for the effective treatment of various skin diseases [4-6].

This chapter is an overview of polymeric micelles as nano-sized carriers for the skin delivery of drugs, with an emphasis on micelle-forming copolymers, types of polymeric micelles, the preparation of polymeric micelles, the factors affecting the drug loading capacity of the micelles and the characterisation of micelles. Skin structure and penetration pathways are also briefly reviewed for background information. Finally, recent studies in which micelles have been developed for the cutaneous delivery of drugs.

14.2. MICELLES

Micelles, created from two different regions with opposite affinities towards a particular solvent, are "aggregated colloids" between 5 and 200 nm in size, which are spontaneously formed from amphiphilic or surfactant agents at a defined concentration and temperature. Amphiphilic molecules, while found separately at low concentrations in an aqueous solutions, create aggregation of micelles as the concentration is increased. The monomeric amphiphilic concentration at which micelles are observed is called the critical micelle concentration (CMC) [1]. Below the CMC, the concentration of amphiphiles adsorbed at the water/air interface increases as the total system amphiphile concentration increases. After a period of time the interface and system

monomers become saturated and CMC is obtained. Any amphiphiles added after this concentration has been reached assemble to form micelles in the system, and thus free energy reduces in the system.

Micelles are nano-sized colloidal carriers with a hydrophobic core and hydrophilic shell (Figure 1). While the core acts as a reservoir for hydrophobic drugs, the shell of micelles provides hydrophilic properties for the system [2,3].

Figure 1. The formation of drug loaded micelles

Depending on the weight of the molecule, these systems can be divided into two groups; low molecular weight surfactant micelles, and polymeric micelles [7]. Polymeric micelles formed through the use of amphiphilic copolymers have a lower CMC compared with surfactant micelles, and they are therefore more stable under *in vivo* conditions [8,9]. Another advantage of polymeric micelles is their lack of serious side effects [10].

14.3. POLYMERIC MICELLES

Polymeric micelles are composed of block copolymers consisting of hydrophilic and hydrophobic monomer units. In some special cases, the components of copolymer may also be two hydrophilic blocks. One of these blocks is modified by coupling it with a hydrophobic agent (such as taxol, cisplatin or hydrophobic diagnostic agents) and an amphiphilic copolymer-formed micelle occurs [11]. By controlling the length of the hydrophilic/hydrophobic blocks, copolymers of differing hydrophilic-lipophilic balance (HLB) and molecular weights can be synthesised. The physicochemical and biological properties of the copolymers can be controlled by the molar ratios of the different blocks inside the copolymers. The aggregation number of

polymeric micelles is approximately a few hundred amphiphiles, dependent on size, which have diameters within the range of 10–100 nm. The size of the micelle is dependent on the relative proportion of hydrophilic and hydrophobic chains, the molecular weight of the amphiphilic block copolymer and the number of amphiphile aggregations [8,12].

Polymeric micelles provide several advantages, such as their nano-size, ease of scale-up studies, increased drug solubility and chemical stability. Given these advantages, there has been much research into their use as drug and gene delivery systems *via* parenteral [13,14], oral [15,16], nasal [17,18], ocular [19,20], and topical/transdermal [21,22] applications.

14.3.1. Micelle-forming copolymers

Polymeric micelles made from amphiphilic blocks (di- or tri-) or of graft copolymers (Figure 2) have received much attention in recent years [10,23]. For synthesised copolymers to form micelles, there needs to be a balance between the hydrophilic blocks forming the micelle shell and the hydrophobic block forming the core. For this reason, some simple arrangements are made for the amphiphilic unimers. Poly(ethylene glycol) (PEG) blocks with a molecular weight of 1–15 kDa should be used to form the shell, for example, while the length of the hydrophobic block forming the core should be around the same length or slightly shorter than the hydrophilic block [10].

Figure 2. Main structural types of copolymers and micelles formed from amphiphilic copolymers (reprinted with permission from [24], John Wiley and Sons)

The most amphiphilic block copolymers contain polyester, polyether or a poly(amino acid) derivative as hydrophobic block. Generally, the hydrophobic

core comprises a biodegradable polymer such as poly(ϵ -caprolactone) (PCL), poly(D,L-lactic acid) (PDLL) or poly(β -benzoyl-L-aspartate) (PBLA), and acts as a reservoir for drugs with poor water solubility and protects them from contact with the aqueous medium. The block which forms the core can also be a water-soluble polymer rendered hydrophobic by the chemical conjugation of a hydrophobic drug [*e.g.* poly(aspartic acid) (PASP)]; polystyrene with good stability given its glassy properties (PST) a non-biodegradable polymer such as poly(methyl methacrylate) (PMMA); an alkyl chain or diacyl lipid (*e.g.* distearoylphosphatidylethanolamine (DSPE)) [8].

The hydrophilic polymer forming the shell of the polymeric micelle is responsible for the interaction with cell membranes, and for providing effective steric protection for micellar structure. The shell structure determines the hydrophilicity, charge, size of the micelles, the surface density of the hydrophilic block, and the presence of a suitable reactive group for the addition of targeting molecules. These characteristics control the important biological properties of the micellar carriers, such as pharmacokinetics, biodistribution, biocompatibility, circulation time in the blood, the surface adsorption into biomacromolecules, adsorption into bio-surfaces and targeting [9,10]. PEG, with high solubility in water and the ability to easily combine with hydrophobic blocks, is usually used as the hydrophilic block. In addition, poly(acrylamide), poly(hydroxyethyl methacrylate), poly(*N*-vinylpyrrolidone) (PVP) and poly(vinyl alcohol) (PVA) can also be used as the hydrophilic block [8,10,23].

The physicochemical and biological properties of the copolymer can be controlled by the molar ratios of the different blocks inside the copolymer. The proper arrangements for a specific focus can be made by modifying core functions and the surface chemistry [8,10].

14.3.2. Types of polymeric micelles

Polymeric micelles, which resist the various intermolecular forces and keep the core separate from the aqueous medium, can be divided into three categories.

14.3.2.1. Conventional micelles

These micelles are formed by the hydrophobic interaction between the core and the shell in the aqueous medium. One of the simplest amphiphilic block copolymers, poly(ethylene oxide)- β -poly(propylene oxide)-*b*-poly(ethylene oxide) forms micelles as a result of hydrophobic interactions [25].

14.3.2.2. Polyion complex micelles

Like polyelectrolytes, the electrostatic interactions between two oppositely charged parts also allow the formation of micelles. Oppositely charged polymers penetrate the shell of the micelles when added to the solution, and polyion micelles are formed. Electrostatic forces and van der Waals interaction forces control the shell structure and size of the charged micelle. These micelles easily and spontaneously occur in aqueous media, are structurally stable and have a high drug loading capacity [25].

14.3.3.3. Non-covalently bounded polymeric micelles

Here, polymeric micelles are obtained through the self-assembly of random copolymers, graft copolymers, homopolymers or oligomers and powered by the driving force of interpolymer hydrogen bonding complexation. The core and shell are non-covalently bounded by the ends of their homopolymer chains, either through intermolecular interactions such as H-bonding, or metal-ligand interactions occurring in their structure, and as such are known as non-covalently bounded polymeric micelles [25].

14.3.3. Preparation of polymeric micelles

Simple equilibrium, dialysis, o/w emulsion, solution casting and freeze-drying methods are used in the preparation of polymeric micelles [26] (Figure 3). If the block copolymer is water-soluble, a simple equilibrium method is used; if not, the dialysis method [10]. While the drug is loading into the micelles, its physicochemical properties are crucial. Hydrophobic drugs can be loaded into the micelle by chemical or physical interaction [8,26]. In order to load hydrophilic compounds such as proteins into the micelles, the molecules should be made chemically hydrophobic. In order to load the drugs *via* ionic interactions into the micelles, there must be an opposite charge on the surface of the copolymers' hydrophobic block. In the event that a drug is to be chemically or electrostatically bound to the hydrophobic block, the formation of micelles and their combination with the drug should be carried out simultaneously. Strong polymer-drug interaction increases the load on the micelle core, but reduces the micelles' drug release. For this reason, the loading amount and drug release kinetics must be optimised. Micelles have also been obtainable through microfluidic technology in recent years [27].

14.3.4. Factors affecting the drug loading capacity of the micelles

There are many factors that affect the loading capacity of hydrophobic drugs to the micelle-forming amphiphilic copolymers. These factors are summarised below.

Figure 3. Common drug-loading procedures: (A) simple equilibrium, (B) dialysis, (C) o/w emulsion, (D) solution casting, and (E) freeze-drying

14.3.4.1. Factors belonging to copolymers

The copolymer concentration, the length and hydrophobicity of the blocks forming the core, and the structure and length of the block forming the shell affect the loading capacity of micelles [28]. An increase in copolymer concentration, hydrophobic block length and the hydrophobicity of the core increases the loading capacity. When the length of the hydrophilic block is increased, the CMC also increases and the loading capacity decreases. By affecting the hydrophobic/hydrophilic balance of the drug molecule, where the drug core or shell are placed and the loading capacity are determined. Drug molecules situated on or close to the micelle shell are released quickly. For this reason, in order to delay the release of the drug, the drug molecules should be dissolved in the core of the micelle or be loaded to the core in a separate phase [23].

Interactions between the drug and the micelle core (hydrophobic, hydrogen bonding, ionic interactions, etc.). These interactions depend on properties such as the polarity, hydrophobicity and charge of the drug. Sometimes the interaction between the drug, hydrophilic shell, and soluble drug can also affect the dissolution process either positively or negatively [10,23].

Micellar preparation methods and process-specific parameters (such as the structure of the organic solvent, solvent ratio) affect the drug loading capacity [23].

The polymer-drug miscibility is a crucial parameter for drug loading capacity of the micelles. Hildebrand-Scatchard solubility parameters are mostly used for this [29] and drug loading capacity can be calculated using the following formula, the Flory-Huggins theory. If the Flory-Huggins parameter is a low value (< 0.5), it signifies that the drug is well dissolved in the core of the polymeric micelle.

$$X_{\text{drug-polymer}} = (V_{\text{drug}} / R \cdot T) (\delta_{\text{drug}} - \delta_{\text{polymer}})^2 \quad (1)$$

where; $X_{\text{drug-polymer}}$ is the Flory-Huggins interaction parameter between the drug and the polymer, V_{drug} is the volume of the drug, R is the ideal gas constant, T is the temperature, and δ_{drug} and δ_{polymer} are the Hildebrand-Scatchard solubility parameters of the drug and the polymer, respectively [30,31].

14.3.5. Characterisation of micelles

14.3.5.1. Size and size distribution

One of the most interesting properties of polymeric micelles is their small size. A micelle's size rarely reaches 100 nm. This situation depends on factors including the relative proportions of hydrophobic and hydrophilic chains, the number of amphiphile aggregations, the molecular weight of the amphiphilic copolymer and the micelle preparation method [8]. Kim and colleagues [32], also found that the solvent used to form micelles affected the size and size distribution of micelles. The hydrodynamic size and polydispersity of micelles can be measured by dynamic light scattering (DLS) in an isotonic buffer or in the water. Micelle size can also be calculated using atomic force microscopy (AFM), transmission electron microscopy (TEM) or scanning electron microscopy (SEM) studies. These methods also allow the micelle size distribution and morphology to be characterised [8,33].

14.3.5.2. Morphology

It is generally accepted that there are spherical particles with a clear distinction between the micelle core and shell. In aqueous media, amphiphilic

block copolymers self-aggregate towards spherical, worm-like or cylindrical micelles, polymer vesicles or polymersomes. Here, the main factor controlling micelle morphology is the hydrophilic volume fraction (f) defined by the hydrophilic-hydrophobic balance of the block copolymer [25]. Along with this, the copolymer aggregation, the organic solvent used to prepare the micelles, and the copolymer composition can be considered the main morphogenic factors [10].

14.3.5.3. Zeta potential

The stability of the colloidal particles is the basic parameter with regards to the zeta potential (ζ -potential) of micelles. It is also affected by the interactions of biological elements such as cell membranes (which define cell uptake and the particles' pharmacokinetics) and proteins [34]. Generally, the absolute value of ζ -potential is 20–50 mV. The charge of the colloidal particles is also very important in terms of system stability. In many cases, with a higher ζ -potential value, there is stronger repulsive interaction between the surface charge of the colloidal particles and the dispersed particles, and as such higher stability and a more uniform diameter is observed [35].

14.3.5.4. Stability

The determination of the stability of polymeric micelles is important for their characterisation, and their stabilities can be examined as thermodynamic stability and kinetic stability. Thermodynamic stability is crucial for *in vivo* conditions, and kinetic stability is crucial for *in vitro* conditions.

The thermodynamic tendency which breaks the individual chains of the micelles reflects CMC [23]. When the polymer concentration is above the CMC in the aqueous medium, the polymeric micelles are thermodynamically stable. If below the CMC, the amphiphilic block copolymers in the aqueous medium are found to have single chains in the bulk phase at the air-water interface. When the polymer concentration is increased above the critical micelle concentration, as a result of the hydrophobic interactions between the hydrophobic blocks, amphiphiles self-aggregate and the system's Gibbs energy (ΔG) is reduced to the lowest level [12].

The kinetic stability of a micelle system is related to the single polymer chain exchange rate between the bulk and micelles. If the block forming the micelle core is semi-crystalline, the structure of the micelle is dependent on the glass transition temperature (T_g) and/or the melting temperature (T_m), and even at dilution levels below the CMC, the micelles remain kinetically stable for a long period of time. The dissociation speed of the micelles is related to the strength of interactions in the micelle core. Those interactions are dependent on factors such as the physical structure of the polymer comprising the core (crystalline or amorphous); the presence of the solvent in the micelle core; the length of

the hydrophobic block; the hydrophilic/hydrophobic block ratio; and the encapsulation of hydrophobic compounds [23,26].

To avoid stability problems, polymeric micelles should have a glassy or crystalline core at their preferred body temperature, and should be formed of copolymers with a low CMC [12]. With the end goal of increasing the thermodynamic and kinetic stability of drug-loaded micelles by reducing the CMC, approaches such as increasing physical interaction/covalent cross-linking, modifying the micelle-forming polymers, and enhancing drug-polymer interactions have been discussed [26].

Briefly, stability tests of micellar solutions consist of observing whether or not there is any basic phase dispersion determining particle size in order to ascertain aggregation, and analytically measuring the concentration of drug and block copolymers in the formulation [8,10].

14.4. MICELLES FOR DRUG DELIVERY *via* SKIN

14.4.1. The structure of human skin

Human skin is a unique, well-designed membrane and its fundamental functions are to protect organisms from environmental factors and, to regulate transepidermal water loss from the body. Histologically, it is composed of three main layers, the *epidermis*, the *dermis*, and the *hypodermis* (subcutaneous tissue) [36-38]. The *epidermis* is also divided into two layers, the *stratum corneum* and viable *epidermis*. The *stratum corneum* consists of *corneocytes* which are dead, flattened, keratin-rich cells. The *corneocytes* are embedded in the mixture of intercellular lipids. The *stratum corneum*, the outermost layer of *epidermis*, is an extremely effective barrier for the penetration of most drugs due to its excellent structure. It behaves as a rate-limiting barrier for diffusion for almost all drugs due to its well-ordered structure [38,39]. In topical treatment, in most cases drugs should pass the *stratum corneum* to reach deeper layers of the skin for the efficiency of therapy, but, the main problem in effective skin delivery is the low diffusion rate of drugs across the *stratum corneum*. As well as the physicochemical characteristics of drugs, the features of topical formulation are also effective parameters in dermal drug delivery. Overcoming the barrier characteristics of skin for the improvement of cutaneous drug delivery is thus the major challenge [41-43].

14.4.2. The skin penetration pathways

Drugs pass through the skin barrier *via* three potential pathways: *transcellular*, *intercellular* and/or *transappendageal* (shunt) routes (hair *follicles*, sweat glands, and *sebaceous* glands) [36,37,44]. The contribution of each pathway to the permeation of drugs across the skin is mainly related to the physicochemical properties of the drugs. While the *intercellular* route has been

regarded as the main transport pathway of most drugs and, the *transcellular* route has become more important as a polar route. Since appendages such as hair *follicles* and glands called as shunt pathway comprise only 0.1 % of the human skin surface area, their contribution to skin penetration is considered less significant. It has been suggested that the shunt route may provide advantageous delivery of polar and ionized drugs that would not be easily delivered *via* the lipid domain of the *stratum corneum* [36,37,44,45]. It has also been indicated that transport pathways for the penetration of topically applied drugs could be important in targeting the skin appendages, in particular targeted follicular delivery. Follicular penetration is suggested as a possible pathway for the rigid particulate carriers [46-49]. Prow *et al.* indicated that nanoparticles (> 10 nm) are unlikely to penetrate the *stratum corneum* and the nanoparticles would accumulate in the hair *follicle* openings [50]. They emphasised that the topical delivery of nanoparticles through skin takes place in three major sites, including the *stratum corneum* surface, furrows, and the openings of hair *follicles* (*infundibulum*) (Figure 4). On the other hand, it was demonstrated that polymeric nanoparticles (20–200 nm) penetrate only into the surface layers, based on the confocal microscopy images [51]. The researchers mostly demonstrated that nanoparticles only permeate the superficial layers of the skin [50-54].

Figure 4. Delivery of nanoparticles into possible sites of skin: (a): *stratum corneum* surface; (b): furrows in skin; (c): opening of hair *follicles* (*infundibulum*); *stratum corneum* (SC); *viable epidermis* (E); *dermis* (D) (reprinted with permission from [50], Elsevier)

14.5. APPLICATIONS OF POLYMERIC MICELLES AS DRUG CARRIERS IN TOPICAL TREATMENT

Topical treatment is an attractive option for curing cutaneous diseases, as it has advantages such as targeting drugs to the site of the disease and reducing the systemic side effect risk of drugs. The efficiency of therapy in skin diseases could be enhanced and high patient compliance can be provided. The success of the topical treatment depends on the penetration of drugs into the targeted layers of skin, however, and the achievement of effective drug levels in these skin layers. In this context, the contribution of topical formulation composition on the efficiency of cutaneous drug delivery is considerable high. In most cases, conventional dosage forms may be insufficient to ensure effective drug concentrations in targeted layers of skin due to poor skin penetration of drugs. The delivery of drugs to target regions of the skin is thus a great challenge in terms of improving therapy.

Numerous attempts have been made to develop novel topical drug delivery systems, including different types of nano carriers that can improve partition and/or drug penetration across skin. Micro- and nano-sized particulate drug carriers have been optimised to carry the drugs to the targeted layers of the skin [4,56-63]. Micelles are one of the polymeric nano-sized drug carriers particularly used to improve the aqueous solubility of drugs and to enhance the permeability of drugs across membranes [5,6]. Micellar particle technology for transdermal delivery of estradiol and other steroid compounds were patented for the first time in 1997. Estrasorb® is a lotion type topical product which consists of micelles loaded 17 β -estradiol, which has been commercially available since 2003. It was claimed that the amount of estradiol in the micellar carrier was improved due to increasing the solubility of drug, and it was anticipated that micellar carriers would act as depots for estradiol in *stratum corneum* and *viable epidermis*. It was also indicated that Ostwald ripening observed in micelles had not occurred in that product, and that the product had stabile structures with a three year shelf-life [6].

In recent years, micelles as nano-sized carriers have also been investigated for the delivery of other drugs *via* the skin. In these studies, micellar carriers have been developed for the treatment of *psoriasis* (tacrolimus and cyclosporine) [64,65]; and photo-aging (all-*trans* retinoic acid) [66]; breast cancer (endoxifen) [67]; and skin cancer (oridonin) [68], fungal infections (clotrimazole, econazole nitrate and fluconazole) [21], and acne (benzoyl peroxide) [69], and the skin permeation of drugs from micelles was also examined. The micellar carriers of quercetin and rutin as antioxidant compounds [70], and polymeric micelle loaded sumatriptan for the treatment of pain in migraine [71] have also been optimised, and the efficacy of these formulations have been evaluated with *in vitro/in vivo* studies. In another study, an anti-inflammatory drug was loaded into a core of polymeric micelles, which resulted in delayed drug release and slow drug permeation due to the

core and shell structure. Based on that data, it was reported that these structures could be also considered to delay or inhibit dermal delivery of drugs [72]. In another study, when compared to its ethanolic solution, the structures resembling micelles increased the solubility of a lipophilic compound, resulting in efficient treatment for chronic wounds and burn therapy [73]. None of the micellar carriers of these drugs have been clinically approved yet, however.

Researchers have also focused on the possible pathways for micelles to pass across skin. It has been shown that polymeric micelles provide the localization of drugs in skin layers following hair follicle pathways based on data obtained from confocal laser microscopy. The deposition of micelles into hair *follicles*, and between coenocytes and in the inter-cluster regions have been shown with confocal microscopy studies, and the micelles have been proposed as potential carrier for targeted delivery to hair *follicles* [21,64,65].

The studies performed on the development of polymeric micellar carriers for cutaneous drug delivery have been summarised below, and the polymers used in the formulation of micelles and the features of micelles optimised are given in Table 1.

14.5.1. Cyclosporin

Cyclosporin A is an immunosuppressant and it is currently indicated in the treatment of psoriasis *via* the oral route [74]. Lapteva *et al.* prepared polymeric micelles using biodegradable and biocompatible diblock copolymers to increase skin delivery of cyclosporin A for dermatological use [64]. Micelle loaded cyclosporin was reported as homogeneous and spherical in shape, with a range of 25–52 nm particle size, and the low aqueous solubility of cyclosporin had been increased approximately 500 times using micellar carriers. In this study, the localisation of both drugs and copolymer was also investigated using confocal laser scanning microscopy. Both copolymer and cyclosporin A were chemically bounded to fluorescent dyes. Based on the images obtained from confocal laser scanning microscopy, it was reported that micelles were localised between corneocytes and in the inter-cluster regions. The authors also indicated that inter-cluster penetration was likely the preferred transport route of micelles, and that it provided enhancement of the cutaneous delivery of cyclosporin A. The authors also emphasised that the efficiency of micellar carriers should be validated *in vivo* with diseased skin due to the features of psoriatic skin.

Table 1. Micelles prepared for skin delivery in the literature

Active compounds	Polymers used in the composition of micellar carrier	Method	Size of micelles	Ref.
Clotrimazole Econazole nitrate Fluconazole	Amphiphilic methoxy-PEG-hexyl substituted polylactide (MPEG-hexPLA) block copolymers	Sonication / film hydration method	30–40 nm	[21]
Tacrolimus	Methoxy-PEG-dihexyl substituted polylactide diblock copolymer	Solvent evaporation method	10–50 nm	[64]
Cyclosporine	Methoxy-PEG-dihexyl substituted polylactide diblock copolymer	Solvent evaporation method	25–52 nm	[65]
Retinoic acid	PEG conjugated phosphatidylethanolamine	NG	6–20 nm	[66]
Endoxifen	PCL with multiple hydrophilic PEG chains mediated by a generation 3 (G3) polyester dendron	NG	40–50 nm	[67]
Oridonin	Monomethoxy PEG-PCL	Film hydration method	25 nm	[68]
Benzoyl peroxide	PEG-b-poly(propylene glycol)-PEG	Film method	25–30 nm	[69]
Quercetin and Rutin	PCL-b-PEG	NG	NG	[70]
Sumatriptan	PEG-b-poly(propylene glycol)-PEG	Emulsification method	NG	[71]

NG = not given

14.5.2. Tacrolimus

Tacrolimus is also a potent macrolide immunosuppressant compound [75]. The same researchers prepared the polymeric micelles of tacrolimus and evaluated the possibility of delivering tacrolimus into targeted layers of the skin [65]. They showed that the accumulation of tacrolimus in the *stratum corneum*, *viable epidermis*, and upper *dermis* has been increased. Based on confocal laser scanning microscopy data, it was reported that copolymers used in the composition of micelles would not pass through skin and that micelles were deposited in hair *follicles*. They also emphasised that micellar carriers of tacrolimus could be considered effective due to their superior efficiency in its conventional ointment formulation.

14.5.3. Sumatriptan

Sumatriptan, 5-hydroxytryptamine 1D (5-HT_{1D})-receptor agonist, is used in the treatment of migraine *via* oral and parenteral administration routes [76], but it has problems of low bioavailability due to its pre-systemic metabolism in oral administration. In addition, nausea or vomiting problems have also been seen in migraine attacks, which lead to insufficiency in oral treatment. In order to overcome these disadvantages of the oral route, the efficiency of transdermal delivery of sumatriptan *via* micellar carriers has been assessed [71]. Lesitin organogels of sumatriptan composed of thermoreversible micelles were optimised to improve its stability and the permeation of sumatriptan across the skin. The authors indicated that the optimised formulation was stable, without any significant changes at room temperature. The improved topical delivery of sumatriptan has been attributed to improved drug solubility. It was also proposed that the prepared sumatriptan micelles containing lecithin and pluronic copolymers were considered to be a safe and stable drug delivery system.

14.5.4. Endoxifen

Endoxifen, one of the active metabolites of tamoxifen, was shown to be effective in the prevention and treatment of oestrogen-positive breast cancer [77], however, severe side effects are observed following its oral administration. The dendron micelles with various surface groups ($-NH_2$, $-COOH$, or $-Ac$) of endoxifen were optimised to increase the localisation of endoxifen in the targeted tissue following its topical administration [67]. The modification of end-groups of micelles were reported to affect the drug loading capacity of micelles, and that resulted in the highest encapsulation efficiency, with micelles having $-COOH$ surface end groups. When the skin delivery of endoxifen was examined, it was determined that the dendron micelles increased the permeation of endoxifen across both mouse and human skin, and the dendron micelles with $-COOH$ end groups showed the highest endoxifen flux through skin. Based on these results, the authors claimed that dendron micelles could be an effective carrier for the topical delivery of endoxifen as a potential alternative administration route.

14.5.5. Oridonin

Oridonin, a natural tetracycline diterpenoid isolated from *Rabdosia rubescens*, has been reported to be a potent cytotoxic agent [78]. Micellar carriers were prepared in order to increase aqueous solubility, and its permeation across excised mouse skin was studied [68]. It was shown that the micellar carrier of oridonin had higher transdermal delivery compared to its saturated solution. The authors indicated that the micelles of oridonin could be considered for intravascular administration as a transdermal drug delivery system in cancer chemotherapy.

14.5.6. Clotrimazole, econazole nitrate and fluconazole

Clotrimazole, econazole nitrate and fluconazole are azole group antifungal compounds which are widely used in their conventional formulations, such as ointment, topically [79] but the efficiency of topical antifungal treatment is affected due to the low aqueous solubility of drugs. Bachav *et al.* optimised the micellar carriers of these antifungal drugs to improve the deposition of these antifungals in the target layer after application on both porcine and human skin [21]. It was demonstrated that the deposition of econazole in both human and porcine skin was significantly higher than in its commercial liposome formulation. The authors reported, according to confocal laser scanning microscopy data, that the micellar carriers may increase targeted follicular delivery.

14.5.7. Benzoyl peroxide

Benzoyl peroxide is one of comedolytics frequently used in the treatment of mild and moderate acne [80]. Although commonly used by the patients, it has several side effects including skin irritation depending on doses of benzoyl peroxide, skin dryness, contact allergy, burning, scaling, itching and erythema, resulting in poor patient compliance. The deposition of anti-drugs is also required in the *pilosebaceous* units of the skin for the efficiency of topical acne treatment. benzoyl peroxide (BPO) loaded polymeric micelles were prepared using the thin film hydration method and various solvents to decrease the side effects of BPO and increase the deposition of BPO in the *pilosebaceous* units [69]. These were about 25 nm in hydrodynamic diameter with a narrow polydispersity index in the water and had encapsulation efficiency. Confocal laser scanning microscopy studies showed that Nile red loaded polymeric micelles were localized in the hair *follicles*.

14.5.8. Retinoic acid

The topical application of all-*trans* retinoic acid (ATRA) has been used in the treatment of several dermatological diseases such as photo-aging [81]. Polymeric micelles of retinol have been formulated to improve of photo-stability of retinol, because retinol is very sensitive to light, heat, and oxidizing agents. ATRA entrapped in polymeric micelles with various PEG and PE structures have thus been prepared [66]. The authors reported micelles of ATRA composed of PEG (molecular weight of 750 Da) and that conjugation of dipalmitoylphosphatidylethanolamine (PEG750-DPPE) showed the highest entrapment efficiency (82.7 %) among the tested micelles. It was demonstrated that up to 87 % of ATRA were measured following the storage of the PEG750-DPPE micelle solution in ambient media for 28 days. Based on that data PEG750-DPPE micelles of ATRA were proposed as an alternative carrier for the formulation of cosmeceutical formulations due to its improved photo-stability.

14.5.9. Quercetin and rutin

The flavonoids rutin and quercetin have been described as cell-protecting agents because of their antioxidant, antinociceptive, and anti-inflammatory actions [82]. Micellar carriers of quercetin and rutin which are antioxidant compounds were prepared and the permeation of these drugs across skin using Franz diffusion cells was examined *in vitro* [70]. The aqueous solutions of both quercetin and rutin were used as the control groups. The authors showed that quercetin and rutin loaded micelles had more efficient skin permeation than those of the control groups. In this study, a safety assessment of quercetin and rutin loaded micelles on skin was made to evaluate the application possibility of these polymeric micelles to cosmetics. No adverse symptoms were observed following the application.

14.6. CONCLUSIONS

Topical treatment of most skin disorders would be useful in terms of delivering drugs to the diseased layers of skin and preventing the systemic side effects of drugs, however, skin – particularly its *stratum corneum* layer – is a strong barrier to the effective drug concentrations in its deeper layers in cutaneous drug delivery. Conventional forms of dosage such as creams and gels are unsatisfactory for topical treatment due to the poor penetration of drugs into targeted layers of skin and inadequate deposition in the skin, resulting in low topical bioavailability. The development of novel drug carriers is an important challenge for delivering drugs topically to treat topical diseases. In recent years, nano-sized drug carriers have been used as a popular strategy for delivering drugs into the skin. Micelles are also one of the drug carriers that improve the delivery of drugs *via* skin. Improved cutaneous targeted delivery of several drugs has been observed for these systems when compared to conventional topical formulations in the studies. Based on recent findings, micelles seem to be promising carriers which provide the deposition of some drugs in particular superficial layers of the skin and hair *follicles*.

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