

Effect of a non-ionic surfactant on skin-retention of cationic minoxidil microparticles suspended in an anionic surfactant solution

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Abstract—The effect of Brij 78, a nonionic surfactant, on the interactions between cationic minoxidil (MXD) microparticles and sodium lauryl ether sulfate (SLES) in an aqueous phase was investigated. Cationic MXD microparticles were prepared by high pressure homogenization, where distearyldimethylammonium chloride (DSDMAC) was used as a cationic dispersant. The positive surface charge of MXD microparticles was neutralized at the equimolar ratio of SLES/DSDMAC and became negative in the presence of excess amount of SLES, whether Brij 78 was included in the MXD suspensions or not. On the other hand, when nonionic surfactant was included in the suspension so that the molar ratio of Brij 78/DSDMAC was 0.063 : 1, the suspension of the cationic microparticles was stable in terms of turbidity change even in the presence of excess amount of SLES. It means that while electrostatic interactions between DSDMAC and SLES were occurring, the aggregation of cationic MXD microparticles was prevented with the aid of Brij 78. Due to the cationic microparticle-stabilizing effect of Brij 78 in the presence of the anionic surfactant, the substantivity of the cationic MXD microparticles having Brij 78 was about two times higher than that of the microparticles without the nonionic surfactant.

Key words: Minoxidil, Distearyldimethylammonium Chloride, Brij 78, Sodium Lauryl Ether Sulfate, Substantivity

INTRODUCTION

To obtain a high therapeutic effect of a particulate drug contained in rinse-off cosmetics, the particles should be colloidal stable in the products during storage, skin-retentive when rinsing off the applied cosmetics from skins, and permeable to skin. The colloidal stability is related to the sedimentation and the agglomeration of the particles. The sedimentation can be prevented by reducing the particle size in a homogenization process. The agglomeration can be avoided by preparing electro-statically charged-particles or using a dispersant. A high skin permeability of drug can be achieved by reducing the particle size. Particles less than 50 nm are reported to penetrate into skin through space between corneocytes [1], and particles of few microns can penetrate into hairy skin through follicles [2]. The skin-retentive particles can be obtained by making the surface potentials positive, since skins are negatively charged [3]. Retentive property, so-called substantivity, of particles is a prerequisite for the high therapeutic effect of a particulate drug especially in rinse-off cosmetics. Recently, it was reported that minoxidil (MXD), a potent hypertrichotic agent used topically in treating alopecia androgenetica, exhibits a high substantivity and a significant after-rinsing hair growth promotion when the surface is modified with a cationic surfactant [3].

The cationic MXD particle, however, tends to aggregate in rinse-off products, since many of the anionic surfactants, such as sodium lauryl sulfate (SLS) and sodium lauryl ether sulfate (SLES), are contained in the products. The electrostatic interaction of cationic particles with anionic surfactants neutralizes the positive charges of the

particles and it agglomerates them [3]. In this study, in order to circumvent the shortcomings, Brij 78, a nonionic surfactant, was included in the preparations of cationic MXD microparticles, and the effect of the nonionic surfactant on the interactions between cationic MXD microparticles and SLES were investigated through the measurements of zeta potentials and turbidities. In parallel, the effect of Brij 78 on the substantivity of cationic MXD microparticles suspended in SLES solution was observed.

EXPERIMENTAL

1. Materials

Distearyldimethylammonium chloride (DSDMAC), a cationic surfactant, was gifted from TCI (Japan). MXD (98%) was purchased from INFA (Milan, Italy). Sodium lauryl ether sulfate (SLES) was obtained from Henkel. Brij78 was provided by Sigma Chemical Co. All other reagents were in analytical grade.

2. Preparation of Cationic MXD Microparticles

Cationic MXD microparticles were prepared as described previously [3]. In brief, 34 g of MXD and 12 g of DSDMAC were mixed in 300 mL of distilled water. And, various amount of Brij78 were added to the mixture so that the molar ratios of the nonionic surfactant to the cationic one were 0 : 1, 0.017 : 1, 0.063 : 1, and 0.123 : 1. Coarse MXD particles were crushed into smaller ones with a colloid mill (Tokushu Kika Kogyo. Co. Ltd.). And then, the crushed MXD particles were further processed by a microfluidizer (Microfluidics M-110EHI), operating at 1,000 bar.

3. Effect of Brij 78 on Zeta Potentials and Turbidities

To investigate the effect of a non-ionic surfactant (Brij78) on the interaction between cationic MXD microparticles and an anionic surfactant (SLES), various amounts of SLES were added to each

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cationic MXD suspension containing Brij78 so that the molar ratios of SLES to DSDMAC were 0 : 1, 0.25 : 1, 0.5 : 1, 1 : 1, 1.25 : 1 and 2 : 1. The zeta potentials of the cationic MXD particles in the presence of Brij 78 and/or SLES were measured by using ZetaPlus (Brookhaven Instrument Co.). The pHs were adjusted to 7.0 with 1 mM NaOH and 1 mM HCl solutions. In parallel, the turbidities of the suspensions were determined at 600 nm with a UV-spectrophotometer (Jenway 6505, UK).

4. *In Vitro* Substantivity

The method was described in a previous report [4]. After sacrificing female hairless mice (type SKH) aged 8-14 weeks with ether, the dorsal skin of each hairless mouse was excised. For *in vitro* substantivity test, the suspensions of MXD microparticles, where the molar ratios of Brij 78/SLES/DSDMAC were either 0/1/1 or 0.063/1/1, were employed. Each suspension was applied on the skin and then the skin was rinsed with distilled water. Six pieces of the washed skin were punched out by using a biopsy punch (Stiefel, 6 mm in diameter) and put into an eppendorf tube. After 1 ml of ethanol was added to the tube, it was vortexed and left for 24 h to dissolve MXD out of the skin. The concentration of MXD was determined by HPLC. The assay was performed in a Waters liquid chromatograph equipped with a UV detector. A Microsorb-MV column was eluted with acetonitrile (10^{-2} M NaClO₄)/H₂O (10^{-2} M NaClO₄, pH 3) (9 : 1, v/v) at a flow rate of 1.0 μ l/min and a sample of 15 μ l was injected. The detection wave length was 283 nm.

5. Effect of Dilution on Zeta Potential of MXD Microparticles

The rinsing step of skins in the experiment of *in vitro* substantivity involves the dilution of MXD suspensions. To figure out what the surface potentials of MXD microparticles will be during the rinsing step, the effect of dilution on the change in the zeta potentials of MXD microparticles were investigated, as shown in Fig. 4. The molar ratio of Brij 78/DSDMAC was varied from 0 : 1 to 0.123 : 1 and the molar ratio of SLES to DSDMAC was fixed to 1.25 : 1.

RESULTS AND DISCUSSION

1. Preparation of Cationic MXD Microparticles

Fig. 1 shows the photo of MXD microparticles which were obtained by using only DSDMAC as a dispersant. The microparticles

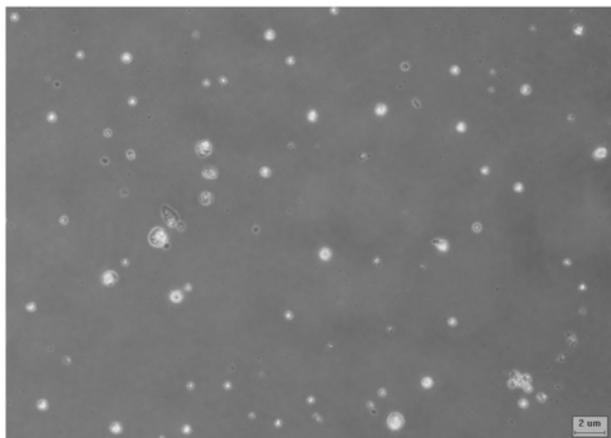


Fig. 1. Microphotograph of MXD microparticles, prepared using DSDMAC as a dispersant ($\times 400$). Bar represents 2 μ m.

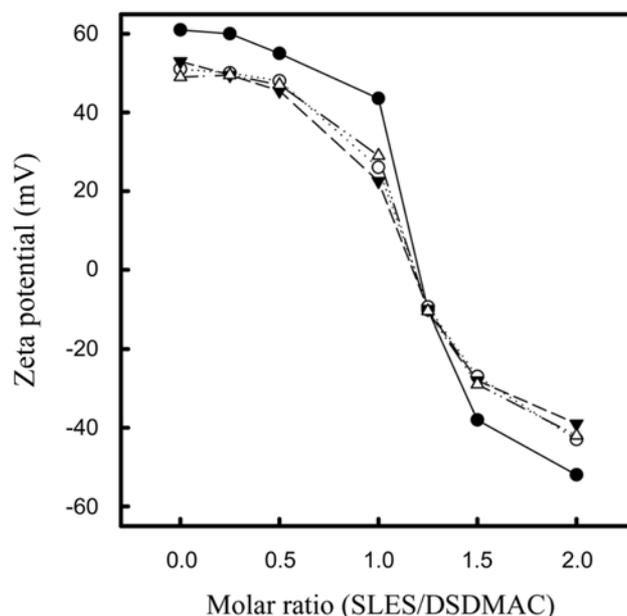


Fig. 2. The effect of Brij 78 on the zeta potentials of cationic MXD microparticles. The cationic MXD microparticles were suspended in aqueous solutions containing variable amounts of SLES. The ratios of Brij 79/DSDMAC are 0/1 (●), 0.017/1 (○), 0.063/1 (▼), and 0.123/1 (△).

were quite homogeneous in terms of size and the size was about 5-10 μ m. When Brij 78 was added as an adjuvant dispersant, no significant difference in the shape and the size was observed. It is hard to obtain micron-sized particles of MXD due to its physicochemical property. The use of a good dispersant and the application of high mechanical energy are required for obtaining homogeneous small particles. In this context, DSDMAC is believed to be a good dispersant for MXD.

2. Effect of Brij 78 on Zeta Potentials and Turbidities

Fig. 2 shows the effect of Brij 78 on the zeta potentials of cationic MXD microparticles suspended in aqueous solution containing SLES. When no Brij 78 was included, the surface potential of cationic MXD microparticles was about +60 mV at SLES/DSDMAC ratio of 0 : 1. It was reported that DSDMAC is a good dispersant for MXD and it covers the surface of MXD with the heads facing aqueous phase [3]. This would account for the reason why the MXD microparticles exhibited a strong positive charge. As the ratio of SLES/DSDMAC increased to 2 : 1, the value decreased to -53 mV. SLES could be adsorbed on the surface of the cationic particles due to its high surface activity. In addition, it also could be adsorbed on the surface due to its electrostatic interaction with DSDMAC. Therefore, when the molar ratios of SLES to DSDMAC were less than 1, adsorption of SLES would occur mainly due to an electrostatic interaction. And, above the ratio of 1, where the surface potential is negative, SLES would be adsorbed possibly due to its hydrophobic interaction with the hydrocarbon chains of DSDMAC. In case Brij 78 was included as an adjuvant dispersant, the trends of zeta potential change were similar to that of the microparticles free of the non-ionic surfactant. The absolute values of the zeta potentials, however, were less. For example, the values were +45 mV to +50 mV at the SLES/DSDMAC ratio of 0, and they were -35 mV to -45 mV at the SLES/

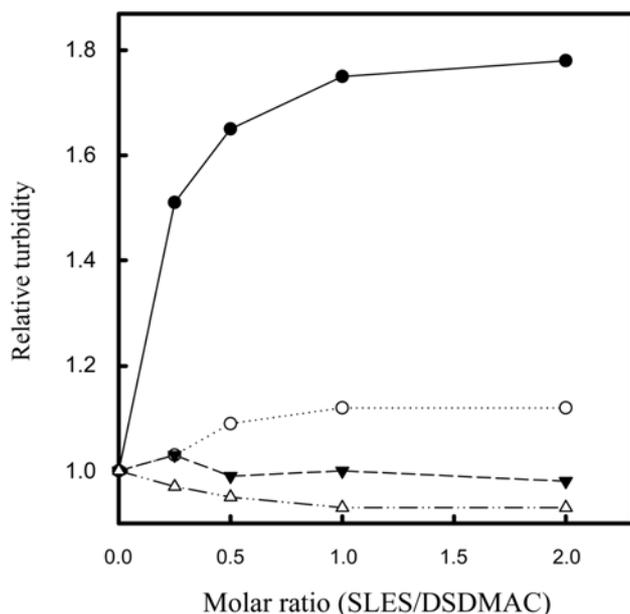


Fig. 3. The effect of Brij 78 on the turbidities of cationic MXD microparticles. The cationic MXD microparticles were suspended in aqueous solution containing variable amounts of SLES. The ratios of Brij 79/DSDMAC are 0/1 (●), 0.017/1 (○), 0.063/1 (▼), and 0.123/1 (△).

DSDMAC ratio of 2. Brij 78 has a hydrocarbon chain (C_{18}) as a hydrophobic tail, and it has an ethylene oxide chain ($n=20$) as a hydrophilic chain. It is believed that Brij 78 is adsorbed on the surface of cationic microparticles due to hydrophobic interactions between their hydrocarbon chains and those of DSDMAC. In this circumstance, the surfactants would protrude their long chains of ethylene oxide. Thus, not the interface of charged heads of DSDMAC and water, but that of the layer of ethylene oxide and water would be a surface for the potential measurement. This could be responsible for the decreased surface potentials.

Fig. 3 shows the effect of Brij 78 on the turbidities of cationic MXD microparticles, suspended in aqueous solution containing SLES. When no Brij 78 was included, the turbidity increased in a saturation manner as SLES/DSDMAC ratio increased up to 2. The anionic surfactant will be readily adsorbed onto the cationic surface, leading to the increased size of particles and the increased turbidity of the suspension. The adsorption will also give a rise to the neutralization of positive surface charge (See Fig. 2). As a result, repulsion force between MXD microparticles will decrease, resulting in the agglomeration of particles and increased turbidity. On the other hand, when Brij 78 was included so that the molar ratio of Brij 78/DSDMAC was 0.017 : 1, the turbidity increased with the ratio of SLES/DSDMAC but the increment was much smaller than in case when no Brij 78 was included. When the molar ratio of Brij 78/DSDMAC was further increased to 0.063 : 1 and 0.123 : 1, no significant changes in turbidity were observed. Following the result of zeta potentials (Fig. 2), the adsorption of SLES and the neutralization of surface charge obviously occurred even when Brij 78 was included. Nevertheless, the changes in turbidity with increasing SLES/DSDMAC ratio were insignificant. Ethylene oxide chains of the nonionic surfactant would form hydrophilic corona and they could

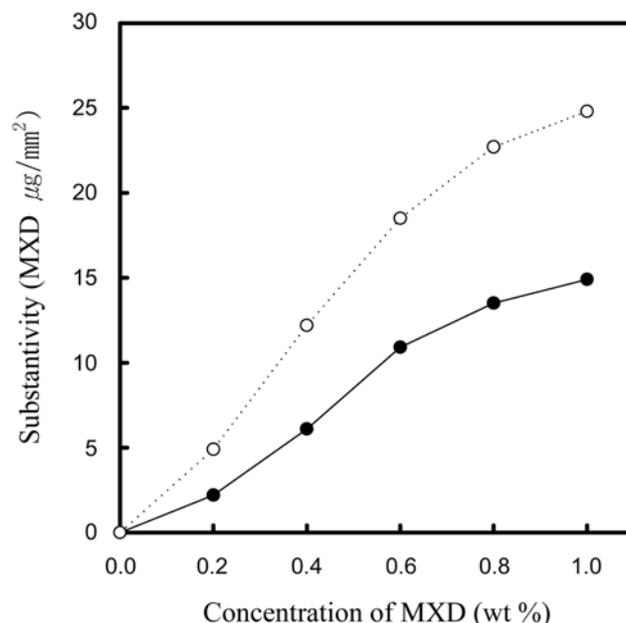


Fig. 4. The amount of MXD left on a skin after rinsing. Cationic MXD microparticles without Brij 78 (the molar ratios of Brij 78/DSDMAC: 0/1 (●)) and with Brij 78 (the molar ratios of Brij 78/DSDMAC: 0.063/1 (○)) were suspended in aqueous solutions containing SLES. The molar ratio of SLES/DSDMAC was 1.25/1.

prevent the aggregation and agglomeration of MXD microparticles. Ethylene oxide chains are hydrophilic and flexible. Due to their high mobility, they are known to prevent the adsorption of plasma proteins on the surfaces of biomaterials. They tend to take an extended form in an aqueous phase to get a high degree of freedom [5]. If MXD particles aggregate with each other, ethylene oxide chains would be compressed and the degree of freedom (entropy) would decrease. To increase entropy, the compressed chains should stretch out and the aggregated particles will push away each other. This may explain why the change in turbidity of the suspension containing Brij 78 was insignificant.

3. In Vitro Substantivity

Fig. 4 shows the amount of MXD left on a skin after rinsing. The amount increased in a saturated manner with increasing the concentration in suspension. When Brij 78 was contained in the MXD suspension (the molar ratios of Brij 78/SLES/DSDMAC were 0.063/1/1), the substantivity was about two times higher than that of MXD suspension including no Brij 78. One of the major factors determining the substantivity was reported to be the surface potential of the particles. According to the result of the surface potential measurements (Fig. 2), positive charge was almost neutralized at SLES/DSDMAC ratio of 1 : 1, whether Brij 78 was included in the MXD suspension or not. The molar ratio of SLES/DSDMAC, 1.25 : 1, was employed for the measurement of substantivity, so the surface potential of MXD microparticles was about -10 mV. Nevertheless, significant amounts of MXD were detected after rinsing skin. How could it be possible? This conflicting phenomenon was addressed in a previous report [4]. In brief, SLES is a one-tailed and water-soluble detergent but DSDMAC is a two-tailed surfactant and the solubility is relatively low, so SLES is more readily desorbed from

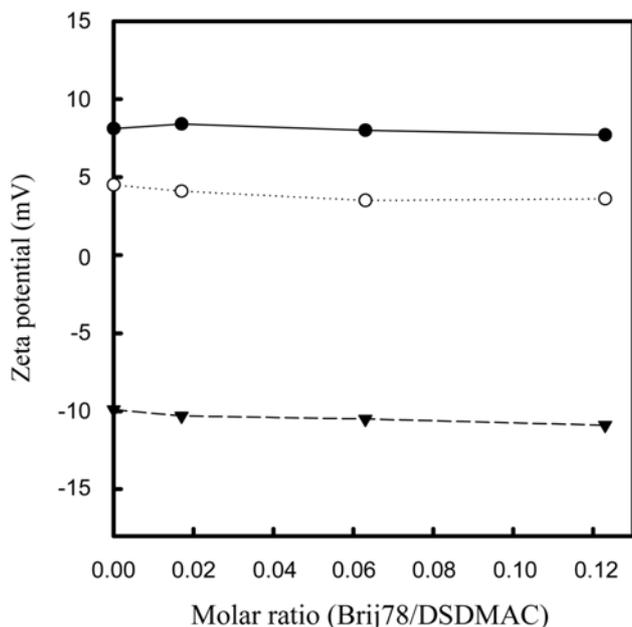


Fig. 5. The effects of dilution on the change in the zeta potentials of cationic MXD microparticles. The molar ratios of Brij 78/DSDMAC in cationic MXD microparticles were varied from 0/1 to 0.123/1. Each cationic MXD microparticle was suspended in aqueous solutions containing SLES. The molar ratio of SLES/DSDMAC was 1.25/1. Each suspension (▼) was diluted water 10 times (○) and 20 times (●) with distilled.

the surface of MXD microparticle while rinsing skin. As a consequence, the surface would become positive during rinsing skin and the electrostatic interaction with skin will lead to an appreciable amount of MXD left on the rinsed skin. Now, the question is why the substantivity of MXD microparticles with Brij 78 is higher than that of the particle without Brij 78. During the rinsing step of skins, did the surface potential of MXD microparticles with Brij 78 become more positive than that of the particle without Brij 78?

4. Effect of Dilution on the Zeta Potential of MXD Microparticles

The rinsing step of skins in the experiment of *in vitro* substantivity involves the dilution of MXD suspensions. To figure out what the surface potentials of MXD microparticles will be during the rinsing step, the effects of dilution on the change in the zeta potentials of MXD microparticles were investigated, as shown in Fig. 5. The molar ratio of Brij 78/DSDMAC was varied from 0 : 1 to 0.123 : 1 and the molar ratio of SLES to DSDMAC was fixed to 1.25 : 1. Before dilution, the zeta potentials were around -10 mV at all the molar ratio of Brij 78/DSDMAC. Upon 10 time and 20 time dilution, whatever the molar ratio of Brij 78/DSDMAC was, the zeta potentials increased to about +5 mV and +10 mV, respectively. The desorption of SLES by dilution would be responsible for the in-

creased zeta potentials [3]. The increment in zeta potentials by dilution was the same whether Brij 78 was included in the MXD suspension or not. That is, the nonionic surfactant had little effect on the desorption of SLES from the surface, and thus the surface potentials after dilution were almost the same at all the molar ratio of Brij 78/DSDMAC. Therefore, it is concluded that the higher retention on skin of MXD microparticles in the suspension containing Brij 78, shown in Fig. 4, was not due to their positive surface potentials since MXD microparticles in the suspension containing no Brij 78 also exhibited the same positive charge after dilution. Following the effect of Brij 78 on the aggregation of cationic MXD microparticles in the presence of SLES, the nonionic surfactant prevented the aggregation. Accordingly, when the nonionic surfactant was included in the suspension of MXD microparticles, the specific surface area of the microparticles would be higher and thus the electrostatic interaction with negatively-charged skins would be stronger. This may account for the higher substantivity.

CONCLUSIONS

Cationic MXD particles electrostatically interact with SLES even in the presence of Brij 78, leading to the loss of the positive surface charge. The electrostatic interactions led to the agglomeration of the cationic microparticles when the nonionic surfactant was absent. The nonionic surfactant, however, could prevent the agglomeration of cationic MXD microparticles even in the presence of excess amount of SLES. The substantivity of cationic MXD microparticles with Brij 78 was about two times higher than that of the particles without the nonionic surfactant. On the other hand, the positive charges of cationic MXD microparticles could be recovered upon dilution, whether Brij 78 was included in the suspension of cationic MXD microparticles or not. Therefore, the higher substantivity could be ascribed to the cationic microparticles-stabilizing effect of Brij 78.

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