Study of Interactions between Non-ionic Surfactants, Polyethylene Glycol, Methotrexate and Olmesartan Ester

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Keywords: Gemini non-ionic surfactant; polyethylene glycol; methotrexate; olmesartan ester; surface tension; particle size; electronic potential

Abstract: Objective: To explore the interactions between various components of novel non-ionic surfactant vesicles, to prepare better vesicle system with higher quality and higher encapsulation efficiency, this study investigated the interactions among non-ionic Gemini surfactants, polyethylene glycol, and various drugs. **Methods:** Different concentrations of Gemini non-ionic surfactant solution and its mixed system with polyethylene glycol, methotrexate and olmesartan ester were prepared, and the relationship between surface tension, particle size, and potential and concentration was determined. **Results:** Tension measurements showed that the critical micelle concentration of Gemini surfactant was 0.5% ~ 0.7%; 0.01% ~ 1.0% of PEG-6000 and 0.05% ~ 0.3% of methotrexate (mass concentration) have no effect on the surface tension of the Gemini surfactant solution. Olmesartan ester (0.01% ~ 0.25%, mass concentration) may decrease the surface tension of the solution. Measurement results of both the particle size and the electronic potential show that there are inflection points at concentrations of 0.5% ~ 0.7%. **Conclusion:** Using surface tension method and measurement of particle size and electronic potential, it can be concluded that PEG-6000 and methotrexate have no interaction with Gemini surfactants; olmesartan ester can decrease the surface tension of the solution, so better effects may be obtained if it is mixed with Gemini surfactants.

1. Introduction

Gemini surfactants are a new class of surfactants formed by two hydrophilic groups and two oleophilic groups joined by a linking chain. Compared with traditional surfactants, it has low critical micelle concentration, very low Krafft point, biosafety and degradability. It is widely used in washing, medicine, oil recovery and other industries [1-4] . Gemini nonionic surfactant and water-soluble polymer have higher surface activity, stability and safety after being compounded, which makes it have broad application prospects in the development of new drug formulations [5-9]. In recent years, drug-loaded lipid vesicles prepared with nonionic surfactants as the main capsules have become popular drug carriers in the medical field due to their advantages of sustained release, targeting, and low toxicity [10-14]. Ding Lin et al [15-16] prepared nonionic surfactant vesicles by double emulsion lyophilization method, studied the encapsulation effect of vesicles on water-soluble drug methotrexate; prepared non-ion by membrane hydration-ultrasonic method The type of gemini surfactant vesicles was investigated for the effect of NaCl on the physicochemical properties and encapsulation efficiency of ofloxacin vesicles. Wei Jun [17] studied the encapsulation of Gemini surface active vesicles on the water-soluble drug fluorouracil and its in vitro release behavior. However, studies on the interaction between Gemini nonionic surfactants and polymers and drugs have rarely been reported. In this experiment, the surface tension method was used to qualitatively and quantitatively study the interaction between Gemini nonionic surfactant and polyethylene glycol and different drug molecules methotrexate and olmesartan. The particle size and potential of the system were determined. To provide reference for the development and application of a new drug formulation, vesicle system.

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2. Material

8010 type stirring ultrafiltration cup (MILLIPORE COMPANY); electronic balance (Beijing Sartorius Instrument System Co., Ltd.); super constant temperature water bath type 501 (Shanghai Experimental Instrument Factory Co., Ltd.); PHS-3C acidity meter (Shanghai Kangyi Instrument Co., Ltd.) Company); DCAT11EC (Germany by dataphysics instruments CmbH); ZEN 3690 Malvern Zetasizer (Malvern Instruments Limiteo); 85-1 magnetic stirrer (Jintan City, the head of Guorui Experimental Instrument Factory); KQ-500DB type CNC ultrasonic cleaning (Kunshan Ultrasonic Instrument Co., Ltd.); JY92-II ultrasonic cell pulverizer (Ningbo Xinzhi Biotechnology Co., Ltd.).

Gemini nonionic surfactant (2,4,7,9-tetramethyl-5-decyne-4,7-diol isooxide) (SIGMA-ALDRICH.CHEMIE GmbH); PEG-6000 (analytically pure, Shanghai Pudong Gaonan Chemical Plant); methotrexate standard (China National Institute for the Control of Pharmaceutical and Biological Products, batch number: 140726-201503); olmesartan ester standard (China National Institute for the Control of Pharmaceutical and Biological Products, batch number: 160831201410); Ethanol (analytical grade, Yantai Sanhe Chemical Reagent Co., Ltd.); potassium dihydrogen phosphate (analytical grade, Xuzhou Chemical Plant); sodium dihydrogen phosphate (analytical grade, Tianjin Bodi Chemical Co., Ltd.).

3. Methods and results

When the concentration of the surfactant solution is greater than its CMC value, the molecules automatically form micelles in the solution. After the micelles are formed, certain properties of the solution change, such as surface tension, electrical conductivity, and micelle diameter. Therefore, in this experiment, the surface tension, particle size and potential of different concentration systems were determined, and the changes of various properties of the system were investigated.

Weigh Gemini surfactant and PEG-6000 0.01 g, 0.03 g, 0.05 g, 0.07 g, 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g, respectively, and dilute to 100 mL with distilled water. The surface tension was measured separately, and the results are shown in Fig. 1.

Weigh the Gemini surfactant and PEG-6000 0.01 g, 0.03 g, 0.05 g, 0.07 g, 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g, respectively, and mix the two with equal mass. The distilled water was adjusted to a volume of 100 mL, and the surface tensions of different concentrations of Gemini surfactant and PEG-6000 mixed solution were measured. The results are shown in Fig. 1.

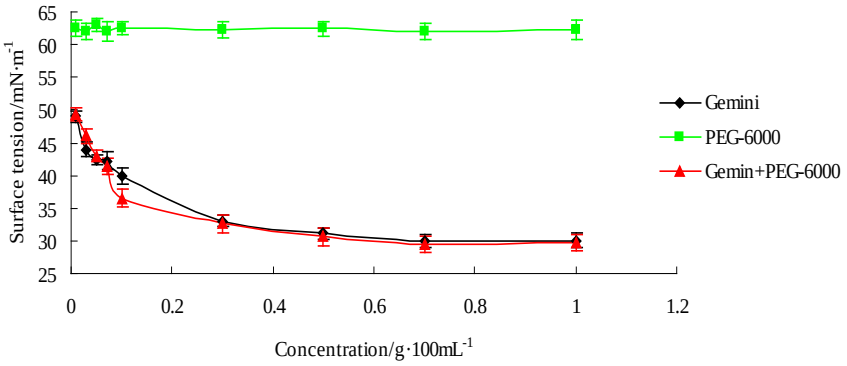

Fig.1 Measurement of surface tension for Gemini and PEG-6000 systems. n=3, $\bar{x} \pm s$

It can be seen from Fig. 1 that the surface tension of PEG-6000 solution is almost independent of its concentration; the surface tension of Gemini surfactant solution decreases with the increase of its concentration, when its mass concentration reaches 0.5%~0.7% g/mL, the surface The tension is basically stable, indicating that the concentration is the CMC value of the Gemini surfactant; the surface tension of the Gemini surfactant solution after adding PEG-6000 is basically unchanged, indicating that there is no interaction between PEG-6000 and Gemini.

Preparation of phosphate buffer solution with pH=7.5: Weigh 3.12 g of sodium dihydrogen phosphate, dilute to 1000 mL with distilled water, shake well, and adjust pH to 7.5 with NaOH.

Weighed 0.05 g, 0.1 g, 0.15 g, 0.2 g, and 0.3 g of Gemini surfactant and methotrexate, respectively, and fixed to 100 mL with phosphate buffer solution of pH=7.5, and measured the surface tension. The result is shown in Figure 2.

Weigh 0.05 mg, 0.1 g, 0.15 g, 0.2 g, and 0.3 g of Gemini surfactant and methotrexate respectively. Mix the two equal masses and dilute to 100 with phosphate buffer solution of pH=7.5. In mL, the surface tension of different concentrations of Gemini surfactant and methotrexate mixed solution was determined. The results are shown in Fig. 2.

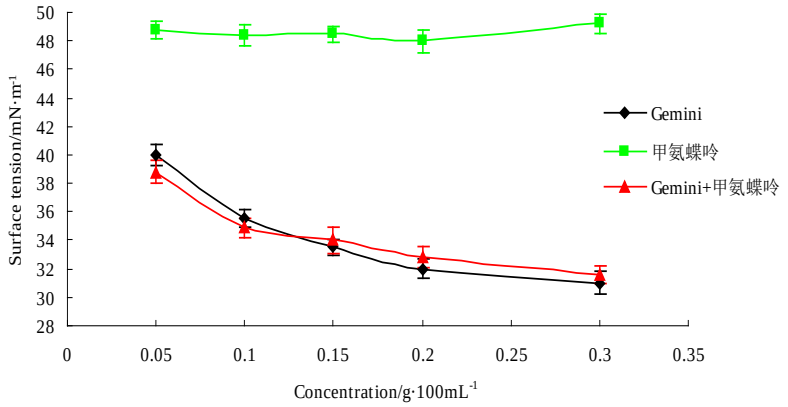

Fig.2 Measurement of surface tension for Gemini and methotrexate systems. n=3, $\bar{x}$ ±s

It can be seen from Fig. 2 that the surface tension of the methotrexate solution is almost independent of its concentration; the surface tension of the Gemini surfactant solution decreases with increasing concentration; the surface tension of the Gemini surfactant solution after the addition of methotrexate There was essentially no change, indicating no interaction between methotrexate and Gemini.

Weigh 0.01 g, 0.05 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g of Gemini surfactant and olmesartan medoxomil. Dissolve in 5 mL of absolute ethanol and dilute to 100 mL with distilled water. The surface tension was measured separately, and the results are shown in Fig. 3.

Weigh 0.01 g, 0.05 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g of Gemini surfactant and olmesartan medoxomil, respectively, and mix the two with equal mass, then dissolve with 5 mL of absolute ethanol, then use distilled water. The volume was adjusted to 100 mL, and the surface tension was measured. The results are shown in Fig. 3.

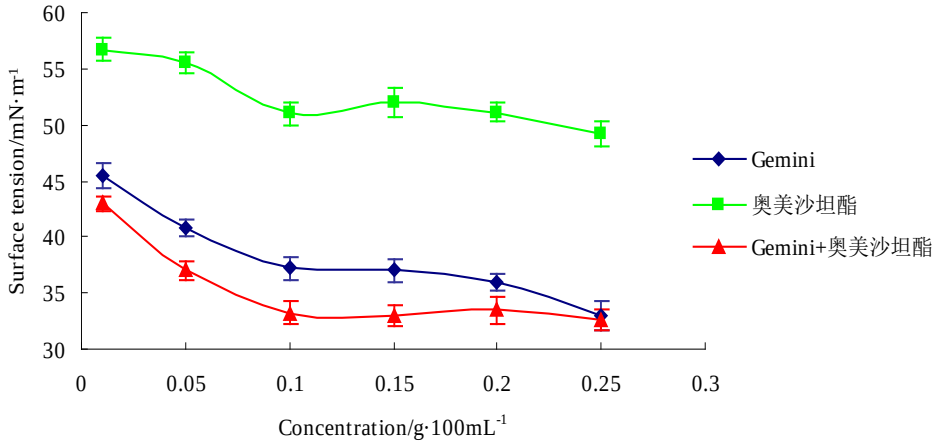

Fig.3 Measurement of surface tension for Gemini and Olmesartan medoxomil systems. n=3, $\bar{x}$ ±s

It can be seen from Fig. 3 that the surface tension of the olmesartan medoxomil solution decreases slightly with the increase of its concentration; the surface tension of the Gemini surfactant solution decreases with the increase of its concentration; after the addition of olmesartan medoxomil in the Gemini surfactant solution The surface tension is slightly lower than that of Gemini alone, indicating that olmesartan medoxomil has synergistic effect with Gemini surfactant to reduce surface tension.

The particle size of the Gemini surfactant with a mass concentration of 0.3% was measured by the following three methods:

Method 1: Ultrasonic two minutes using a KQ-500DB CNC ultrasonic cleaner.

Method 2: The JY92-II ultrasonic cell pulverizer was sonicated 40 times, once every 3 s, and the power was 80 W.

Method 3: Ultrafiltration cup filtration.

It can be seen from Table 1 that the second method uses the JY92-II ultrasonic cell pulverizer to have the highest precision and the method is more effective.

Weigh 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g Gemini surfactant, dilute to 100 mL with distilled water, ultrasonically 40 times with JY92-II ultrasonic cell pulverizer, and once every 3 s. The power is 80 W and the particle size is measured, as shown in Figure 4.

Weigh 0.1 mg, 0.3 g, 0.5 g, 0.7 g, and 1.0 g of Gemini surfactant and PEG-6000, respectively, and mix the two with equal mass, and dilute to 100 mL with distilled water. Ultrasonic cell pulverizer is used for ultrasonication. After that, the particle size was measured, and the results are shown in Fig. 4.

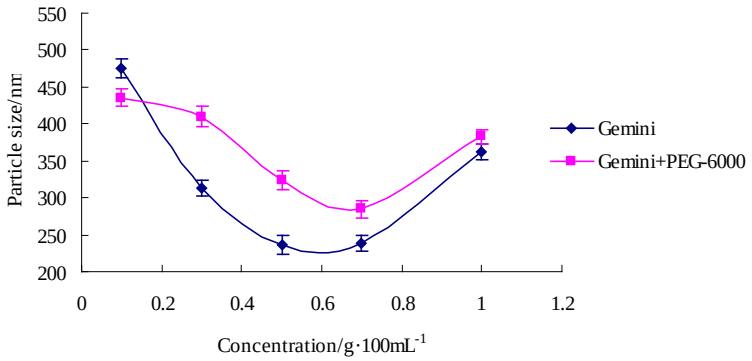

Fig.4 Measurement of particle size for Gemini and PEG-6000 systems. n=3, $\bar{x} \pm s$

It can be seen from Fig. 4 that the particle size of the Gemini surfactant solution decreases first and then increases with the increase of its concentration. When the mass concentration reaches about 0.6%, the particle size is the smallest, indicating that the concentration is the CMC value of Gemini; Gemini The particle size of the mixed system with PEG-6000 decreases first and then increases with the increase of concentration. When the mass concentration reaches 0.6%~0.7%, the particle size is the smallest, indicating that the concentration is the CMC value of Gemini; Gemini surfactant The critical micelle concentration did not change substantially after the addition of PEG-6000 to the solution, indicating that PEG-6000 did not affect the critical micelle concentration of Gemini.

Investigation of Gemini surfactant and methotrexate system

1) Weigh 0.07 g, 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g Gemini surfactant, and make up to 100 mL with pH=7.5 phosphate buffer solution, respectively, and use JY92-II ultrasonic cell pulverizer for ultrasonication. For 40 times, every 3 s ultrasound, the power is 80 W, and the particle size is measured, as shown in Figure 5.

2) Weighed 0.05 g, 0.1 g, 0.15 g, 0.2 g, 0.3 g, and 0.35 g of Gemini surfactant and methotrexate respectively. After mixing the equal masses, the volume was adjusted with pH=7.5 phosphate buffer solution. After 100 mL, ultrasonication with an ultrasonic cell pulverizer, the particle size was measured, as shown in Fig. 5.

3) Weigh 0.07 g, 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g of Gemini surfactant and 0.1 g of methotrexate, respectively, and then make up to 100 mL with phosphate buffer solution of pH=7.5. After the cell pulverizer was ultrasonicated, the particle size was measured, as shown in Fig. 5.

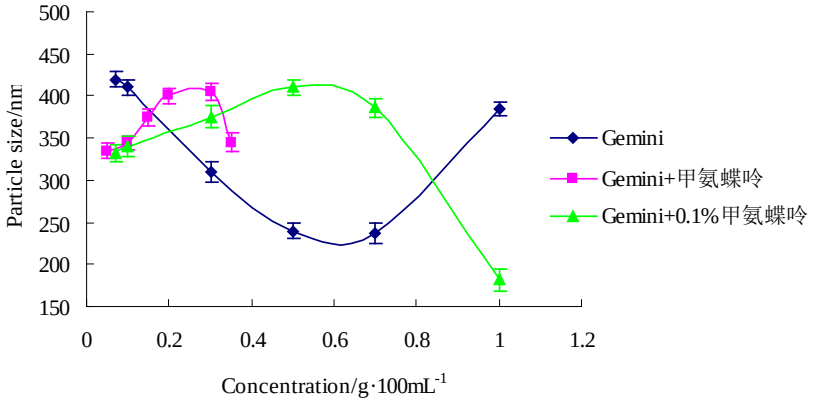

Fig.5 Measurement of particle size for Gemini and methotrexate systems. n=3, $\bar{x} \pm s$

It can be seen from Fig. 5 that the particle size of the Gemini surfactant solution (pH=7.5) decreases first and then increases with the increase of the concentration. When the mass concentration reaches 0.6%~0.7%, the particle size is the smallest, indicating that the concentration is The CMC value of Gemini; the particle size of the mixed solution of Gemini and methotrexate increases first and then decreases with the increase of concentration. When the concentration of Gemini and methotrexate is 0.25%~0.3% or the concentration of Gemini is 0.6%, A When the concentration of methotrexate is 0.1%, the particle size is the largest, indicating that vesicle formation occurs at this concentration.

Weigh 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g Gemini surfactant, dissolve them in 5 mL absolute ethanol, dilute to 100 mL with distilled water, and invert 40 times with JY92-II ultrasonic cell pulverizer. The ultrasonic particle size was measured every 3 s and the power was 80 W. The results are shown in Fig. 6.

Weigh 0.01 g, 0.05 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g of Gemini surfactant and olmesartan medoxomil, respectively. After mixing the two masses, use 5 mL of water. The ethanol was dissolved, and the volume was adjusted to 100 mL with distilled water. After ultrasonication with an ultrasonic cell pulverizer, the particle size was measured, and the results are shown in Fig. 6.

Weigh 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g Gemini surfactant mixed with 0.05 g of olmesartan medoxomil, dissolved in 5 mL of absolute ethanol, and made up to 100 mL with distilled water, using ultrasonic cells. After the pulverizer was ultrasonically measured, the particle size was measured, and the results are shown in Fig. 6.

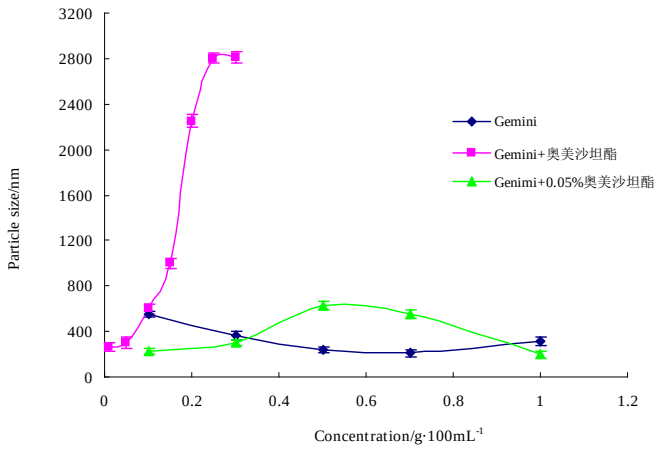

Fig.6 Measurement of particle size for Gemini and Olmesartan medoxomil systems. n=3, $\bar{x} \pm s$

It can be seen from Fig. 6 that the particle size of the Gemini surfactant solution first decreases and then increases with the increase of the concentration. When the mass concentration reaches 0.6%-0.7%, the particle size is the smallest, indicating that the concentration is the CMC of the Gemini surfactant. The particle size of Gemini surfactant and olmesartan medoxomil system increases with the increase of concentration. When the mass concentration is 0.25%, the particle size no longer increases and tends to be stable, indicating that there is vesicle at this concentration. form;

The particle size of Gemini and 0.05% olmesartan medoxomil system increased first and then decreased with the increase of concentration. When the concentration of Gemini was 0.6% and the concentration of olmesartan medoxomil was 0.05%, the particle size was the largest, indicating that there was a capsule at this concentration. Bubble formation.

Weigh 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g Gemini surfactant, dilute to 100 mL with distilled water, ultrasonically 40 times with JY92-II ultrasonic cell pulverizer, power 80 W, every 3 s ultrasound once, measure the potential, see Figure 7.

Weigh 0.1 mg, 0.3 g, 0.5 g, 0.7 g, and 1.0 g of Gemini surfactant and PEG-6000, respectively, and mix the two with equal mass, and dilute to 100 mL with distilled water. Ultrasonic cell pulverizer is used for ultrasonication. After that, the potential was measured and the results are shown in Fig. 7.

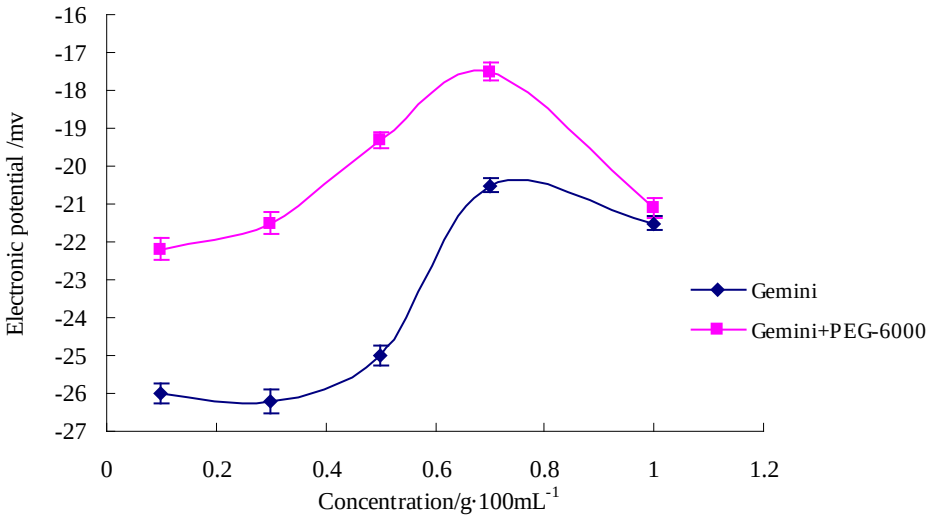

Fig.7 Measurement of electronic potential for Gemini and PEG-6000 systems. n=3, $\bar{x} \pm s$

It can be seen from Fig. 7 that the potentials of the Gemini surfactant solution and the Gemini and PEG-6000 systems increase first and then decrease with the increase of the concentration. When the mass concentration reaches about 0.7%, the absolute value of the potential is the smallest, indicating that the The concentration is the CMC value of the Gemini surfactant; the critical micelle concentration of the Gemini surfactant after adding PEG-6000 has no significant change with the addition of PEG-6000.

Weigh 0.07 g, 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g Gemini surfactant, dilute to 100 mL with pH=7.5 phosphate buffer solution, and use ultrasonic JY92-II ultrasonic cell pulverizer 40 The power is 80 W, and the ultrasound is measured every 3 s, and the potential is measured, as shown in Fig. 8.

Weigh Geji surfactant and methotrexate 0.05 g, 0.1 g, 0.15 g, 0.2 g, 0.3 g, 0.35 g, respectively, and make up to 100 mL with pH=7.5 phosphate buffer solution. After ultrasonication by an ultrasonic cell pulverizer, the potential is measured, as shown in Fig. 8.

Weigh 0.07 g, 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g of Gemini surfactant and 0.1 g of methotrexate, respectively, and dilute to 100 mL with phosphate buffer solution of pH=7.5. After ultrasonication with an ultrasonic cell pulverizer, the potential was measured, as shown in Fig. 8.

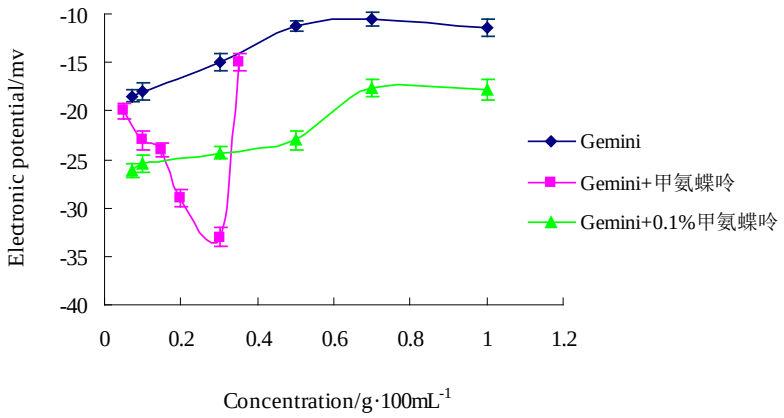

Fig.8 Measurement of electronic potential for Gemini and methotrexate systems. n=3,x ±s

It can be seen from Fig. 8 that the potential of the Gemini surfactant solution (pH=7.5) increases first and then decreases with the increase of the concentration. When the mass concentration reaches about 0.7%, the absolute value of the potential is the smallest, indicating that the concentration is Gemini surface. Compared with Figure 7, the CMC value of the active agent makes the potential of the system smaller than that of the phosphate buffer solution with pH=7.5; the potential of the same concentration of Gemini and methotrexate system decreases first and then increases with the increase of concentration. When the mass concentration is 0.25%~0.3%, the absolute value of the potential is the largest, indicating that there is vesicle formation at this concentration; the potential of Gemini and 0.1% methotrexate system increases first and then decreases with the increase of concentration. When the Gemini concentration was 0.7% and the methotrexate concentration was 0.1%, the absolute value of the potential was the smallest, indicating that vesicle formation occurred at this time.

Weigh 0.1 g, 0.3 g, 0.5 g, 0.7 g, 1.0 g Gemini surfactant, dissolve with 5 mL of absolute ethanol, dilute to 100 mL with distilled water, and use JY92-II ultrasonic cell pulverizer for ultrasonication. 40 times, the power is 80 W, and the ultrasound is measured every 3 s, and the potential is measured, as shown in Fig. 9.

Weigh 0.01 g, 0.05 g, 0.1 g, 0.15 g, and 0.2 g of Gemini surfactant and olmesartan medoxomil, respectively. Mix the two equal masses and dissolve them with 5 mL of absolute ethanol. The volume was adjusted to 100 mL with distilled water, and after ultrasonication with an ultrasonic cell pulverizer, the potential was measured, as shown in Fig. 9.

Weigh 0.1 g, 0.3 g, 0.5 g, 0.7 g, 0.9 g, 1.0 g Gemini surfactant, mix with 0.05 g of olmesartan medoxomil, add 5 mL of absolute ethanol, and then dilute with distilled water. After up to 100 mL, after ultrasonication with an ultrasonic cell pulverizer, the potential was measured, as shown in Fig. 9.

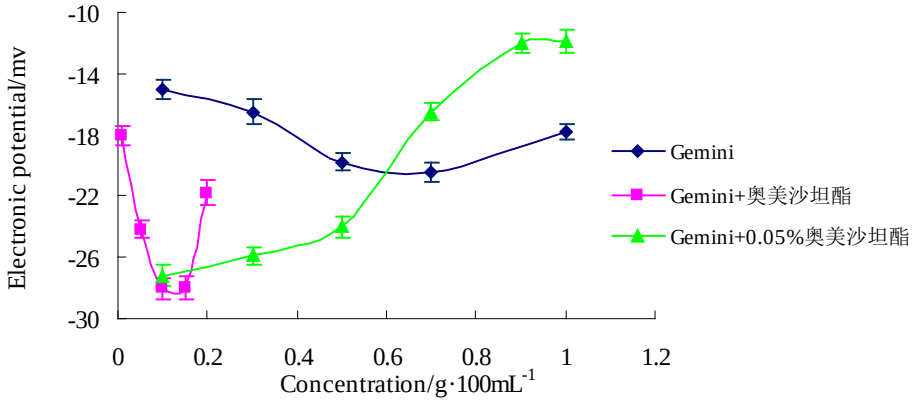

Fig.9 Measurement of electronic potential for Gemini and Olmesartan medoxomil systems. n=3, x ±s

It can be seen from Fig. 9 that the potential of the Gemini surfactant plus 5mL absolute ethanol dissolved and constant volume system decreases first and then increases with the increase of concentration. When the Gemini concentration is 0.6%~0.7%, the absolute value of the potential is the largest, indicating This concentration is the critical micelle concentration of Gemini surfactant; the potential of the mixed system of Gemini and olmesartan ester decreases first and then increases with the increase of concentration. When the concentration of both is 0.1%~0.15%, the absolute potential The value is the largest, indicating that there is vesicle formation at this concentration; the potential of Gemini and 0.05% olmesartan medoxomil mixed system increases with increasing concentration, when the Gemini concentration is 0.9% and the olmesartan medoxomil concentration is 0.05%, the potential The absolute value is the smallest and then stabilizes, indicating that there is vesicle formation at this concentration.

4. Discussion

In this experiment, the surface tension of the liquid was measured by the hanging piece method. The factors affecting the measurement of the hanging sheet method are the cleanliness of the platinum-iridium alloy sheet, the cleanliness of the sample chamber, the temperature of the sample chamber, the stability of the table, the concentration of the solution, and the solvent. In order to ensure the cleanness of the platinum-rhodium alloy sheet, the flame-burning platinum-rhodium alloy sheet was used in the experiment.

The surface tension test results show that the critical micelle concentration of Gemini surfactant is 0.6%~0.7%; the concentration of 0.01%~1.0% PEG-6000 and 0.05%~0.3% methotrexate to Gemini surfactant The surface tension of the solution has no effect; olmesartan medoxomil at a concentration of 0.01% to 0.25% can reduce the surface tension of the solution.

The results of particle size and potential measurement showed that when the concentration of Gemini and methotrexate was 0.25%~0.3%, the concentration of Gemini was 0.6%, the concentration of methotrexate was 0.1%, and the concentration of Gemini and olmesartan was 0.25%. When the concentration of Gemini is 0.6% and the concentration of olmesartan medoxomil is 0.05%, the particle size is the largest, and stable vesicles can be formed at this time.

5. Conclusion

Using surface tension method, particle size and potential measurement to study the interaction between nonionic Gemini surfactant and polyethylene glycol and different drugs, short time, small PDI, good uniformity, inflection point and particle size measurement of potential measurement The inflection point is consistent, the method is simple and easy, and the result is accurate. This study provides a theoretical basis and experimental basis for the rational application of Gemini nonionic surfactant in the field of medicine.

Acknowledgements

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