Development and Evaluation of Estradiol-Loaded Microemulsion-Based Gel

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ABSTRACT SUMMARY
The purpose of this study was to develop and evaluate microemulsion-based gel for transdermal delivery of Estradiol (E2). The E2-loaded microemulsion-based gel was evaluated by physicochemical characteristics, stability, in vitro and in vivo permeation test. Compared to control group and commodity, the E2-loaded microemulsion-based gel with higher permeation rate, 20.0~21.3 fold and 2.33~2.42 fold respectively, was expected to provide effective therapeutic concentration in a workable administration.

INTRODUCTION
Estradiol is effective in treatment of postmenopause hormonal deficiency. However, oral administration of estradiol would be inactivated by gastrointestinal digestion and liver first-pass metabolism effect; hence, the transdermal administration route was the most suitable for estadiol.

Microemulsions are the mixtures of oil, aqueous phase, surfactant, and co-surfactant. Because of several advantages such as thermodynamic stability, optical isotropy, high solubilization capacity and easy formation, it has been widely used in recent years. In many studies, microemulsions have demonstrated a great potential for improving the systemic and local bioavailability of hydrophobic and hydrophilic therapeutic agents. However, the characteristic of low viscosity would be restricted its application.

Carbomer is a series of polymer of acrylic acid. It could be swelled well in water to produce gelling statement and applied on the skin without irritation or inflammation. Poloxamer is polyoxyethylene and polyoxypropylene block nonionic copolymer. Because of poloxamer have temperature sensing characteristic, it could provide the statement which a temperature rise, the molecular network structure would be produced to increase the viscosity.

In previous studies, we had used Response Surface Methodology to develop the optimal formulation. The E2-loaded microemulsion with higher permeation rate was expected to provide effective therapeutic concentration in a workable administration. The aim of this study was to develop the E2-loaded microemulsion-based gel for transdermal delivery.

EXPERIMENTAL METHODS
The proportion of microemulsion was set according to the preliminary studies; hence, in this study, the various gelling agents would be added to prepare the microemulsion-based gel.

The preparation as following steps:

- **Method 1**
  Carbomer was dissolved in double-distilled water and adjusted to pH=7 with 1 N NaOH. Then, 10% Carbomer gel was added to E2-loaded microemulsion and stirred at 200 rpm for 12 hr. The total amount of microemulsion-based gel was 10 g.

- **Method 2**
  The mixture of surfactant and co-surfactant was mixed well and the oil phase was added into the mixture and shaken by a vortex. The aqueous phase of microemulsion was prepared with carbomer as Method 1. Then, the carbomer gel was added into the mixture of surfactant, co-surfactant and oil, and stirred at 200 rpm for 12 hr.

- **Method 3**
  The E2-loaded microemulsion was mixed with carbomer powder, and stirred at 200 rpm for 12 hr. The pH value was adjusted by the microemulsion itself.
Method 4

As following the Method 1, Method 2 and Method 3, however, the drug was added into the formulation after the blank microemulsion-based gel had prepared completely.

The preparation of poloxamer microemulsion-based gel was set according to Method 3.

Viscosity measurement was carried out by using Brookfield's viscometer. All of the samples were placed in the plate of viscometer and maintained at 37°C by a thermostatic water pump. The shear rate of the samples were rotated at 0.05, 5 and 10 rpm. All of the measurements of viscosity were repeated in triplicate and averaged.

According to I.C.H. Q1A (R2) guideline, stability measurement was placed the samples in constant temperature and humidity chamber. At predetermined intervals, a sample of 0.5 g was withdrawn and was analyzed by high-pressure liquid chromatography (HPLC) to determine the drug content and was measured by viscometer to determine the viscosity. Each data point represented the average of three determinations.

The samples were applied on the Wistar rat abdominal skin to determine in vivo permeation study and the skin irritation. In this study, the optic system of a portable color spectrophotometer was set at D65 /10 and all of the measurements of were repeated in triplicate and averaged.

Transmission electron microscopy was used to determine the droplet size.

RESULTS AND DISCUSSION

The in vitro permeation study result was shown in Figure 1. Carbomer is more suitable to prepare E2-loaded microemulsion-based gel.

Figure 1. In vitro permeation study of poloxamer series and carbomer series.

Figure 2. Compared to control group and commodity, carbomer E2-loaded microemulsion-based gel with higher permeation rate.

Figure 3. Stability test for 28 days.

Figure 4. In vivo permeation study of Carbomer and commodity.

CONCLUSION

E2-loaded microemulsion-based gel could be developed successfully by adding carbomer polymers. Method 3 is the best preparation for E2-loaded microemulsion-based gel. Compared to control group and commodity, the E2-loaded microemulsion-based gel of carbomer polymer with higher permeation rate, 20.0~21.3 fold and 2.33~2.42 fold respectively, was expected to provide effective therapeutic concentration in a workable administration.

REFERENCES
