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SMEDDS (Self-MicroEmulsifying Drug Delivery System) As An Intraurethral Prostaglandin E_1 Delivery System

Sangkil Lee*†, Sangok Jeon*, Jae Seon Kang*, Jaehwi Lee and Young Wook Choi**†**

**Department of Pharmaceutical Engineering, Inje University, 607 Obang-dong, Gimhae, Gyeungnam 621-749, Korea*
***College of Pharmacy, Chung-Ang University, 221 Heuksuk-dong, Dongjak-gu, Seoul 156-756, Korea*

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ABSTRACT – Prostaglandin E_1 (PGE_1) was formulated as two self-microemulsifying drug delivery systems (SMEDDS) composed of Cremophor EL® or Cremophor ELP® as a surfactant, ethanol as a cosurfactant and Labrafac CC® as an oil to develop liquid preparation for the treatment of erectile dysfunction. In pseudo-ternary phase diagram, viscous gel area and microemulsion area were defined. In the measurement of viscosity, the viscosity of two formulations increased gradually upon the addition of water and it decreased from the water contents over 40%. With excessive water, the present systems formed a microemulsion spontaneously. From these results, we could expect that the present liquid PGE_1 SMEDDS formulations might stay within the urethra in the viscous state when contacting the moisture of the urethra and can be easily eliminated by urination. In long-term stability study, we could select one formulation more stable at the shelf storage condition of 4°C.

Key words – Erectile dysfunction, Intraurethral, Prostaglandin E_1, SMEDDS, Self-emulsifying drug delivery system

It has been known that nearly 10% of men of the world were suffered from the erectile dysfunction.[1] It induces physical and psychical side effects such as impair of sexual performance, diminish of self-esteem and disrupt of personal relationship.[2] Unlike other diseases, it becomes more frequent with age but normal aging is not an inevitable cause of erectile dysfunction.[3] To treat this disease, injection formulations of phenoxybenzamin, papaverin hydrochloride, phentolamin mesylate and prostaglandin E_1 were developed. However, the injection of these drugs to the intracoporeal area practically induces side effects such as pain, priapism, penile hematomas and fibrosis, which is the main reason for discontinuation of this therapy.[2,4-6]

Before the emergence of oral formulations (e.g. Viagra®, Pfizer), prostaglandin E_1 (PGE_1) has been known as one of the most potent compound for erectile dyscfunction.[7] PGE_1 induces the increase of intracellular 3,5-cyclic adenosine monophosphate (cAMP) concentration,[8] which causes the relaxation of arterial and trabecular smooth muscle in the corpus cavernosum and thereby causes penile erection.[7] For years ago, a non-invasive intraurethral PGE_1 suppository (MUSE®, Vivus Inc.) has been introduced,[1] however, intraurethral suppository caused discomforts like feeling of foreign body and pain induced by bulky insertion device.[9,10]

For those reasons, the liquid formulation is thought as an adequate formulation for intraurethral PGE_1 delivery. The liquid type formulation has advantages in the aspects of patients' compliance because i) the drug may be delivered in a non-invasive way, ii) the patients can administrate formulation easily into the urethra than solid suppository, and iii) the pain induced by the bulky device can be avoided.

In this study, we suggest SMEDDS (Self-MicroEmulsifying Drug Delivery System) as a candidate for the intraurethral PGE_1 delivery system because in some cases this system would provide viscous property by the addition of water,[11-13] and this may offer an increased residence time of PGE_1 within urethra. Finally, we compared the long-term stability of PGE_1 within two SMEDDS formulations.

Experimental

Materials

Prostaglandin E_1 (PGE_1; 11α, 13E, 15(S))-11, 15-dihydroxy-9-oxoprosta-13-en-1-oic acid) was provided by Cascade Biochem Ltd. (Cork, Ireland). Cremophor EL® and Cremophor ELP® (polyoxyl 35 castor oil) were purchased from BASF (Germany) and Labrafac CC® (caprylic/capric triglyceride) was purchased from Gateffosse (France). Other chemicals and solvents were of reagent grade and used as received.

†본 논문에 관한 문의는 이 저자에게로
Tel : 055)320-3783, E-mail : skdavid@inje.ac.kr or ywchoi@cau.ac.kr

Preparation of phase diagram

To make a pseudo-ternary phase diagram, we first made the SMEDDS with surfactant (Cremophor EL® or Cremophor ELP®), co-surfactant (ethanol) and oil (Labrafac CC®). The water was added to SMEDDS and the final solution was equilibrated for 1 day. The pseudo-ternary phase diagram was defined simply as follows; clear systems but showing semi-solid characteristics was classified as gel phase (G) and a blue transparent solution was termed as microemulsion (M).

Measurement of viscosity

The change of viscosity was measured with a viscometer (Haake RV100, Germany) as a function of water content at 37°C to define gel area within the phase diagram.

Observation of self-microemulsification property

Self-microemulsification has been defined with the optical outer appearance, time for emulsification. To characterize the self-emulsification properties, 1 ml of SMEDDS was added to 200 ml of 37°C distilled water and it was gently stirred with 60 rpm. The evaluation criteria for emulsification was followed by the definition of Khoo et al.[14]

Measurement of droplet size

The size of microemulsion droplet was measured with a dynamic light scattering system (PCS4700, Malvern Co., UK) at the conditions of scattering angle of 90° and 12,000 counts per sec.

Stability of PGE_1 within SEMDDS

The composition of two SMEDDS formulations used in the stability test were 5:2:3 mixture of Cremophor EL®:Ethanol : Labrafac CC® and 5:2:3 mixture of Cremophor ELP®: Ethanol:Labrafac CC®, and the PGE_1 concentration was 1 mg/ml. The compositions were determined from the phase diagram which passed through the center of G and M area.

The stability test was performed at a constant humidity of 75% RH and varing temperature from 4 to 40°C. At appropriate time intervals, the remaining amount of PGE_1 and the degraded byproducts were analyzed with HPLC.

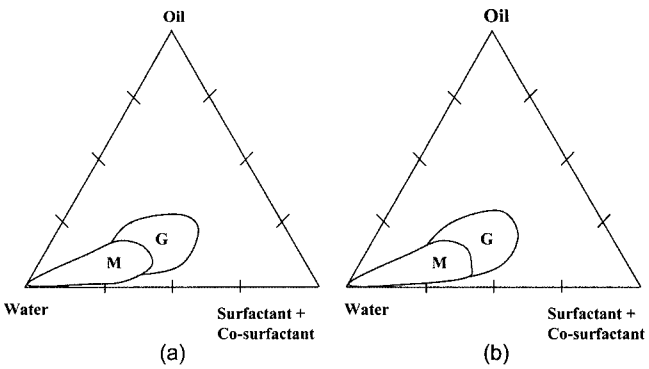

Figure 1–Phase diagrams of PGE_1 intraurethral formulation composed of Cremophor EL®(a) or Cremophor ELP®(b)/ethanol/LabrafacCC® showing microemulsion (M) and gel (G) regions.

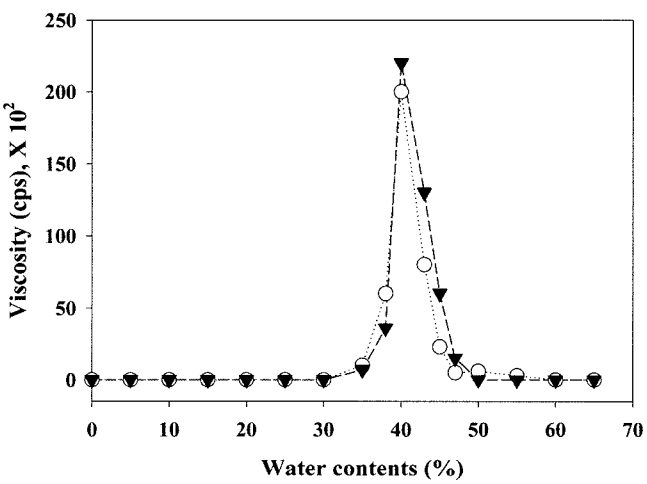

Figure 2–Viscosity change profiles of PGE_1 intraurethral SMEDDS formulation upon the addition of water at 37°C. ○; Cremophor EL® formulation, ▼; Cremophor ELP® formulation.

Analytical condition

Reverse phase Capcell Pak C_{18} (4.6 × 150 mm, particle size 5 μm) column was used to determine PGE_1 and the degraded byproducts. Acetonitrile : 0.02M phosphate buffer (pH 4.9)= 40:60 (v/v) was chosen as mobile phase. The flow rate was 1.0 ml/min, detection wavelength and injection volume was 200 nm and 20 μl, respectively.

Table I–*The Result of Self-emulsification Test*

Formulation	Optical Grade[a)]	Time to self-emulsification (sec)[b)]	Size (nm)[c)]
Cremophor EL® Preparation	A	<30	145.0±11.1
Cremophor ELP® Preparation	A	<30	166.2±3.2

a) Grade "A" is defined when clear or slightly bluish microemulsion is formed within 1 min.
b) The emulsification time was measured with gentle hand shaking.
c) Data are presented as mean±S.D. (n=3).

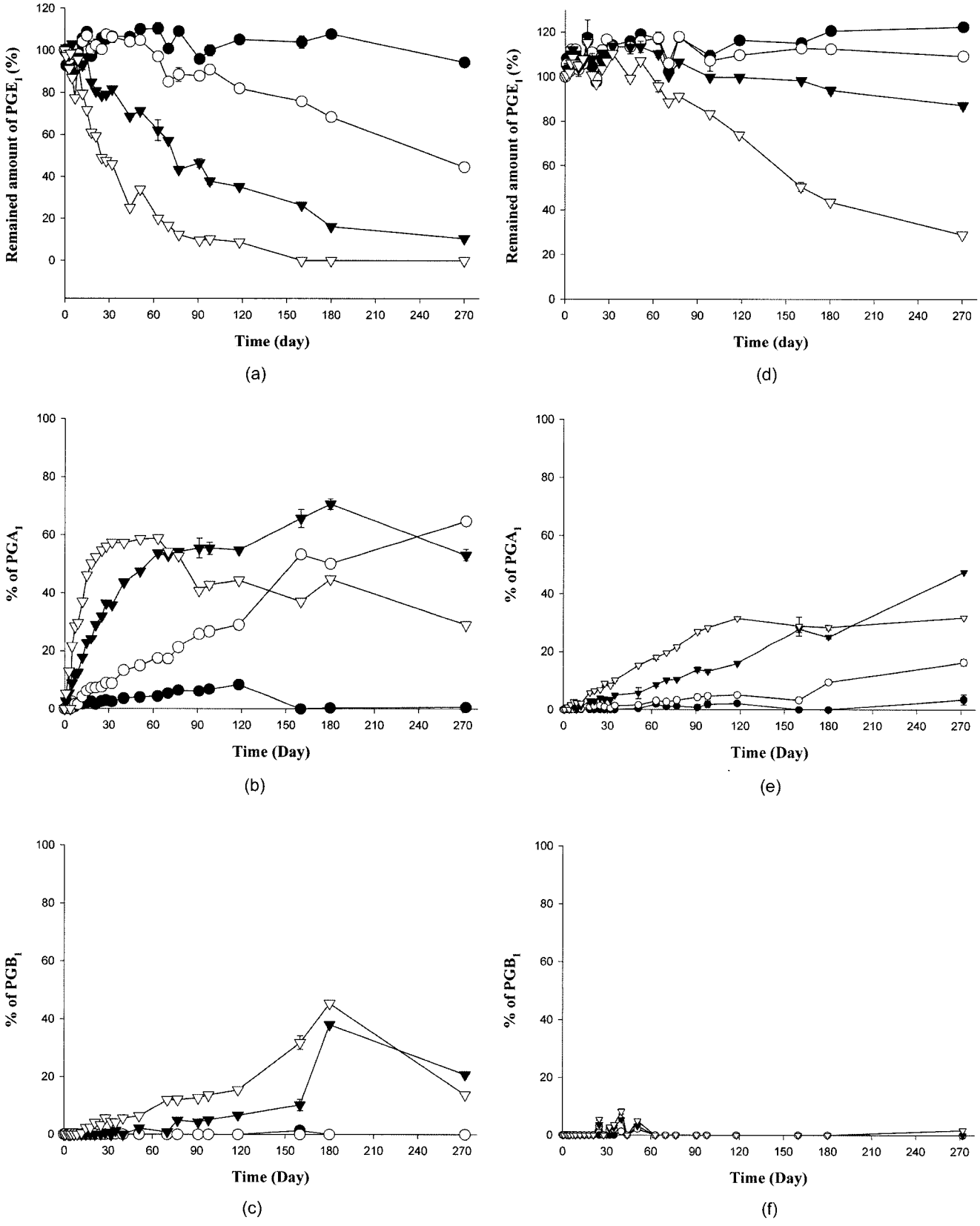

Figure 3–Stability of PGE_1 in intraurethral SMEDDS formulation. (a), (b) and (c) is result of Cremophor EL® formulation. (c), (d) and (e) is result of Cremophor ELP® formulation. K_m value which represents the weight ratio of surfactant to co-surfactant was 2.5 in all the formulation used in the stability test. Data were presented as mean±S.D.(n=3).

Results and Discussion

To design a intraurethral PGE_1 delivery system as liquid type, we considered that SMEDDS is a suitable system because i) it can be easily injected within urethra because it has a liquid like fluidity ii) it would reside within the urethra by gel like property after contact with water, and finally iii) it would be eliminated easily by urination after emulsification with excessive urine.

The two phase diagrams constructed with surfactant (Cremophor EL® or Cremophor ELP®), cosurfactant (ethanol) and oil (Labrafac CC®) were depicted in Figure 1. No significant differences were found between two phase diagrams. The gel (G) and microemulsion area (M) appeared between oil/(surfactant+co-surfactant) ratio of 0.1 to 0.4.

To predict the behavior of the SMEDDS within the human urethra, we observed the viscosity profile. As shown in Figure 2, the viscosity profiles of two formulations were similar to each other. The viscosity increased gradually until water content reached 35% of total mass and it increased steeply until water content got to 40%, and the viscosity was decreased rapidly over 40% of water.

In the self-emulsification test, two SMEDDS formulations have shown the optically clear microemulsion having particle size under 200 nm which was formed spontaneously within 30 sec by a gentle shaking (Table 1). From the definition of Khoo et al,[14] clear or slightly bluish microemulsion which was formed within 1 min considered to be very successful result for the self-emulsification. The result of time for emulsification, the final appearance and particle size have revealed that the present two SMEDDS had good self-emulsification property.

From the preparation of phase diagram, viscosity change profiles and self-emulsification test, it was anticipated that the current two SMEDDS formulations may easily be input into urethra due to its low viscosity as itself, however when this system meets small amount of water, it would become highly viscous system. These results suggest that the present two formulations would be applicable as a PGE_1 intraurethral formulation.

Before we enter into the *in vivo* animal or human study, stability test was performed to decide optimal formulation for intraurethral use. To confirm the stability of PGE_1 in the SMEDDS formulations, we accomplished long-term stability test at 4, 20, 30 and 40°C for about three hundred days. As shown in Figure 3, PGE_1 degraded exponentially. Also, more PGE_1 was degraded and more degradation products were generated from the Cremophor EL® formulation compared to Cremophor ELP® formulation. Newly emerging peaks followed by the degradation of PGE_1 were considered as PGA_1 and the peak area of PGA_1 peak increased with the degradation of PGE_1 peak. We also observed that the PGB_1 peak appeared after PGA_1 peak and this was well proved by many authors.[15,16] From the stability test, the extrapolated stability of PGE_1 within Cremophor ELP® formulation at the shelf temperature of 4°C was estimated over 1 year.

We assumed that the advanced PGE_1 stability of Cremophor ELP® formulation was owing to the difference in the composition of Cremophor grades. Cremophor EL® and Cremophor ELP® is a non ionic surfactant made by castor oil and ethylene oxide in a molar ratio of 1:35. However, Cremophor ELP® is followed by a purification process. Therefore, Cremophor ELP® has much lower water content than Cremophor EL®. The water content of Cremophor ELP® is below 0.5%[17] and that of Cremophor EL® reached 3%.[18] It was well known that PGE_1 is very unstable under aqueous conditions due to the degradation of PGE_1 to prostaglandin A_1 (PGA_1), which is accelerated by acidic and basic environment and PGA_1 is further isomerized to prostaglandin B_1 (PGB_1).[15]

Conclusion

To design a intraurethral PGE_1 formulation, SMEDDS was selected. Pseudoternary phase diagrams composed of Cremophor EL® or Cremophor ELP® as a surfactant, ethanol and Labrafac CC® as a co-surfactant and oil respectively, were constructed. From the phase diagram study, observation of viscosity profile and self-emulsification test, the current two SMEDDS formulations had shown that they might be input into urethra with easy and this system would be eliminated easily when it contact with water (i.e. urine). From the stability test, we could decide the final formulation for the *in vivo* animal or human study such as irritation test and pharmacological study.

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