The effect of nanoemulsions on the transdermal delivery of citalopram
Chi-Te Huang, Yu-Hsuan Lin, Li-Tse Fu, Pao-Chu Wu*
School of Pharmacy, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung City 80708, Taiwan.
E-mail:pachwu@kmu.edu.tw

Abstract
The aim of this study was to evaluate the potential of nanoemulsions as a drug carrier vehicle for the transdermal delivery of citalopram. The computerized statistical technique of response surface methodology (RSM) with mixture design was used to investigate the influence of the formulation compositions including mixed surfactants Brij 30/Brij 35 , isopropyl alcohol and distilled water on the drug-loaded nanoemulsions properties including permeation rate (flux) and lag time. The 10% citalopram-loaded nanoemulsion showed a flux of 513.8 μg/cm²/h, indicating that the formulation could supply effective therapeutic concentration in a practical administration area.

1. Introduction
Citalopram is a selective serotonin reuptake inhibitor. It was approved to treat the symptoms of major depression by the Food and Drug Administration of USA in 1998 (Suresh et al., 2010). After oral administration, common side effects in GI are nausea (21%) and xerostomia (20%). The nausea is caused when the 5HT3 receptors are activated by the serotonin, when the receptor is exhibited in the digestive tract. The 5HT3 receptors also stimulate vomiting. The administration dose must be adjusted when this side effect occurs. Hence, the transdermal delivery system of citalopram was developed.

2. Experimental methods
2.1. Construction of phase diagrams
The phase diagrams were made by using the water titration method to obtain the level range of each component for the existence range of nanoemulsions.
2.2. Preparation of nanoemulsions
The constrained mixture design consisting of three independent variables was used in this study to prepare the systemic model citalopram-loaded nanoemulsions. The amount of mixed surfactant, IPA, and double-distilled water were used as independent variables. The range of independent variables was selected according to the phase diagrams. The compositions of citalopram-loaded nanoemulsions are listed in Table 1.

2.3. Microemulsion characterization
The viscosity and droplet sizes of citalopram-loaded nanoemulsions were determined by a cone-plate of viscometer (Brookfield, Model LVDV-II, USA) and a photo correlation spectroscopy equipped with laser light scattering (Zetasizer 3000HSA, Malvern, UK), respectively.

2.4. Skin permeation study
A modified Franz glass diffusion cell and abdominal skin of excised SD rat were used in in-vitro permeation study.

3. Results and discussion
3.1. Construction of phase diagrams
As shown in Fig 1, larger nanoemulsion regions were obtained when the nanoemulsion was prepared with IPA.

3.2. Physicochemical characteristics of nanoemulsion
The size of droplets, polydispersity index and viscosity are listed in Table 1. The droplet size ranged from 14.5 to 31.4 nm. The viscosity of citalopram-loaded nanoemulsions at 37°C ranged from 7.53 to 13.07 x 10³ cps.

3.3. In Vitro skin permeation study
The permeation profiles of model nanoemulsions and aqueous control are plotted in Fig. 2. A zero-order release kinetic was suitable to fit the curves of all formulations (R²> 0.9920). The flux (μg/cm²/h) was calculated. The first time of detected drug was set as the lag time. The permeation parameters of all formulations are summarized in Table 1. The flux of nanoemulsions ranged from 153.77 to 245.62 μg/cm²/h, while the LT ranged from 0.83 to 3.0 h. The wide deviations demonstrated
that the permeability of citalopram from nanoemulsions was significantly influenced by the composition proportion of mixed surfactant/cosurfactant/aqueous phase.

The response surface plot was constructed to illustrate the relationship of independent and dependent variables used (Fig. 3). It was found that the higher flux was observed in nanoemulsion with specific ratios of surfactant/cosurfactant/aqueous phase (e.g., X1 at low level, and X2 as well as X3 at medium level).

The RSM predicted an appropriate formulation with flux and LT values of 180.23 µg/cm²/h and 1.60 h respectively, when X1, X2, and X3 values were 0.24, 0.23 and 0.43 respectively. A new drug-loaded nanoemulsion (F15) was prepared according to these levels of formulation factors to obtain flux and LT values (F15) was prepared according to these levels of formulation factors to obtain flux and LT values of 179.63±20.44 µg/cm²/h and 1.67±0.58 h respectively. Observed and predicted values showed no significant difference, indicating that the RSM is a potential tool and can be utilized to design citalopram-loaded nanoemulsions.

As shown in Fig. 4, the flux increased with the increase of drug concentration.

4. Conclusion

The permeation rate of citalopram from nanoemulsions was conspicuously increased and the lag times were also shortened. RSM is a potential tool to investigate the influence of the independent variables on the dependent variables (responses) and obtain an appropriate formulation.

References


Table 1

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Table 1 The composition, physicochemical properties and permeability parameters of model citalopram-loaded nanoemulsions.

Fig. 1. The pseudo-ternary phase of nanoemulsion composed of IPM, mixed surfactant of Brij 30/Brij 35 and aqueous solution containing 40% different cosurfactants. IPA (A), PEG 400 (B), and PG (C).

Fig. 2. In vitro penetration-time profile of citalopram model formulations and aqueous control of 40% IPA containing 3% citalopram through rat skin. (n=3)

Fig. 3. Three dimensional of response surface plots illustrating the effect of surfactant (X1), IPA (X2) and distilled water (X3) on the flux and lag time (LT) of citalopram from nanoemulsions.

Fig. 4. The cumulative amount at 12 h of various concentration citalopram-loaded nanoemulsions. (n=3)