CHAPTER VI

CONCLUSIONS

This work attempted to apply acrylate polymer, i.e. ERS or ERL, as release controlling agents in implantable controlled release drug delivery system in order to expand their utilization in pharmaceutical system. The E_2 and NET Geomatrix® implants using ERS as the release controlling agent released 80 % of E_2 and NET within 7 days and 14 days, respectively. The solubility of NET was two times lower than that of E_2, the extended release of NET was two times longer than that of E_2. This supported the finding that the extended drug release period of matrix system containing poorly water-soluble drug depended on the solubility of the incorporated drug. The lower solubility of the incorporated drug, the longer extended release was obtained. Furthermore, the 60 % of E_2 or NET released from Geomatrix® implants followed the zero-order model. Thus, the influences of weight percents of E_2 or NET in ERS used as the active cores and type of polymer used in the core or in the barrier of Geomatrix® system on E_2 or NET release profiles were investigated in order to examine whether drug release profile was modulated by Geomatrix® design.

The increase of weight percent of E_2 or NET used in the cores of Geomatrix® implants could not elevate E_2 or NET release rates. The porosity upon drug depletion and the tortuosity did not play as important factors in modulation of E_2 or NET released from Geomatrix® implants.

The difference of polymer used as the barrier layers applied to the same cores did not change NET release profiles but the difference of polymer used in the cores of Geomatrix® implants with the same barriers changed NET release profiles obviously. The barriers had less influence on the NET release modulation, while the cores containing drugs were predominant in controlling the NET release. Furthermore, NET release profiles obtained from implants having barriers on both sides of the cores and implants without barriers were similar. This supported the finding that the barrier part of Geomatrix® implant did not affect the NET release while the core containing NET played the leading role in controlling drug release. Thus, the property of poorly water-soluble drug in the core might be stronger modulation in controlling drug release than the Geomatrix® design did.

The NET release rates (k_0) obtained from fitting with the zero-order model of Geomatrix® implants using ERS or ERL as barrier layers and ordinary matrix implant without barrier were not significantly different (P>0.05). Thus, the Geomatrix® system did not perform as a major factor in controlling the NET release.

The apparently constant release rates of E_2 and NET were not resulted from Geomatrix® design. In matrix system containing poorly water-soluble drug, dissolved drug and non-dissolved drug coexist in the matrix pores during release study, non-dissolved drug is not available for diffusion and remains within the system. The non-dissolved drug acts as a drug reservoir for keeping constant drug concentration

gradient. The zero-order release kinetics can be achieved under this condition. This non-dissolved drug effect overcompensates the porosity, the tortuosity and the geometry effects. Therefore, Geomatrix® implant containing poorly water-soluble drug exhibited zero-order release kinetic resulted from the inherent solubility of drug providing the drug dissolution controlled release system.

Although the duration of NET released from implant using ERS as the release controlling agent is long enough to be used for an indication of HRT, the duration of E_2 released from implant is too short to be used for this indication. The E_2 released from this kind of implant should be modified in order to achieve the desired rate and duration, which is suitable for HRT. Due to the E_2 release controlled by the drug dissolution, the inherent solubility of E_2 under the given condition is an important factor influencing release profile and release kinetics of E_2 implant using ERS as a release controlling agent. Solid state of E_2 in solid dispersion directly affects the solubility of E_2 and consequently changes E_2 release kinetics. In solid dispersions containing E_2 at 1 % and 2 % w/w, E_2 existed in the amorphous form. The solubility of E_2 did not play as the limiting step in controlling E_2 released, so that E_2 released from implants produced from these solid dispersions deviated from the zero-order model. At 10, 20, and 30 % w/w E_2 in ERS solid dispersions, E_2 existed in the crystalline state, the dissolution rate of E_2 acted as the limiting resistance to drug released from implants produced from these solid dispersions. E_2 released from these implants could be described by the zero-order model.

E_2 can exist either the amorphous state or crystalline state when blended with ERS in solid dispersion. These kinds of binary mixtures are nearly identical with the blend of amorphous polymers or the blend of a crystalline polymer with an amorphous polymer. The criteria used to indicate the miscibility of polymer blends, i.e. melting point depression and a single T_g point, can be applied for indicating the miscibility of E_2 and ERS in solid dispersion, so that thermal analysis can be employed as a technique for determining the miscibility of E_2 and ERS.

The T_g behavior of E_2 in ERS solid dispersion can adequately be predicted by Gordon-Taylor and Kwei equations. Kwei equation fits the experimental data better than Gordon-Taylor equation, so that at least two factors affect T_g of E_2 in ERS solid dispersion, the weight fractions of the amorphous components and the interaction between the components in solid dispersion. This corresponds to the inter-associated hydrogen bonding between the hydroxyl group of E_2 and the ester C=O group of ERS.

The melting point depression of E_2 in ERS solid dispersion can be predicted by Nishi-Wang equation based on the Flory-Huggins theory. The negative B value obtained from fitting Nishi-Wang equation to experimental data supports the occurrence of the interaction between E_2 and ERS in molten state.

ERS is miscible with E_2, so that the uniformity of E_2 dispersed or dissolved in the ERS matrix can be achieved and a consistent drug release can subsequently be obtained. A consistent drug release is not only the primary goal in development of E_2 implant, but the rate of drug release is also achieved at the desired level. E_2 released from implant using ERS as a release controlling agent is controlled by a combined

dissolution- and diffusion-controlled release mechanism. In order to achieve the desired rate of E_2 release, dissolution rate of E_2 crystal in the matrix pores should be modulated. Further study should be done to investigate factors affecting E_2 crystal growth in solid dispersion, which is used to produce E_2 implant, on E_2 release profile. The size of E_2 crystal dispersed in solid dispersion should affect E_2 dissolution and subsequently alters the rate of E_2 released from implant.