CHAPTER III

RELEASE OF 17β-ESTRADIOL AND NORETHINDRONE FROM GEOMATRIX® IMPLANTS USING ACRYLATE POLYMERS AS RELEASE CONTROLLING AGENTS

3.1 Introduction

Hormone replacement therapy (HRT) has widely been recognized in controlling early menopausal symptoms. Furthermore, long-term therapy can prevent cardiovascular disease and osteoporosis (Andersson et al., 2000; Paoletti et al., 2001). 17β-estradiol (E_2) has been advocated as the estrogen replacement of choice because it is the most potent naturally occurring estrogen and it is the major estrogen secreted during the reproductive years. Continuous administration of E_2 combined with progestin results in less endometrial hyperplasia than that of E_2 only (Anderson et al., 2002). Norethindrone (NET) is a potent progestin in low dose that prevents estrogen-induced endometrial hyperplasia and can be delivered in combination with E_2 (Pentikis et al.; 1998; Stadberg et al., 1999). E_2 administration is normally continuous for one menstrual cycle and NET administration is continuous for half a cycle (Prough et al., 1987). Non-oral E_2 administration avoids hepatic first-pass effect allowing smaller dose to be used and prevents undesirable changes from liver stimulation (Pentikis et al., 1998; Munoz, 1999; Rohr, Nauert, and Stehel, 1999; Andersson et al., 2000; Paoletti et al., 2001; Anderson et al., 2002). Although transdermal administration of E_2 offers a number of advantages over traditional oral route, transdermal patch needs to adhere to patient's skin throughout the application period in order to deliver the drug efficiently and effectively. If patch becomes detached then the patient will not receive optimum treatment (Munoz, 1999). Subcutaneous implant delivery system may be favorable choice for HRT. This system offers similar advantages over oral route as transdermal system but it can overcome the limitation of transdermal system. Moreover, matrix implant with 2 mm in diameter can be easily inserted into the implantation site by implantable applicator.

Matrix implant is monolithic system in which the release rate of drug is inversely proportional to the square root of time. A disadvantage frequently cited is the inability to achieve zero-order release kinetics (Higuchi, 1961; Higuchi, 1963; Higuchi and Hiestand, 1963; Higuchi et al., 1963; Chien, 1982; González-Rodriguez et al., 1997; Costa and Lobo, 2001; Siepmann and Peppas, 2001). To maintain drug level in the therapeutic range, thereby avoiding the ineffectiveness or unwanted toxic effects, a zero-order release has always been one of the primary goals of controlled-release systems, especially for drugs with a narrow therapeutic index. Over the last two decades, considerable efforts have been expended in development of new designs of matrix system in order to achieve zero-order or near zero-order release (Hsieh et al., 1983; Colombo et al., 1990; Conte et al., 1993; Fassihi and Ritschel, 1993; Conte and Maggi, 1996; Peppas and Colombo, 1997; Qiu, Chidambaram, and Flood, 1998; Chidambaram, Porter, and Flood, 1998; Conte and Maggi, 2000; Maggi, Bruni, and Conte, 2000; Abdul and Poddar, 2004; Liu and Hsu, 2005). The Geomatrix®

technology, a multi-layered matrix system, is one of the drug delivery devices giving constant release rate. It consists of an active core containing drug substance and one or two polymeric barriers applied on one or both faces of the core. The barriers delay the interaction of drug with release medium by limiting the surface available for drug release and controlling release medium penetration rate at the same time. Furthermore, the barriers provide a further diffusion path length to drug diffusion. Thus, burst effect can be reduced and the release can be maintained at a relatively constant level (Abdul and Poddar, 2004). For poorly water-soluble drug, the surface area available for the interaction of drug with release medium is extremely critical parameter for the overall release process. In this condition, an excessive reduction of the release rate may be obtained with poorly water-soluble drug (Conte and Maggi, 1996). Therefore, Geomatrix® technology may be useful in extended release dosage form requiring very slow release rate of drug for HRT.

Ammonioethyl methacrylate ester copolymers have widely been used as release controlling agents in orally controlled release system. Although the excellent biocompatibility of poly(meth)acrylates was affirmed (Lehmann, 1997), the usage in implantable controlled release system has not been found extensively. Poly(ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride) 1:2:0.1 and 1:2:0.2 or Eudragit® RS (ERS) and Eudragit® RL (ERL), respectively have been used for many years as pharmaceutical coatings or a matrix forming agent. Their permeability depends upon the content of quaternary ammonium groups. For this reason, ERL is more permeable than ERS. Due to their good binding properties, Geomatrix® implant using ERS or ERL as release controlling agents can be produced by direct compression.

The objectives of this study were

(i) to apply ERS or ERL as release controlling agents in implantable controlled release system. The attempt of this work was to expand the usage of this group of polymer in order to increase their utilization.

(ii) to apply Geomatrix® technology in the development of subcutaneous implant. This work tried to fabricate matrix implant providing drug release with a constant release rate.

(iii) to investigate the effect of percent by weight of poorly water-soluble drug in polymer used in the active core of Geomatrix® implant on drug release profile.

(iv) and finally to investigate the effect of Geomatrix® components on the release characteristic of poorly water-soluble drugs.

The last two objectives were purposed to examine whether drug release profile was modulated by Geomatrix® design. In the case of Geomatrix® design regulating drug release profiles, the change of Geomatrix® components either in the cores or in the barriers should alter drug release profiles.

3.2 Materials and Methods

3.2.1 Materials

17β-estradiol (E_2) and Benzalkonium chloride (BAC) were purchased from Fluka Chemica (Germany). Norethindrone (NET) was purchased from Sigma (Germany). Eudragit® RS PO and Eudragit® RL PO (Röhm Pharma GmbH, Germany) were kindly donated by JJ Degussa (Thailand). Absolute ethanol and dichloromethane were of a reagent grade purchased from Merck (Germany). Acetonitril was of an HPLC grade purchased from Fisher Scientific (UK). Sodium hydroxide and Potassium dihydrogen phosphate were obtained from Mallinckrodt (Mexico) and Asia Pacific Specialty Chemicals Limited (Australia), respectively.

3.2.2 Preparation of E_2 and NET in ERS Solid Dispersions

Solid dispersions of E_2 in ERS at concentration range of 10-30 % w/w and solid dispersions of NET in ERS at concentration range of 30-50 % w/w were prepared by solvent evaporation. Specific weight ratios of ERS and E_2 or ERS and NET were dissolved in minimum volume of absolute ethanol to get clear solution and then poured into Teflon plate (15.5 cm X 15.5 cm). The absolute ethanol was evaporated at room temperature. Dried samples were kept in a desiccator over silica beads for further experiment.

3.2.3 Determination of E_2 and NET Contents in Solid Dispersions

Accurate weight of E_2 in ERS solid dispersion (n=3) and NET in ERS solid dispersion (n=3) were dissolved in absolute ethanol. E_2 and NET content were determined by UV-spectroscopy (Jasco V-530, Japan) at 280 nm and 240 nm for E_2 and NET, respectively. The linear regression equation obtained from the relationship between absorbance and concentration of each drug in the standard solution with 0.1 g % ERS in absolute ethanol as the solvent was used to calculate drug content in solid dispersion. Percent of drug content in solid dispersion was calculated using the following equation:

$$\%\ drug\ content = \frac{amount\ of\ drug\ content\ (mg)}{weight\ of\ solid\ dispersion\ (mg)} \times 100 \qquad 3.1$$

3.2.4 Preparation of Implants

Geomatrix® implant and ordinary matrix implant were produced by direct compression and then treated with solvent vapor. In preparation of Geomatrix® implant, 5 mg of drug free polymer was poured into a die, 2 mm in diameter, as the first layer, then solid dispersion containing drug was poured down as the second layer, followed by 5 mg of drug free polymer as the third layer (see Figure 3.1 for punch and die assembly). These compositions were compressed with a punch at a constant pressure for 15 seconds using hydraulic press. For ordinary matrix implant, only solid

dispersion containing drug was compressed as a single layer without barrier component using the same condition. Compressed implants were placed in an air-tight glass chamber saturated with dichloromethane vapor for 10 min and then left in laboratory room until a constant weight was obtained. Eleven formulations of implants were prepared as presented in Table 3.1.

3.2.5 Drug Release Studies

Release studies of E_2 Geomatrix® implants, NET Geomatrix® implants and NET matrix implants were conducted, in triplicate, in phosphate buffer (PB) pH 7.4 with 3.5 % w/v BAC under sink conditions. The E_2 Geomatrix® implants were individually placed in a screw-capped test tube containing 3.0 ml of release medium. NET Geomatrix® implants and NET ordinary matrix implants were individually placed in screw-capped test tubes containing 30.0 ml of the medium. The sample test tubes were constantly shaken at 120 rpm in a shaking incubator (Labtech International, UK)) at 37 °C. Release medium was taken out periodically and replaced by fresh release medium, then the concentrations of E_2 and NET were assayed by HPLC.

3.2.6 HPLC Assay Method

The development of HPLC analysis was based on the Ye and Chien (1996) study. HPLC analysis was performed using a Shimadzu Class VP (Japan). A Synergi Fusion-RP ODS column (4 μm; 150 x 4.6 mm in diameter, Phenomenex®) was used as an analytical column. Samples of 50 μl were injected and a water/acetonitril combination of 55:45 (v:v) was used as the mobile phase at a flow rate of 1.0 ml/min. The detector was used in dual wavelength measurement mode and set at 240 nm to analyze NET and 280 nm to analyze E_2. The chromatographic peaks of E_2 and NET exhibited retention times of 7.5 min and 8.4 min, respectively.

3.2.7 Determination of Residual Contents of E_2 and NET in Implants after Release Study

After in vitro release study, each implant was dissolved in a mixture of absolute ethanol and dichloromethane (1:1; v:v) and assayed for E_2 and NET spectrophotometrically at 280 nm and 240 nm, respectively. Residual drug content in each implant was calculated from the linear regression equation obtained from the relationship between absorbance and concentration of each drug in the standard solution. 0.1 g % ERS in a mixture of absolute ethanol and dichloromethane (1:1; v:v), which was nearly similar to the medium in sample solution, was used for preparing standard solution. Total drug content in each implant was calculated by addition of total drug release and residual drug content in implant after release study.

3.2.8 Determination of Drug Release Kinetics

Approximately 60 % of drug released from each implant was fitted with three different release models: the zero-order, the first-order, and the Higuchi model, by

linear regression analysis. The coefficient of determination (R^2) obtained from each fit was used as a criterion to choose the best model for drug release phenomena.

3.2.9 Statistical Analysis

Similarity factor (f_2) test was employed to compare drug release profiles of different implant formulation. f_2 test adopted by the Center for Drug Evaluation and Research (FDA) and by Human Medicines Evaluation Unit of the European Agency for the Evaluation of Medicine Products (EMEA) can be defined as the following equation (Costa and Lobo, 2001).

$$f_2 = 50 * \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{j=1}^{n}\left|R_j - T_j\right|^2\right]^{-0.5} * 100\right\} \qquad 3.2$$

where n is the sampling number, R_j and T_j are the percent dissolved of two comparative formulations at each time point j.

Release rate constants were determined by fitting the first 60 % released from different types of implant formulation with the release models and were subjected to ANOVA tests. Scheffe posthoc tests with statistical significance set at $P \leq 0.05$ were used to examine the differences between pairs of different types of barriers.

Table 3.1 Formulations of Geomatrix® implants and matrix implant with various weight percents of drug in polymer used in the cores and various types of polymers used in the components

Formulation code	Drug	Drug content (mg)	%drug in polymer in the core	Polymer in the core	Polymer in the barrier
10-E_2	E_2	0.45	10	ERS	ERS
20-E_2	E_2	0.45	20	ERS	ERS
30-E_2	E_2	0.45	30	ERS	ERS
30-NET	NET	2.50	30	ERS	ERS
40-NET	NET	2.50	40	ERS	ERS
50-NET	NET	2.50	50	ERS	ERS
ERS-B-ERL-C	NET	2.50	30	ERL	ERS
ERL-B-ERL-C	NET	2.50	30	ERL	ERL
ERL-B-ERS-C	NET	2.50	30	ERS	ERL
ERS-B-ERS-C	NET	2.50	30	ERS	ERS
ERS-C	NET	2.50	30	ERS	-

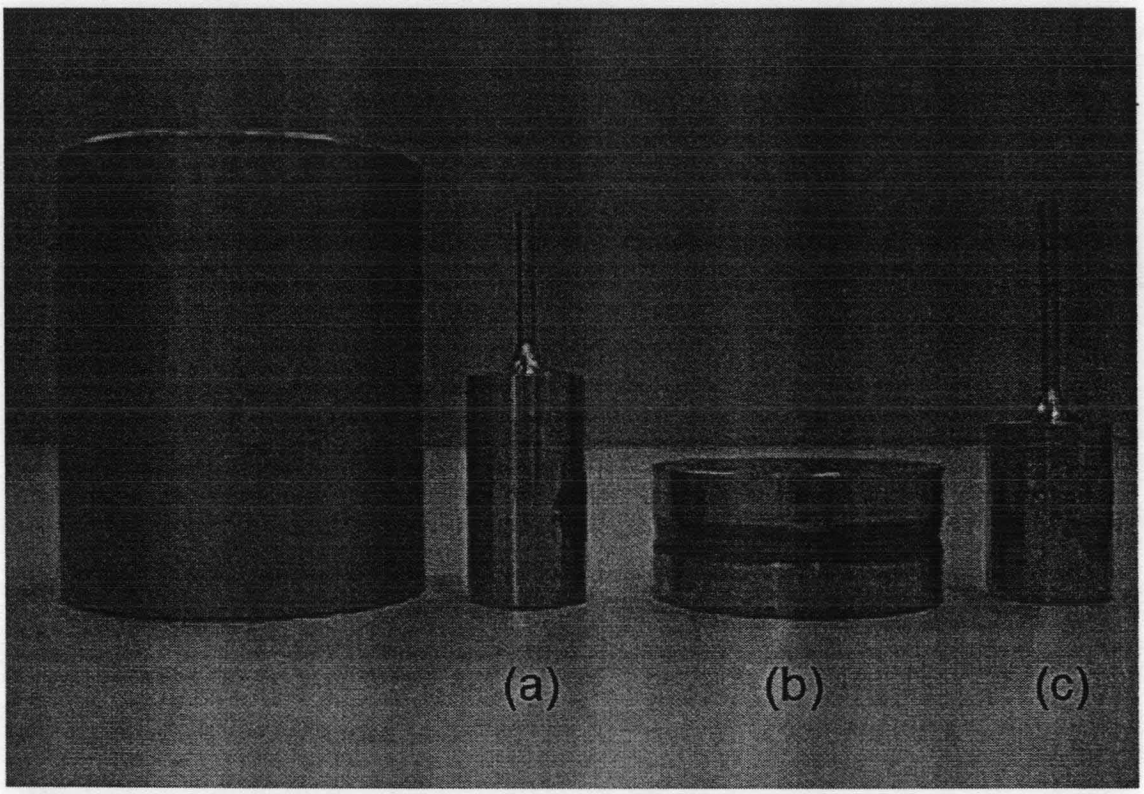

Figure 3.1 Punch and die assembly used in production of implant with 2 mm in diameter: (a) lower punch; (b) die; (c) upper punch

3.3 Results and Discussion

3.3.1 Implant Morphology

E_2 Geomatrix® implant and NET Geomatrix® implant produced by direct compression and then treated with dichloromethane vapor are shown in Figure 3.2 (a) and 3.2 (c), respectively. The barriers on both faces of the core were more translucent than the core containing E_2 or NET in the matrix pores. This suggested that solvent vapor welded the polymer particles together resulting in the increase of the strength of Geomatrix® implant obtained from this study. It was found that Geomatrix® implant produced by this method was difficult to disintegrate during the subsequent release experiments. The inability of using high compression force in producing Geomatrix® implant in order to achieve favorable hardness through specially designed punch and die assembly, only 2 mm in diameter, was no longer a problem. Although the opaque core was observed, the cross section view of matrix implant revealed the welding of the polymer particles throughout the inside of implant. No crumby particle was observed as shown in Figure 3.2 (e). Furthermore, the core of Geomatrix® implant after in vitro release study was as translucent as the barriers shown in Figure 3.2 (b) and 3.2 (d). This indicated that the exposure time to dichloromethane vapor was adequate for the penetration of the vapor throughout the inside of Geomatrix® implant.

3.3.2 Effect of Percent Drug in Polymer Used in the Core on Drug Release Profile

3.3.2.1 Effect of Percent E_2 in ERS Used in the Core on E_2 Release Profile

The cumulative releases of E_2 from Geomatrix® implants containing 10, 20, and 30 % w/w E_2 in ERS used in the cores are shown in Figure 3.3. E_2 release profiles exhibited 80 % of E_2 released within 7 days in all cases. This result suggested that E_2 release was extended for a week with Geomatrix® implant using ERS as a release controlling agent. E_2 daily release rates of Geomatrix® implants containing 10, 20, and 30 % w/w E_2 in ERS used in the cores are shown in Figure 3.4. The increase in weight percent of E_2 in the core did not significantly increase E_2 daily release rate. In order to compare E_2 release profiles obtained from Geomatrix® implants containing different weight percents of E_2 used in the cores, the similarity factor (f_2) was used in the assessment. FDA and EMEA have suggested that two dissolution profiles are declared similar if f_2 is between 50 and 100. The higher f_2 value, the more similar dissolution profiles are obtained (Costa and Lobo, 2001). f_2 values as a function of weight percent of E_2 used in the core of Geomatrix® implant obtained from the in vitro release study are presented in Table 3.2. In all cases, f_2 values were higher than 50. Therefore, E_2 release profiles of Geomatrix® implants containing E_2 in the range of 10-30 % w/w in ERS used as the cores were not different. In case of the increase in weight percent of drug in the matrix, the porosity upon drug depletion is increased and the tortuosity is reduced, so that rate of drug release should increase.

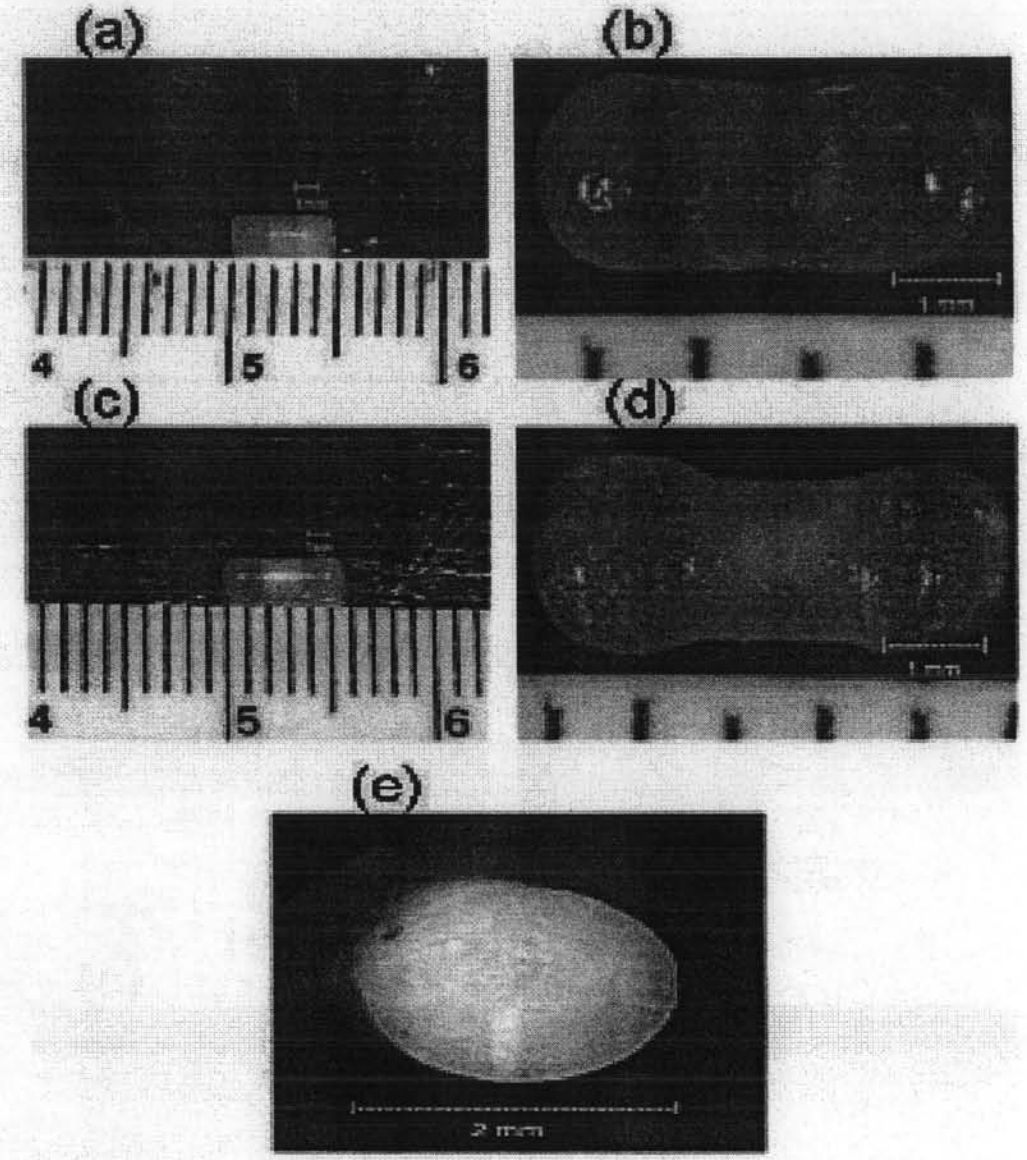

Figure 3.2 Photo-images of Geomatrix® implants using ERS as a release controlling agent: (a) E_2 Geomatrix® implant before in vitro release study; (b) E_2 Geomatrix® implant after in vitro release study; (c) NET Geomatrix® implant before in vitro release study; (d) NET Geomatrix® implant after in vitro release study; (e) cross-sectional view of NET matrix implant

However, rates of E_2 release did not increase when weight percents of E_2 in ERS used as the cores of Geomatrix implants increased. This suggests that the increase in porosity and the decrease in tortuosity in the core of Geomatrix® implant cannot elevate E_2 release rate. The porosity and the tortuosity might not be the important factors in controlling E_2 release from this system.

3.3.2.2 Effect of Percent NET in ERS Used in the Core on NET Release Profile

The cumulative releases of NET from Geomatrix® implants containing 30, 40, and 50 % w/w NET in ERS used in the cores are shown in Figure 3.5. NET release profiles showed 80 % of NET released within 14 days in all cases. This result confirmed that Geomatrix® implant using ERS as a release controlling agent prolonged drug release over a week. From the preliminary study, E_2 solubility and NET solubility in 3.5 % w/v BAC in PB 7.4 at 37°C, 120 rpm were 891.29 µg/ml and 460.16 µg/ml, respectively. The solubility of NET in the release medium is around two times lower than that of E_2 corresponding to two times longer extended release of NET than that of E_2. This indicates that intrinsic solubility of poorly water-soluble drug affects the duration of drug release from this system. NET daily release rates obtained from Geomatrix® implants at different weight percents of NET used in the cores are displayed in Figure 3.6. The increase in weight percent of NET used in the core of Geomatrix® implant did not increase daily release rate of NET in the same way as that of E_2.

Comparison of NET release profiles obtained from Geomatrix® implants containing various weight percents of NET in the cores showed that f_2 values were higher than 50 in all cases as shown in Table 3.3. These results indicated that NET release profiles obtained from Geomatrix® implants containing 30, 40, and 50 % w/w NET in ERS used in the cores were similar. Furthermore, f_2 values obtained from NET release profile comparison were higher than that of E_2 release profile comparison. This indicated more similarity among NET release profiles than E_2 release profiles. Weight percent of NET level in the core of Geomatrix® implant was higher than that of E_2. Higher porosity upon drug depletion and lower tortuosity of matrix core of NET Geomatrix® implant were obtained. However, NET Geomatrix® implant extended drug release longer than E_2 Geomatrix® implant. This indicated that the porosity and the tortuosity did not play the leading role in controlling E_2 or NET release. The solubility of drug in the release medium predominated in controlling the E_2 or NET release.

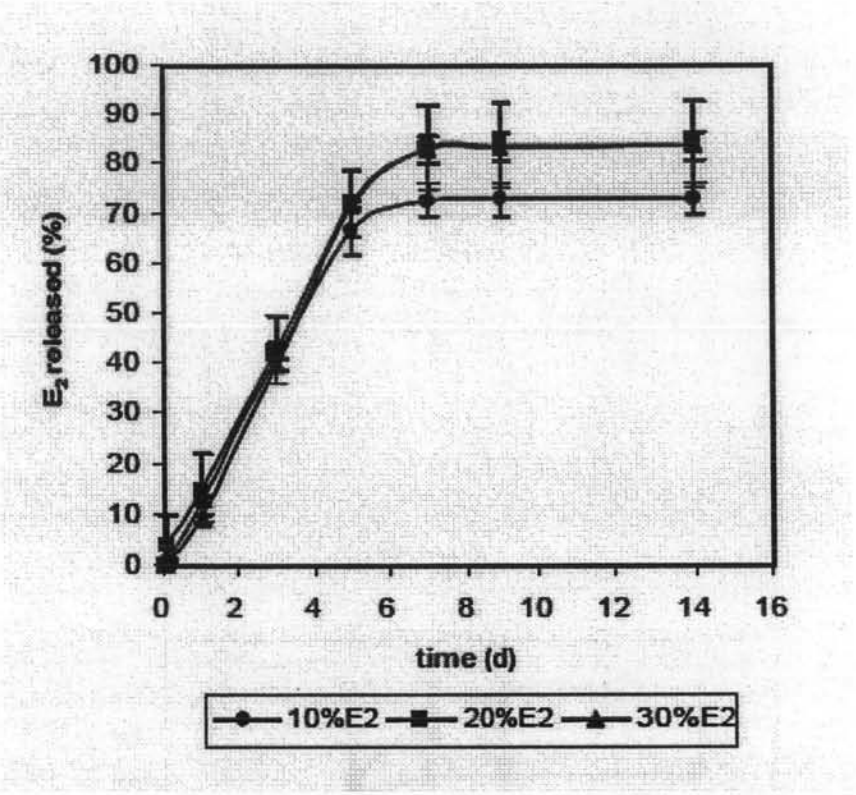

Figure 3.3 E_2 release profiles obtained from Geomatrix® implants containing various weight percents of E_2 in ERS used in the cores

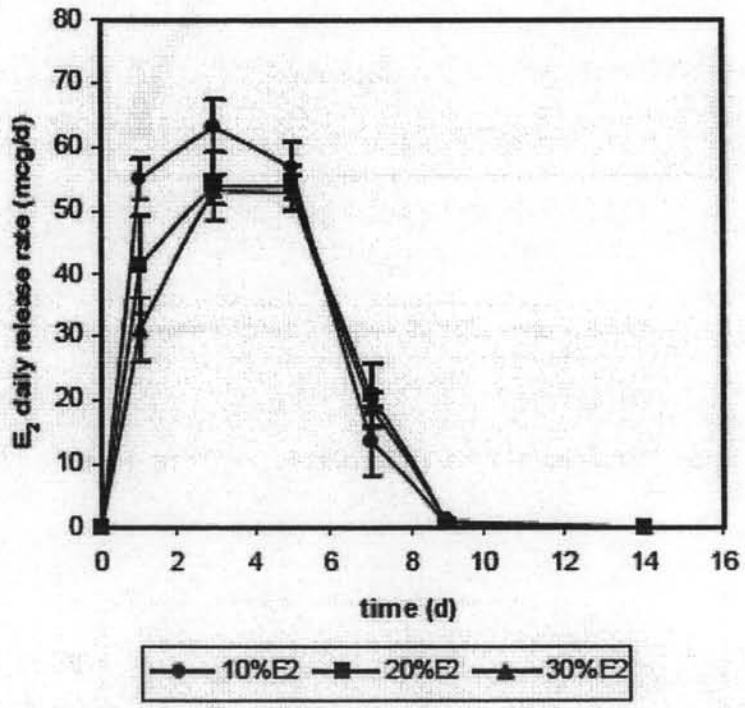

Figure 3.4 E_2 daily release rate of Geomatrix® implants containing various weight percents of E_2 in ERS used in the cores

Table 3.2 f_2 values as a function of weight percent of E_2 in ERS used in the core of Geomatrix® implant obtained from in vitro release study

Implant	weight percent of E_2 in ERS comparison		
	f_2 (10 vs. 20)	f_2 (10 vs. 30)	f_2 (20 vs. 30)
E_2 Geomatrix®	57.18	58.16	77.77

Table 3.3 f_2 values as a function of weight percent of NET in ERS used in the core of Geomatrix® implant obtained from in vitro release study

Implant	weight percent of NET in ERS comparison		
	f_2 (30 vs. 40)	f_2 (30 vs. 50)	f_2 (40 vs. 50)
NET Geomatrix®	73.23	72.55	96.69

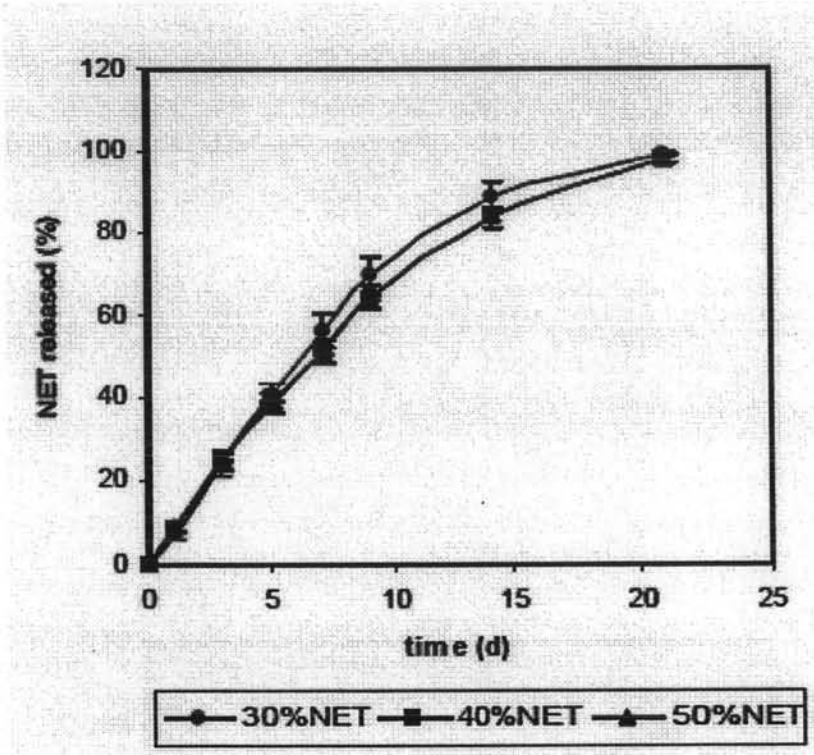

Figure 3.5 NET release profiles obtained from Geomatrix® implants containing various weight percents of NET in ERS used in the cores

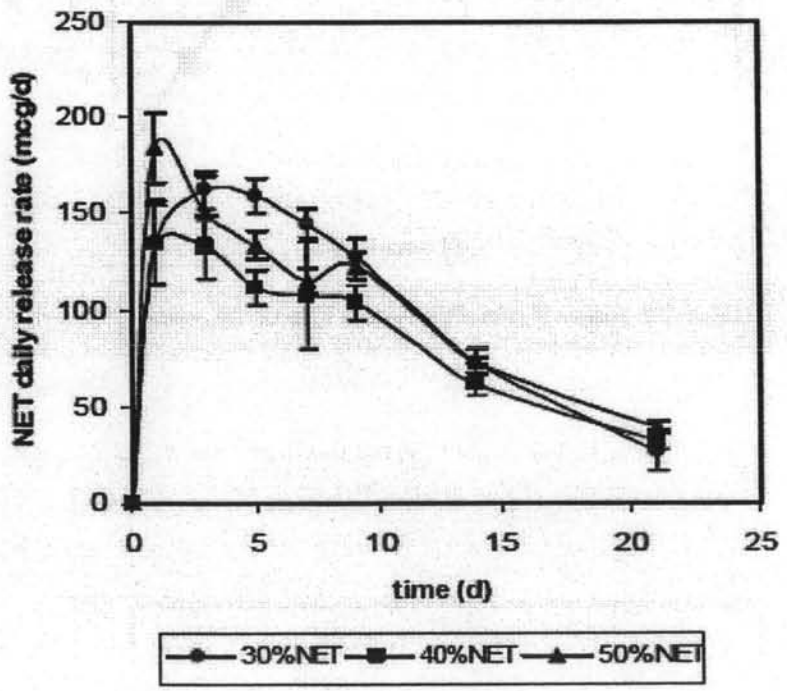

Figure 3.6 NET daily release rate of Geomatrix® implants containing various weight percents of NET in ERS used in the cores

3.3.3 Effect of Geomatrix® Implant Components on NET Release Profile

The cumulative releases of NET from Geomatrix® implants composed of different core and barrier components are shown in Figure 3.7. Geomatrix® implants with 30 % w/w NET which composed of ERL in the cores and ERS or ERL in the barriers released 80 % NET within 2 days whereas matrix implant using ERS as the release controlling agent and Geomatrix® implants composed of ERS in the cores and ERS or ERL in the barriers released 80 % NET in about 14 days. The difference of polymer used in the core significantly changed NET release profile but the difference of polymer used in the barriers did not significantly change NET release profile. This indicated that property of the core exerted more influence in controlling NET release than the barrier did. The result obtained from this study disagreed with the result obtained from Maggi et al. (2000) study using diltiazem hydrochloride as a model drug and two different viscosity grades of hydroxypropylmethylcellulose or polyethylene oxides as release controlling agents. Their study revealed that the core composition had less influence on modulation of drug release, while the barriers played the leading role in controlling drug release from this kind of device. The characteristic of drug release obtained from Maggi et al. (2000) study probably occurs in Geomatrix® system containing hydrophilic drug but it may not happen in Geomatrix® system containing poorly water-soluble drug. Therefore, the modulation of E_2 and NET release profiles did not comply with the release characteristic modulated by the Geomatrix® technology.

Furthermore, this study was found that f_2 values obtained from the comparison of NET release profiles of matrix implant using ERS as the release controlling agent and Geomatrix® implants composed of ERS in the cores and ERS or ERL in the barriers were higher than 50 in all cases as shown in Table 4. NET release profiles obtained from implants having barriers on both sides of the cores and implants without barriers were similar. This indicated 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.

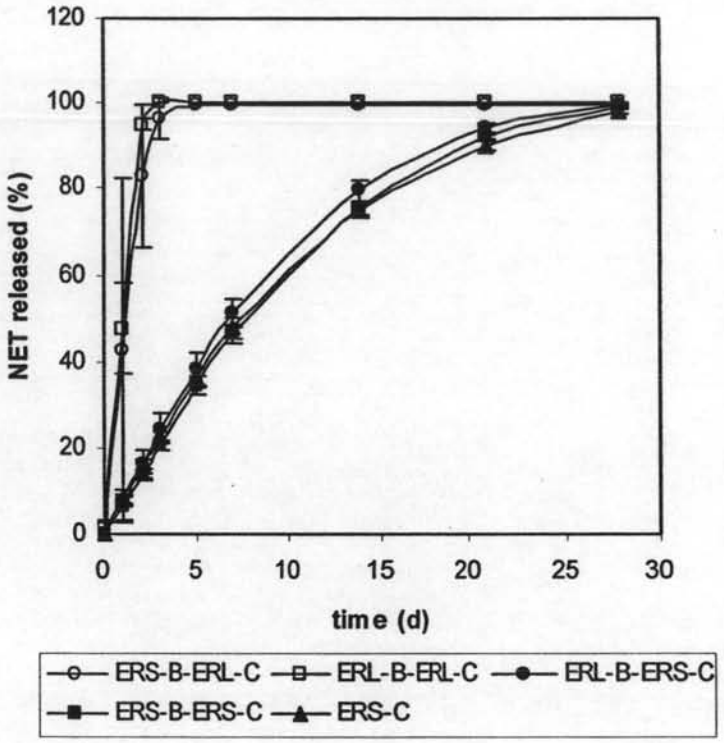

Figure 3.7 NET release profiles obtained from Geomatrix® implants containing various types of polymers used in the components

Table 3.4 f_2 values as a function of barrier type of Geomatrix® implant obtained from in vitro release study

Implant	Type of barrier comparison		
	f_2 (ERS vs. ERL)	f_2 (ERS vs. NB)	f_2 (ERL vs. NB)
NET Geomatrix®	75.36	77.76	86.00

NB, no barrier

3.3.4 Release Models

Release models generally used to describe drug release phenomena are the zero-order model, the first-order model, and the Higuchi model. The zero-order model has been used to describe drug release from pharmaceutical dosage form, which does not disintegrate, so that the area available for drug release does not change and drug release occurs slowly. The pharmaceutical dosage form following this model releases the same amount of drug by unit of time. It is the ideal method of drug release giving a prolonged pharmacological action. The zero-order model can be used to describe poorly soluble drug released from matrix tablet (Ford et al., 1987; El-Arini and Leuenberger, 1995; Varelas, Dixon, and Steiner, 1995; Costa and Lobo, 2001). It has been expressed as the following equation (Costa and Lobo, 2001);

$$Q_t = Q_0 + k_0 t \qquad 3.3$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in release medium, and k_0 is the zero-order release constant.

The first-order model has been originally proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). The pharmaceutical dosage form following this model releases drug in a way that is proportional to the amount of drug remaining in its interior, in such way that the amount of drug released by unit of time diminishes (Costa and Lobo, 2001). The first-order model can be expressed as the following relationship;

$$Q_t = Q_0 * e^{-k_1 t} \qquad 3.4$$

where Q_t is the amount of drug remaining in its interior in time t, Q_0 is the initial amount of drug in its interior, and k_1 is the first order release constant.

The Higuchi model describes drug release as a diffusion process based on the Fick's law, square root time dependent. This relation can be used to describe water soluble drug released from several types of modified release dosage forms (Ford et al., 1987; Chandrasekaran and Paul, 1982; El-Arini and Leuenberger, 1995). The simplified Higuchi model has been expressed as below;

$$Q_t = k_H t^{\frac{1}{2}} \qquad 3.5$$

where Q_t is the amount of drug released in time t, k_H is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories.

Approximately 60 % of experimental data of E_2 or NET released from Geomatrix® implants at different weight percents of drug used in the cores and different polymeric types of Geomatrix® components were fitted with these release models by linear regression analysis. The coefficient of determination (R^2) obtained from each fit is presented in Table 3.5. It is apparent that the zero-order model might

be an appropriate model which could be used to describe the E_2 or NET released from Geomatrix® implants compared with the first-order and the Higuchi models. This result supported the finding that the porosity and the tortuosity did not play the leading role in controlling E_2 or NET released from Geomatrix® implants while it has been suggested that the porosity and the tortuosity are the essential factors in controlling drug release described by the Higuchi model. In addition, it was noted that different design of Geomatrix® component using ERS in the cores and ERL or ERS in barriers and ordinary matrix implant using ERS (ERS-C formulation) as the release controlling agent were likely to follow zero-order release model. Thus, the zero-order model was more appropriate than the Higuchi model for describing NET release in this condition. This suggested that deviation of NET release from the Higuchi model was not a result from Geomatrix® system design. Furthermore, NET release rates (k_0) obtained from fitting with the zero-order model were not significantly different ($P>0.05$) among these implants. This indicated that Geomatrix® design did not decrease NET release rate whereas Conte and Maggi (1996) affirmed that an excessive reduction of the release rate should be obtained because the barrier layer reduced the available surface area for drug release. This result confirmed the finding that the Geomatrix® technology did not perform as a major factor in controlling the NET release. In case of Geomatrix® implants using ERL in the cores and ERL or ERS in the barriers, it was difficult to justify the exact release kinetics because the insufficient release data points at the first 60 % NET released in this experiment.

In matrix system, the factors controlling drug release have been classified into two groups; the matrix parameters such as the porosity, the tortuosity and the inherent properties of drug such as solubility and diffusion coefficient (Hsieh et al., 1983). For poorly water-soluble drug, its solubility predominates and offers as the limiting resistance to drug release (Chandrasekaran and Paul, 1982). This results in the saturated concentration of dissolved drug at the inside of matrix pores when drug loading exceeds the amount of drug soluble under the given condition. Non-dissolved drug is not available for diffusion but it acts as a drug reservoir for keeping constant the absolute amount of drug released within a certain time period. The zero-order release kinetic can be achieved under this condition (Siepmann and Peppas, 2001). Furthermore, Kim (2000b) indicated that geometry was not an important factor for a drug dissolution controlled release system and the increase in the porosity and the reduction in the tortuosity did not influence the release kinetics. Therefore, the zero-order release kinetics of E_2 and NET Geomatrix® implants was a result of the inherent solubility of E_2 and NET providing the drug dissolution controlled release system.

Table 3.5 Release rate and R^2 obtained from fitting approximate 60 % of drug released with the zero-order, the first-order, and the Higuchi models

Formulation code	$Q_t = Q_0 + k_0t$		$Q_t = Q_0 \, x \exp(-k_1t)$		$Q_t = k_Ht^{1/2}$	
	k_0	R^2	k_1	R^2	k_H	R^2
10-E_2	13.367	0.9995	0.2156	0.9835	29.089	0.9368
20-E_2	14.033	0.9980	0.2462	0.9684	30.484	0.9320
30-E_2	14.342	0.9946	0.2427	0.9567	30.629	0.8978
30-NET	7.8742	0.9985	0.1314	0.9828	23.709	0.9262
40-NET	7.1377	0.9975	0.1122	0.9903	21.679	0.9415
50-NET	7.0445	0.9959	0.1111	0.9918	21.509	0.9499
ERL-B-ERS-C	7.4645	0.9967	0.1027	0.9967	19.199	0.9318
ERS-B-ERS-C	6.8830	0.9999	0.0919	0.9912	17.507	0.9143
ERS-C	6.8402	0.9953	0.0916	0.9988	17.766	0.9489

Q_t, the amount of drug released in time t; Q_0, the initial amount of drug released; k_0, the zero-order release rate constant; k_1, the first-order release rate constant; k_H, the Higuchi dissolution rate constant

3.4 Conclusions

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 extended drug release period of subcutaneous implant using ERS as a release controlling agent depended on the solubility of the incorporated drug. The lower solubility of the incorporated drug, the longer extended release was obtained. Geomatrix® technology did not play the leading role in providing zero-order release kinetic of poorly water-soluble drug but the drug dissolution controlled release system dominated. For the drug dissolution controlled release system, the geometry, the porosity upon drug depletion and the tortuosity did not influence the release kinetics. 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. Due to the E_2 release controlled by drug dissolution, modulation of the E_2 release to achieve the desired duration should be done based on solid state of E_2 in polymer matrix. If the release of E_2 is controlled by this mechanism, alteration of the E_2 solid state should change E_2 release characteristic.