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Effect of Hydrophilic-Lipophilic Balance of Drugs on Their Release Behavior from Amphiphilic Matrix

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Abstract: Organic drugs including aspirin, omeprazole, and naproxen with three different levels of octanol/water partition coefficient were examined for their release behavior from the amphiphilic PCL-*b*-PEO-*b*-PCL (PCEC) matrix. Scanning electron micrograph (SEM) of PCEC illustrated a well defined two-phase morphology consisted of dispersed poly(ethylene oxide) (PEO) domain and continuous polycaprolactone (PCL) phase. Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) experiments verified that three model drugs are dissolved as a molecular dispersion in PCEC matrix. The release of hydrophilic aspirin closely followed the water absorption profile of the matrix indicating that its major fraction is present in PEO domain. However, substantial amount of aspirin present in less hydrophilic region displayed discontinuous biphasic release pattern. In the case of omeprazole with intermediate hydrophobicity consistent release behavior was observed for a period of 24 hrs after the rapid liberation of ca. 10% of the drug presumably partitioned in PEO phase. It was ascribed to the fact that the progressive hydration of PCEC matrix gradually increased the chance of drug/water exposure to compensate the exhaustion of device. Naproxen with the highest octanol/water distribution coefficient among three model drugs exhibited a limited release of 35% for 24 hrs. Finally, hydroxypropyl methylcellulose phthalate (HPMCP)/PCEC blend matrix demonstrated an accelerated and quantitative release of hydrophobic naproxen by generating high porosity and thereby expanding polymer/water interface.

Keywords: oral administration, controlled release, PCL-*b*-PEO-*b*-PCL, omeprazole, naproxen.

Introduction

Oral administration, where therapeutic reagents are delivered in the gastro-intestinal tract, has been preferred for the compliance of patients.[1] However, the conventional oral administration does not provide ideal pharmacokinetic profiles regarding that the concentration of therapeutic reagents should be maintained within a therapeutic window to insure the safety and the maximum efficacy. It has been abundantly documented that biodegradable polyesters are formulated to drug carrier devices from which small molecules are discharged via two concurrent mechanisms such as diffusion and bio-erosion.[2-10] Thus, release behavior of therapeutic reagents from the polyesteric matrices must be dictated by the governing mechanism. Drug release driven by diffusion mechanism follows the first order kinetics, whereas bio-erosion leads to the zero-order kinetics. Polyglycolide (PGA), poly(lactide-*co*-glycolide) (PLGA), and polylactide (PLA) exhibit rapid biodegradation in physiological fluid so that drug release from these polyesters proceed via two concurrent mechanisms. On the other hand, poly(hydroxy alkanoate) (PHA) and polycaprolactone (PCL) degrade slowly and hence drug release from these polyesters predominantly depends on diffusion mechanism.[7,12]

In order to achieve an acceptable drug release rate from the hydrophobic matrix in oral administration micro-particulate formulations have been widely employed.[4-8] The micro-particles serve dual purposes of reducing diffusion path for drug molecules as well as providing large solid/liquid interfacial area. However, serious early burst was frequently encountered due to their inherent problems involved with micro-encapsulation techniques.[5] Specifically, small drug molecules are easily entrained to the periphery of micro-particles during the emulsification-solvent evaporation process, which yields a low loading efficiency and later causes rapid release of surface bound species. Various modifications of micro-particle surface and preparation method have been attempted to minimize the rapid release of substance during the initial phase of delivery.[2,4]

As an alternative route to enhance the drug release rate in hydrophobic matrices, hydrophilic segments such as poly

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(ethylene oxide) (PEO) are introduced to manipulate the hydrophilic-lipophilic balance (HLB) of the matrix.[8,13] The presence of PEO promotes the hydration of the polymeric matrix and thereby the diffusion of drug molecules. Recently, delivery of large proteins is of particular interests from ABA triblock copolymers with PEO central block, which produce hydrogel-like environments.

The incorporation of hydrophilic PEO into the hydrophobic polyester inevitably results in multiphase morphology due to their incompatibility. In heterogeneous matrix system organic drugs are subjected to be partitioned according to their hydrophilic-lipophilic balance. Consequently, the release behavior of drugs will be significantly affected by their distribution in respective phase. It was brought to our attention that this aspect has not been sufficiently explored in prior investigations. Most comparative release studies between different therapeutic reagents were made in membrane device or homogeneous matrices.[4,15] Authors were inspired by the observation that hydrophilic proteins often displayed biphasic discontinuous release patterns due to their presence in an aggregate state as well as in a molecular dispersion in incompatible polyesteric matrices.[8,12] In this study, three model drugs with different levels of water solubility were examined for their distribution and release behavior in the PCL-*b*-PEO-*b*-PCL (PCEC) matrix. Model drugs include aspirin, omeprazole, and naproxen in the descending order of water solubility and water/octanol distribution coefficient. Important therapeutic uses for these model drugs are listed in Table I.[14] In a comparative study, three PEO-*b*-PCL (PCE) oligomers with different HLB values were examined to establish the correlation between their distribution and release behavior from the PCEC matrix.

Experimental

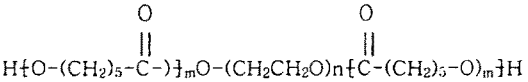
Materials. Epsilon-caprolactone (MW: 114 g/mole, Aldrich Chem Co., USA) was purified by distillation under reduced pressure over calcium hydride. All the solvents were purified according to the standard procedures. Poly(ethylene oxide) methylether (PEOH, 5 and 20 kg/mole) was purchased from Aldrich and was dried in vacuo at 100 °C for 2 hrs before use. Stannous octoate was also obtained from Aldrich and used as received. Model Drugs used in this study were kindly donated from Samyang Co. (Korea) and Chong Kun-Dang Pharm. Co. (Korea).

Synthesis. PCEC triblock copolymers and PCE diblock oligmers were synthesized via ring-opening polymerization of ε-caprolactone in the presence of PEO. In the first, 20 g of PEOH (M_n = 5 and 20 kg/mole) was charged into a 250 mL two-neck round-bottom flask and dried under reduced pressure at 100 °C for 2 hrs. Then, purified toluene and stannous octoate (0.2 wt% to caprolactone) were charged by a syringe to give a 20% (w/v) polymer solution. Finally, a calculated amount of ε-caprolactone, depending on the

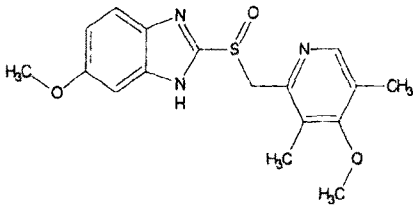
Table I. Physical Properties and Chemical Structures of Model Drugs

Drug	Molecular Formula	M_n (g/mol)	Water Solubility (mg/L) at 25°C	log P^a	Use
Aspirin	$C_9H_8O_4$	180.16	4600	1.19	antihypertension
Omeprazole	$C_{17}H_{19}N_3O_3S$	345.42	82.3	2.23	antiulcer
Naproxen	$C_{14}H_{13}O_3$	230.3	15.9	3.96	nonsteroidal antiinflammatory

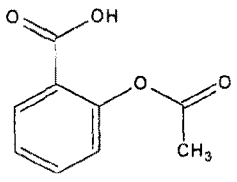
PCEC



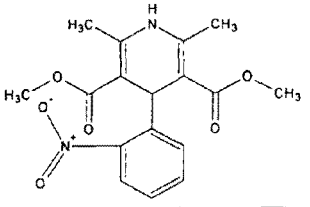
Omeprazole



Aspirin



Naproxen



[a]Octanol/water partition coefficient in log.

target molecular weight of the copolymer, was introduced to the reactor by a syringe. The reaction mixture was stirred for 16 hrs at 110 °C. The polymer was precipitated from the solution by introducing the reaction mixture to vigorously agitated diethyl ether. Then, it was subsequently filtered and dried in vacuo to a constant weight. The recovered material was carefully weighed to determine the yield of polymerization.

Characterization. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker 400 MHz spectrometer (Bruker DPX-400, USA) to determine the compositions of the block copolymers. Molecular weights and polydispersity of the copolymers were examined by gel permeation chromatography (GPC, Waters, Model 515 pump, equipped with 410 Differential Refractometer) using three micro-styragel column (CHR2, HR4, and HR5E) from 500 to 4×10^6 Å connected in series. Tetrahydrofuran was eluted with a rate of 0.3 mL/min at 30 °C. Polystyrene standards were employed to generate a calibration curve. The crystalline structure of drug/PCEC blends were examined using X-ray diffractometer (XRD, RINT2000, Rigaku Denki Co., Japan) equipped with a monochrometer and graphite crystal (Cu-Kα radiation).

Preparation of Drug/Polymer Blend Films. PCEC copolymer and a calculated amount of model drug were mixed in tetrahydrofuran or chloroform and then, poured onto a petri-dish. After the solvent was dried under a reduced pressure the film was compression molded to a desired thickness at 80 °C and 700 psi.

Drug Release from PCEC Matrix. Drug release from the PCEC matrix was performed employing a shaker bath installed in an incubator maintained at 37 °C. Typically, 200 mL of phosphate buffered saline solution (PBS: NaCl 8 g, KCl 0.2 g, Na_2HPO_4 1.15 g, and KH_2PO_4 0.2 g/L, at pH 7.4) was charged into a container along with drug/polymer blend film, operating at 70 cycle/min and held at 37 °C. An aliquots of the sample solution was periodically withdrawn from the releasing solution for measurement. Drug concentration in the solution was measured by UV spectrophotometry (Jasco V-550, Shimazu, Japan) at the wavelengths of 209.5, 205, and 230 nm for aspirin, omeprazole, and naproxen, respectively. Extinction coefficient for each drug was determined from the slope of Lambert-Beer plot. Drug concentration was calibrated by a Waters high performance liquid chromatography (HPLC, Waters, USA) system comprising a Waters model 510 pump, a Rheodyne injection valve with a 100 μL loop, μ-Bondapak C18 column (4.6 mm$\times$ 2300 mm, 5 μ), and UV detector (Waters 484). A mixture of 0.01 M PBS, methanol, and acetonitrile (200:350:450) was used as a mobile phase at a flow rate of 1.0 mL/min.

Measurement of Drug Permeability through PCEC Membrane. Drug permeation through the PCEC film was estimated using a home made apparatus composed of donor and receptor compartments and a thin PCEC membrane with 0.12 mm thickness inserted between two compartments. The donor compartment contains aqueous drug solution (100 mL, 0.1 wt/vol% in pH 7.4 PBS) and the receptor compartment was filled with pH 7.4 PBS blank solution. An aliquots of the sample solution was periodically withdrawn from each compartment for measurement.

Morphology. The matrix films were immersed in a distilled water for 24 hrs at 37 °C and subsequently freeze-dried at -40 °C. Then, the polymer films were fractured in liquid nitrogen. The samples were gold-coated by ion sputtering (ID-2, Eiko Engineering Co., Japan) and examined under a field emission scanning electron microscope (FE-SEM, JSM-6330F, JEOL, Japan).

Results and Discussion

Characterization of PCEC Amphiphilic Block Copolymer. The combination of PCL and PEO in PCEC triblock arrangement presents unique features of the individual components. Hydrophobic PCL end blocks in ABA triblock copolymers constitute the continuous phase and provide mechanical strength for monolithic films. Secondly, the presence of PEO phase may well give rise to an accelerated penetration of water to the matrix. Water diffusion route, in turn, may serve as a drug release channel towards the external aqueous phase.

A successful formation of covalent bonding between these segments was verified by GPC measurements. The observed molecular weight by GPC, 56.4 kg/mole, showed a good agreement with the calculated value of 57.8 kg/mole. It can be estimated that the block copolymer is consisted of 18.2 k -20 k-18.2 k (PCL-*b*-PEO-*b*-PCL) because hydroxyl groups of PEOH (20 kg/mole) are equally capable of initiating ring-opening polymerization of ε-caprolactone. ^{1}H-NMR analysis also confirmed the composition of the PCEC block copolymer. The physical blend of PEO and PCL displayed a major phase separation, whereas the PCEC (18 k-20 k-18 k) copolymer exhibited a well defined two-phase morphology with PEO domain uniformly dispersed in the matrix as observed under SEM. Figure 1 contrasts the markedly different images of PEO/PCL physical blend and PCEC triblock copolymer.

In oral administration it is crucial to dissolve organic drugs in the matrix at molecular level to ensure an efficient release and bio-absorption. A prominent advantage of PCEC amphiphilic copolymer is that organic drugs with a wide spectrum of HLB are subjected to be dissolved. Figure 2 shows the DSC heating thermograms of the matrix/drug blends. Distinct melting endotherm corresponding to respective model drug was not found in the heating scan, which can be interpreted as an evidence that these drugs exist in PCEC in amorphous state. Similar approach was also reported by Le Corre *et al.* and Gorner *et al.* to determine whether drugs are present as particulate or dissolved molecular species in

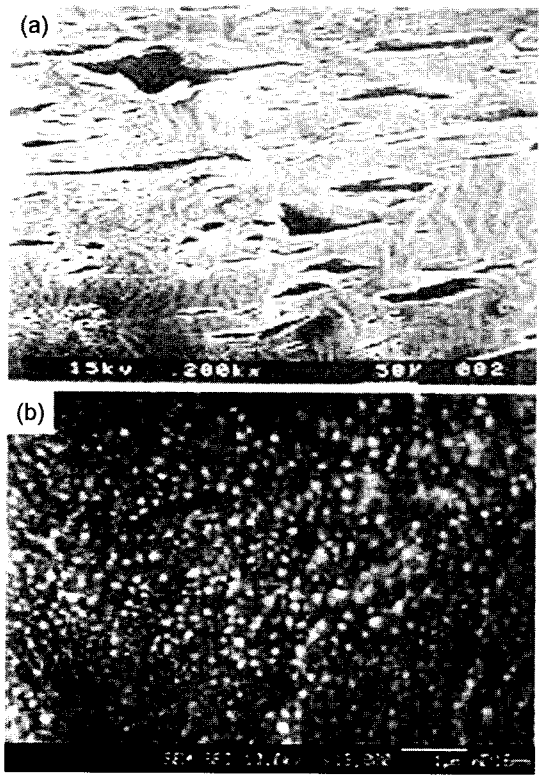


Figure 1. SEM photographs of the cross-sections of PEO (30 wt%)/PCL blend (a) and PCEC (b) after immersed in water for 12 hrs.

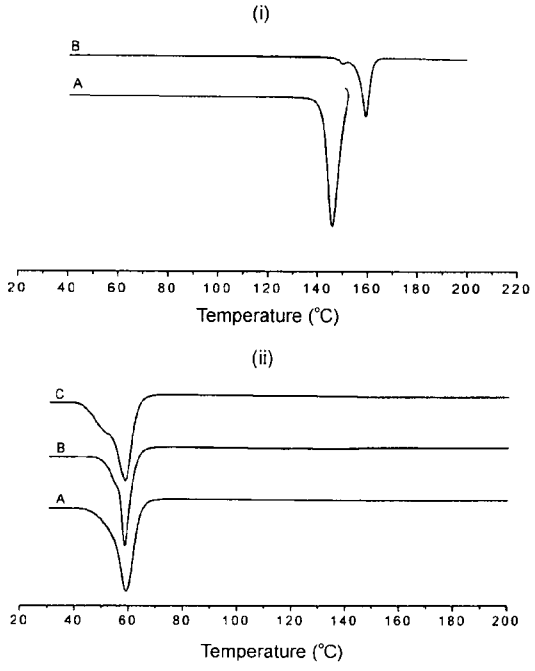


Figure 2. DSC thermograms of (i) drugs; (A) aspirin and (B) naproxen, and (ii) drug/PCEC blends; (A) PCEC, (B) PCEC + aspirin 10 wt%, and (C) PCEC + naproxen 10 wt%.

the matrix.[17,18] XRD experiments also support the fact that these model drugs are dissolved at a molecular level in the PCEC matrix. The crystals of small molecules usually exhibit high intensity in their X-ray diffractograms due to their perfect crystalline structures. Figure 3 displayed XRD patterns of model drugs and their blends with PCEC, where characteristic peaks corresponding to each drug molecule are absent.

Release of Model Drugs from PCEC Matrix. Table I presents the structures, molecular weights, and water solubility of model drugs used in this study. These model compounds represent the families of hydrophilic, intermediate, and hydrophobic organic drugs. The partition coefficients of model drugs between octanol and water are also listed in Table I. *In vitro* release experiments were performed in an incubator maintained at 37 °C. Each blend contains 10 wt% drug with respect to PCEC. The cumulative release profiles

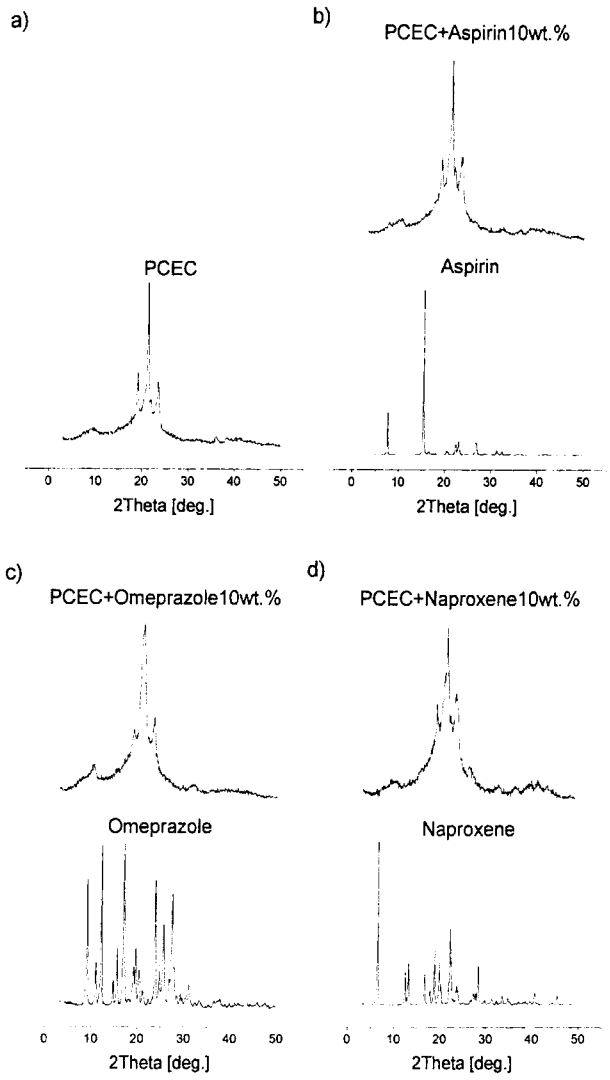


Figure 3. XRD patterns of PCEC, drugs, and drug/PCEC blends.

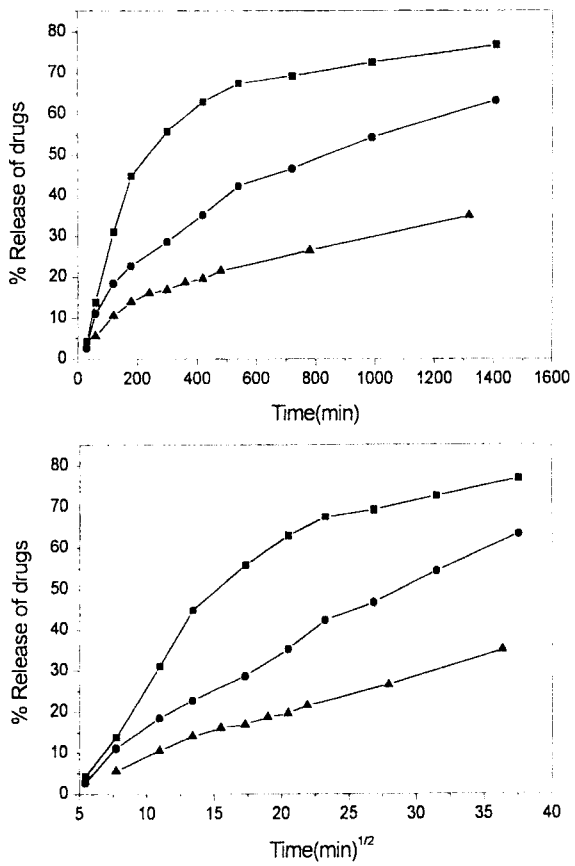


Figure 4. Cumulative release profiles of aspirin (■), omeprazole (●), and naproxen (▲) from PCEC matrices.

of model drugs are collectively plotted in Figure 4. As can be seen in the figure the release of aspirin displayed the first-order release kinetics up to ca. 55~65%. However, substantial amount of aspirin present in less hydrophilic regions resulted in discontinuous biphasic release pattern. An exponential decay in the latter phase of release was attributed to the heterogeneous composition of the PCEC rather than the exhaustion of device. Similar observation was reported when hydrophilic proteins were blended in hydrophobic polyesteric matrices. Hydrophilic proteins often displayed biphasic discontinuous release patterns due to their presence in an aggregate state as well as in a molecular dispersion in incompatible polyesteric matrices.[8,12] Figure 5 presents an evidence that the release of hydrophilic substance is directly related to the water inflow to the hydrophilic phase. As was over-layed in Figure 5 the release of aspirin proceeded in parallel with the water absorption of the PCEC matrix up to ca. 60% over a period of 5 hrs. It may be anticipated that PCEC comprising a higher PEO composition allows a higher partitioning of aspirin in the hydrophilic domain and thus consistency of the release could be extended.

Omeprazole showed a slower release rate apparently due to its higher octanol/water partition coefficient compared to

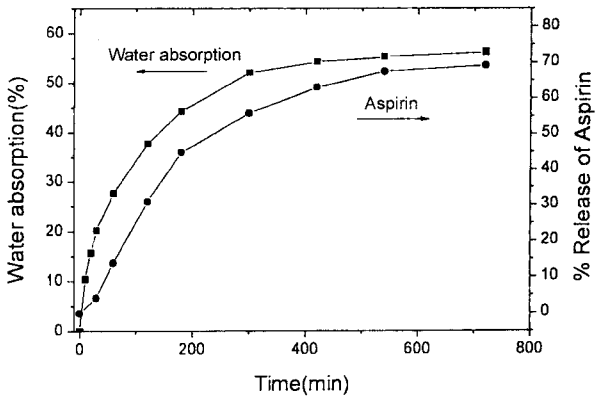


Figure 5. Water uptake of PCEC (■) and release profiles of aspirin (●) from the PCEC matrix.

aspirin. In the meanwhile, its release profile maintained the first-order kinetics up to 24 hrs after a small fraction, ca. 10%, was released at the same rate as aspirin in the initial phase. PCEC can be conveniently divided into three regions, PEO, PCL, and transient region between the respective phase. From the observed release profile of omeprazole it may be concluded that about 10% of the drug is partitioned in PEO phase while a major fraction is distributed in PCL and more preferentially in transient region considering its intermediate hydrophobic nature. Under the circumstances water inflow to the PEO phase does not immediately trigger substantial release of omeprazole other than a small partition in the hydrophilic domain. Progressive migration of water into the transient region continuously increases the chance of drug/water exposure, which may contribute to retain the consistency of release. These effects may compensate the exponential decay observed in conventional matrix system given in equation (2);[19]

$$\frac{dM_t}{dt} = 2M_\infty\left(\frac{D}{\pi l^2 t}\right)^{\frac{1}{2}} \quad (1)$$

up to 40~60% of cumulative fractional release and then, followed by an exponential decay with time;

$$\frac{dM_t}{dt} = 4DM_\infty exp\left(\frac{-\pi^2 Dt}{l^2}\right) \quad (2)$$

Permeability of aspirin and omeprazole through PCEC membrane was measured using an apparatus set up in our laboratory. As was compared in Figure 6, the difference in their permeability through the PCEC membrane is mere 25~30%. Therefore, the exceedingly large difference between aspirin and omprazole in the monolith system may reflect the fact that these two drugs are distributed in different regions of the multiphase matrix. The percent cumulative release of naproxen from the PCEC matrix is also presented in Figure 4. Naproxen exhibited a slower release rate relative

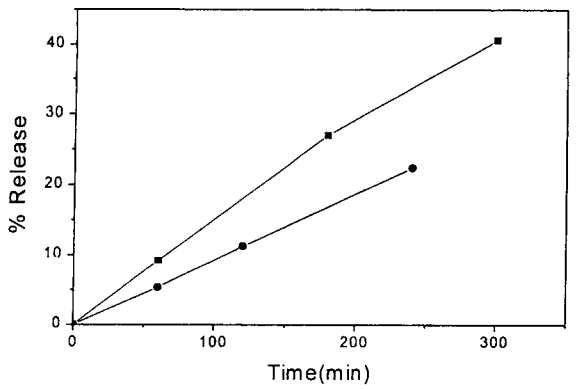


Figure 6. % Permeation of aspirin (■) and omeprazole (●) through PCEC membrane with 0.12 mm thickness.

to omeprazole since it is likely to be concentrated in PCL phase for its extremely hydrophobic nature. Thus, low water permeability in PCL phase may be responsible for a slow and inefficient release of naproxen.

Release of Naproxen from HPMCP/PCEC Blend Matrices. It has been documented that an accelerated release of hydrophobic drug could be achieved in foam type matrix, which practically serves the same purpose as micro-particle formulations in term of providing large water/polymer interface and short diffusion path.[3,5,10] In prior investigations by Mitra and this group reported independently, hydrophilic excipients were incorporated in polyesters to produce porous matrices *in-situ*.[1,10] PEO oligomers are commonly used as a selectively extractable component. In this study, high molecular weight HPMCP was employed as an excipient because of its certain advantages over PEO oligomers; acceptable compatibility with PCL to form dispersed phase of smaller dimension and lower solubility of hydrophobic drug in HPMCP.

Figure 7 illustrates the morphology of the freeze-dried HPMCP/PCEC blends film after HPMCP was extracted in water. It was found that the HPMCP/PCEC blend produced a sponge-like structure with round-shape voids of 1-3 μ in diameter. Presumably, the release of naproxen from the blend

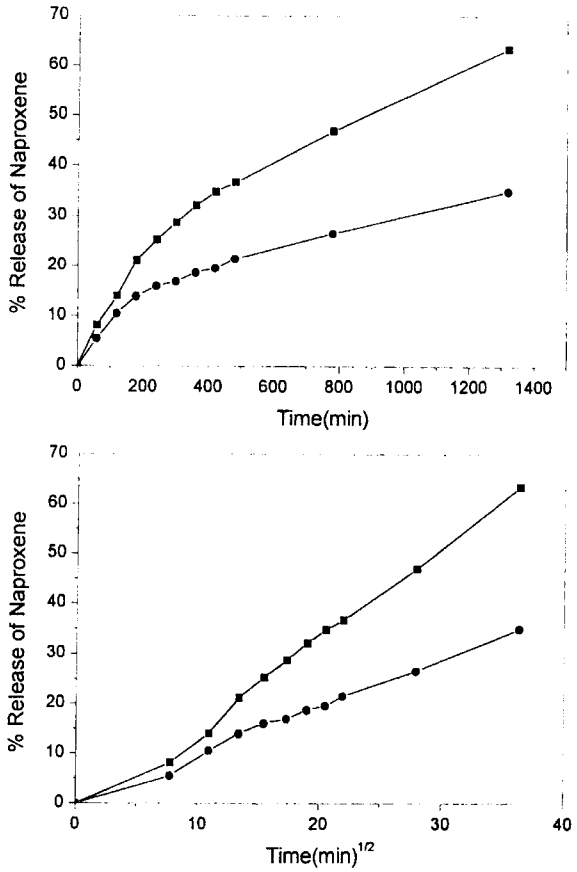


Figure 7. Release of naproxen from PCEC (■) and HPMCP/PCEC blend (●) matrices; naproxen (10 wt%), HPMC (30 wt%).

matrix may take place via two-step process; first, liberation from PCL phase to the water in the voids generated by the dissolution of HPMCP and then, diffusion through the tortuous channel to the outer water. This sequential release process and negligible partitioning of naproxen in HPMCP phase should minimize the possibility of early burst observed in micro-particles. As shown in Figure 8, the HPMCP/PCEC blend released naproxen more effectively and quantitatively compared to PCEC matrix. It is worthwhile to note that this

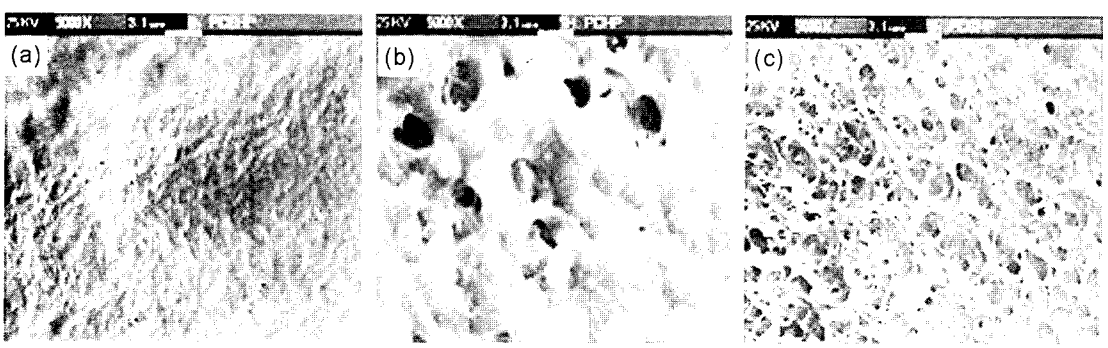


Figure 8. SEM photograghs of HPMCP/PCEC blend films: (a) untreated; cross-section, (b) immersed in water for 24 hrs; surface, (c) immersed in water for 24 hrs; cross-section.

blend matrix demonstrated linear release behavior during the initial phase of release up to 3~4 hrs.

Analogy of PEC Oligomers. One may predict the distribution of PEO-*b*-PCL (PCE) oligomers in PCEC matrix more convincingly than model drugs. Table II listed the compositions and HLB numbers of three PCE oligomers. Figure 9 plotted the release profiles of these oligomers from the PCEC matrix. Although direct comparison between these oligomers and model drugs are not possible because of large difference in their molecular weights, the liberation of 5 k-1.5 k and 5 k-2.5 k oligomers produced the release profiles similar to those observed with aspirin and omeprazole. Hydrophilic oligomer (5 k-1.5 k) revealed the first-order release kinetics and then, exhibited an exponential decay as in the case of aspirin. In contrast, 5 k-2.5 k oligomer showed a slow but consistent first order kinetics as observed with omeprazole. Unfortunately, the release of 5 k-7.5 k oligomer was too slow to make a reasonable comparison with model drugs. Unlike low molecular weight model drugs, 5 k-7.5 k oligomer anchored in PCL phase could not be released. A small amount of 5 k-7.5 k liberated from the matrix must be the fraction comprising shorter hydrophobic PCL segments than its average composition.

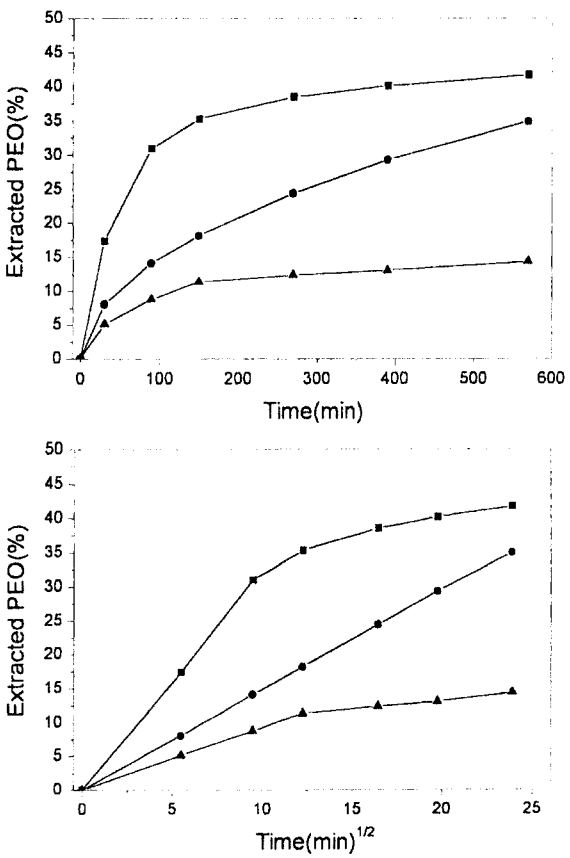


Figure 9. Release of PCE oligomers from PCEC matrices; PCE 5 K-1.5 K (■), PCE 5 K-2.5 K (●), and PCE 5 K-7.5 K (▲).

Conclusions

DSC and XRD experiments verified that organic drugs with a wide spectrum of HLB are dissolved in PCEC amphiphilic copolymer as a molecular dispersion. Omeprazole with medium hydrophobicity exhibited the first-order kinetics release profile without a decay effect ascribable to the fact that a progressive water uptake of the amphiphilic matrix increased the apparent diffusivity of the drugs. On the other hand, aspirin demonstrated a release behavior corresponding to the water absorption profile of the matrix up to ca. 60%. However, substantial amount of aspirin present in less hydrophilic regions resulted in discontinuous biphasic release pattern. Similar results were obtained for PCE oligomers with 5 k-1.5 k and 5 k-2.5 k compositions as in aspirin and omeprazole, respectively. It may be concluded that the HLB of drug dictates its distribution and release behavior in the multiphase matrix. In addition, HPMCP/PCEC blend was proved to be an effective drug carrier for hydrophobic drugs such as naproxen by providing large water/polymer interface and short diffusion path *in situ*.

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Table II. Molecular Weights of PEO-PCL Diblock Oligomers and Corresponding HLB Values

Copolymer	Composition PCE	M_n[a] (g·mol^{-1})	MWD	HLB[b]
I	5k-1.5k	6,350	1.21	12.0
II	5k-2.5k	7,900	1.25	10.5
III	5k-7.5k	11,800	1.15	4.0

[a] M_n and MWD were determined by GPC measurements.
[b] HLB values were estimated by group contribution method.

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