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Anomalous Release of Hydrophilic Drugs from Poly(ϵ-caprolactone) Matrices

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Abstract: In this paper, we investigate the release of two drugs, nicotine and caffeine, from poly ϵ-caprolactone (PCL) matrices, as a model for the delivery of highly hydrophilic drugs. Since PCL does not degrade over the period of our experiments (<30 days), drug diffusion through the matrix is expected to be the dominant mechanism of release. Contrary to expectations, we find that the drug diffusion coefficient increases with increasing drug loading, weakly for caffeine and strongly for nicotine. The water content in the PCL matrices (after all of the drug was released) was found to be orders of magnitude higher than the expected value, increasing with increasing drug loading. We suggest that these phenomena arise from the semicrystalline nature of PCL under our experimental conditions, which inhibits matrix collapse when the drug is released, thereby creating voids into which water can diffuse. We apply a quantitative model for these systems that considers counter-diffusion of water *into* the matrix with drug diffusion out of the matrix. The high solubility of both drugs in aqueous solutions leads to drug partitioning into the polymer-encapsulated water, thereby increasing the effective rate of drug diffusion and release. The model is shown to fit the experimental data of both drugs using only one fit parameter.

Keywords: Drug delivery; controlled drug release; poly(caprolactone); in vitro test

Introduction

The extensive study of polymeric matrices as drug delivery agents is driven by two healthcare issues. First is the failure of most chronic patients to follow prescribed medication regimes,[1–8] where the use of slow-release delivery devices increases patient compliance and improves outcomes.[9–14]

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Second is the need for devices for local delivery such as in-tissue scaffolds[15] or tumors.[16]

One of the dominant challenges in drug delivery is the need for control of the drug level, namely, rate of release: Drug doses must fit within a specific window whose lower limit is above the therapeutic threshold and whose upper limit is below the toxic level. Previous studies show that the rate of drug release from polymeric matrices depends on the polymer properties, environmental conditions, and drug characteristics.[17–27]

Poly(ϵ-caprolactone) is a biocompatible, semicrystalline polyester. It has been widely studied for long-term drug release applications due to its slow biodegradation rate, which takes place via bulk hydrolysis of the ester bonds.[28–34] Moreover, PCL is relatively hydrophobic and does not swell significantly in aqueous solutions;[35] as a result, drug leaching from PCL must occur by slow diffusion through the polymer rather than by rapid diffusion in water-swollen regions. Previous studies have shown that PCL can be used to encapsulate and release a variety of therapeutic agents, ranging from low molecular weight (MW) drugs[34] to ribozymes[31] and other proteins.[34] In most cases, drug release appears to follow two different patterns: First, a relatively

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Table 1. Polymer Properties[37]

	manufacturer	M_w (g/mol)	M_n (g/mol)	T_g (°C)	mp (°C)
PCL-M	Sigma-Aldrich	65000	42500	−60	60
PCL-L	Sigma-Aldrich	14000	10000	−60	60

rapid release of 30–50% of the drug occurs over a period of order ∼10 days (depending on the specific mixture formulation, PCL particle dimensions and drug loading), followed by a very slow release rate over time scales of months.[28–35] The initial release stage has been attributed to drug diffusion and leaching from noncrystalline domains, and the slow, long-term release to drug trapped in crystalline domains that is released by matrix degradation.[28–34]

In this paper, we examine the effect of drug loading on the rate of release from PCL matrices by comparing two similar, highly hydrophilic drugs: nicotine and caffeine. Our goal was not to necessarily develop these systems into nicotine and caffeine drug delivery systems but to study these as a model for other, hyghly hydrophilic drugs of interest. Our study reveals several surprising observations. First, we find that both drugs are completely released within 10–30 days. Thus, contrary to previous studies,[28–34] our preparation method seems to inhibit sequestering in crystalline domains. We find that the drug-depleted matrices contain water in quantities that are much higher than expected by PCL swelling, proportional to the initial drug loading. Most surprising, however, is our finding that the drug release rate cannot be attributed to classical diffusion through polymeric matrices: The effective diffusion coefficient of both drugs increases with increasing drug loading. The correlation between the diffusion coefficient and drug concentration in the matrix is weaker for caffeine and higher for nicotine. We correlate, using a diffusion model, the drug diffusion out of the matrix to water diffusion into the matrix and drug partitioning into the aqueous domains within the polymer particle.

Materials and Methods

The methodology used in this study follows the same procedures as decribed in our earlier publication.[27]

Materials. We use a mixture of 50:50, by weight, low (PCL-L) and medium (PCL-M) molecular weight PCL (Sigma-Aldrich) as listed in Table 1.[36] Caffeine and nicotine were also purchased from Sigma-Aldrich.[36] Their properties are listed in Table 2.

Melt Mixing. Mixtures of PCL and nicotine or caffeine, at the appropriate weight ratios (90:10, 60:40, and 50:50) were placed in an oil bath at 150 °C. Note that this temperature is above the melting temperature of the polymer, namely, the temperature at which crystalline domains dissolve. A Teflon stirrer slowly mixed the viscous material in a polypropylene cup for 30 min. After visually inspecting for homogeneity, the PCL/drug mixture was allowed to cool in the freezer until it hardened and could be removed from the cup with ease. It was then stored at room temperature until ready for compression molding. At room temperature, the polymer is above T_g but below the melt temperature (see Table 1). Thus, although the glassy domains are in the fluid state, crystalline domains are present.

Pellet Press. To create the pellets, the PCL/drug mixture was softened on a hot plate at 70 °C and placed in a 3 mm diameter Teflon-coated window mold. The plate was first pressed at 80 °C and 30000 psi for 30 s and immediately placed in a second press which operated at room temperature and a pressure of 24000 psi until cooled. This procedure was repeated until the pellets reached the density requirement of 1.1 mg/mm^3. The pellets were weighed and measured by a digital caliper.

UV Calibration Curve. The concentrations of drug released were measured using an ultraviolet (UV) spectrometer. A 0.4 mg/mL solution of either drug in phosphate-buffered saline (PBS) was used as the highest concentration on the curve. The solution was vortexed for 2 min and then diluted by half. This was repeated until a total of 10 solutions were made, where pure PBS was the lowest concentration. All concentration studies were in the linear regime of the calibration curve, thereby ensuring accuracy.

In Vitro Assay. For each study, six pellets of the same type were used. Each pellet was placed in 100 mL of PBS solution and placed on a stirrer at 37 °C to simulate a natural body state. Aliquots of 200 μL were taken 3–4 times per week from each jar to measure absorbance by the UV spectrometer. These data are compared to the calibration curve to calculate the concentration and the amount of drug released. For each set of conditions that was examined, corresponding positive and negative controls were present. The positive controls were set at the total drug load of the pellet dissolved in PBS solution. The negative controls were pellets only containing the polymer and no drug.

Results

In Figure 1, we plot the fraction of drug released, f, as a function of time for both caffeine (Figure 1A) and nicotine (Figure 1B) at initial drug loadings of 10, 40, and 50 wt %. We see that, for both drugs, the fraction released at any fixed time is higher for the higher loading system. Although the differences between the different release profiles are weak for caffeine (Figure 1A), they are significant for nicotine

Table 2. Drug Properties[37]

	manufacturer	M_w (g/mol)	chemical formula	mp (°C)	measured molubility (mg/mL)
(−)-nicotine hydrogen tartrate salt	Sigma-Aldrich	462.41	$C_{10}H_{14}N_2 \cdot 2C_4H_6O_6$	79	>200
caffeine	Sigma-Aldrich	194.19	$C_8H_{10}N_4O_2$	232	20

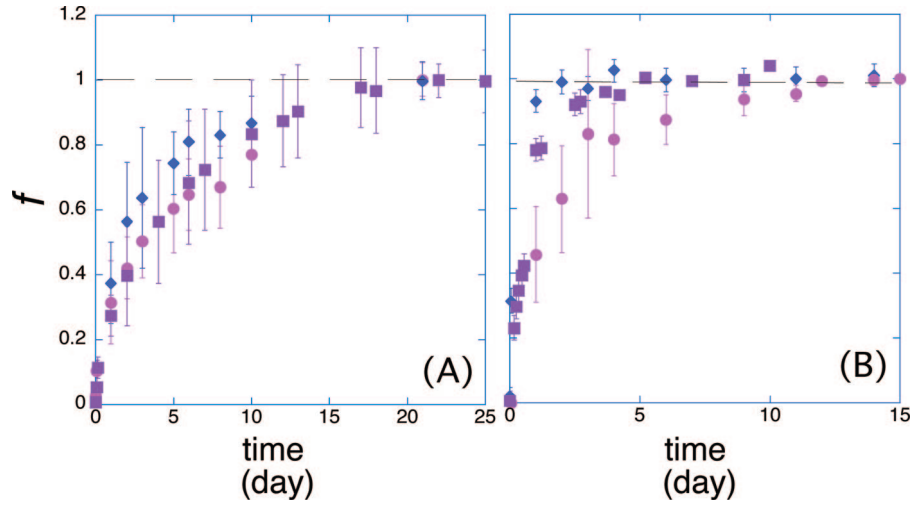

Figure 1. Fraction of drug released, *f*, as a function of time for caffeine (A) and nicotine (B). Circles denote an initial loading of 10%, squares of 40%, and diamonds of 50%. We see that the caffeine release profiles are similar, although the rate of release (as given by d*f*/d*t*) is consistently higher for the higher initial loadings. In the case of nicotine, the rate of release clearly increases with initial loading.

Table 3. Measurement of PCL–Drug Pellet Weight

system	initial weight (mg)	initial drug weight (mg)	wet weight[a] (mg)	dry weight[b] (mg)	weight loss (mg)	% PCL weight loss[c]	water content[d] (%)
40% nicotine	43.5 ± 0.6	17.4 ± 0.3	38.4 ± 0.6	26.7 ± 0.4	16.8 ± 0.6	0	30 ± 0.7
10% caffeine	40.9 ± 0.5	4.1 ± 0.3	37.6 ± 0.5	35.5 ± 0.6	5.4 ± 0.2	3	5.6 ± 0.3
40% caffeine	44.4 ± 0.5	17.8 ± 0.2	37.1 ± 0.5	25.1 ± 0.8	19.2 ± 0.9	3	32.3 ± 2
50% caffeine	44.2 ± 1	22.1 ± 0.6	35.4 ± 0.6	20.4 ± 0.8	23.8 ± 2	4	42.4 ± 1.3

[a] Measured immediately after removal from the buffer solution, at the time point at which 100% release (determined by UV) was obtained. [b] Measured after 3 and 7 days drying in a vacuum oven (no difference between the 3 and 7 day measurement indicating that, indeed, all water was removed). [c] Assuming 100% drug release. [d] The fraction of pellet occupied by water after 100% of the drug was released, as determined by the weight of the evaporated water divided weight of the water swollen (wet) pellet.

(Figure 1B). These release profiles suggest that the rate of drug release from PCL is higher, then, for systems with a higher initial loading of hydrophilic drug, not only in absolute terms (weight/time) but as the *fraction* of the initial loading.

To ascertain that all the drug was released and whether matrix degradation occurred over our study's time, we removed some pellets from the buffer solution at the time point where UV measurements indicated that 100% of the drug was released. The pellets were weighted initially (immediately upon removal from solution) and after drying, as summarized in Table 3. We see that the weight loss from the drug containing pellets is similar to the initial drug loading, thus supporting the UV measurement observation of 100% drug release. Also, as expected, the PCL matrix did not undergo significant degradation over the moderate time scales of the experiment.

Comparing the weight of the wet and dry pellets yields an interesting observation, namely that the final water content increases with increasing initial drug loading (Table 3). The weight fraction of water in these systems is orders of magnitude higher expected from the swelling of pure PCL by water.[35] We attribute this to the partially crystalline nature of PCL matrices at room temperature (see Table 2), since although glassy domains dissolve to an amorphous fluid above −60 °C, crystalline domains do not disperse until 60 °C. We suggest that the crystalline domains prevent the amorphous regions from collapsing: While a completely amorphous polymer above the glass transition will collapse in a poor solvent, so that the final state of the polymer after all drug was released is independent of the initial drug loading, in a semicrystalline polymer the rigidity of the crystalline domains inhibits matrix collapse when the drug diffuses out. As a result, the polymer pellet displays "voids" where the drug was before diffusion, into which water can diffuse, as sketched in Figure 2 (this is somewhat similar to a sponge full of air placed in water: The air will diffuse or bubble out, and water will flow in). Thus, the volume available to the solvent (water) should be proportional to the drug loading, as observed (Table 3).

Discussion and Conclusions

In this paper, we measure the release of two model hydrophilic drugs, caffeine and nicotine, from PCL matrices. We find that the apparent *normalized* rate of release (as given, for example, by d*f*/d*t* and/or by the time required to achieve 100% release) varies with drug loading: Drug is released more slowly from matrices that contained a low initial amount of drug, when compared to matrices with a high initial loading. This correlation is weak in the case of caffeine but quite significant for nicotine. We also find that the amount of water absorbed by the polymer matrix, at the end of the

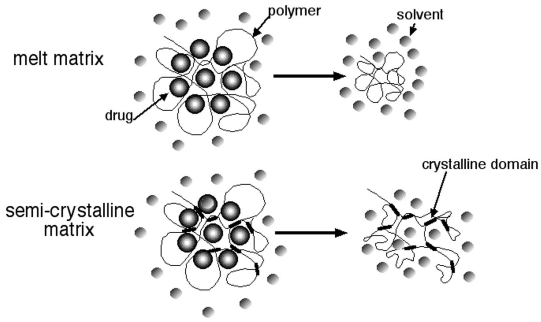

Figure 2. Drug release from melt and semi-crystalline matrices immersed in a poor solvent. In the case of the melt, where polymer chain mobility is high, drug release is accompanied by matrix collapse. However, semicrystalline domains act as a 'scaffold' or cross-links, thereby suppressing collapse. The voids resulting from drug diffusion out of the matrix are filled, then, by the solvent diffusion into the matrix. The result is solvent content in the matrix that is similar to the initial drug loading and independent of the solvent quality.

drug release process, is proportional to the initial drug loading, orders of magnitude higher than expected from PCL swelling.[35]

Drug release from polymeric matrices can occur through two mechanisms:[17–27] drug diffusion out of the matrix and/or matrix degradation. As shown in Table 3, our PCL carriers do not display significant matrix degradation (Table 3). Thus, drug release from PCL, over these time scales, must be dominated by diffusion. Solving the diffusion equation for the fraction of drug released from a (nondegrading) spherical particle, f, as a function of time t yields[37]

$$f = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}e^{-Dn^2\pi^2t/R^2} \qquad (1)$$

where D is the diffusion coefficient of the drug in the matrix and R the radius of the polymer particle. Equation 1 assumes ideal sink conditions, namely, that the drug concentration in solution at the particle interface is zero. In practice, maintaining the solution at drug concentrations well below the drug solubility limit and under vigorous mixing yields conditions similar to an ideal sink. Also, although eq 1 applies to spherical particles rather than to our tablet geometry, the effect of the pellet shape is minor.

Equation 1 predicts that the *fraction* of drug released from a nondegrading or slowly degrading matrix is independent of the initial drug concentration. While it may be argued that eq 1 applies to caffeine (although f of the 50% is *always* higher than that of 10%), it clearly fails for nicotine.

The derivation of eq 1 assumes that the drug environment in the carrier (the polymer matrix) is fixed, namely, does not change with time. Thus, it applies to systems where the degree of matrix swelling by the surrounding suspension is low. We find, however, that although PCL is not expected to absorb a significant amount of water,[35] at the end of the drug release process the polymer contains an appreciable amount of water (Table 3). Moreover, the water content is proportional to the initial drug loading. Therefore, as the drug is diffusing out of the matrix, water is counter-diffusing into the matrix.

Why would water diffuse into our PCL matrices, but not into pure polymeric particles that did not contain drug initially? We suggest that this is due to the fact that, under our experimental conditions, the matrix is semicrystalline. As shown in Table 2, although glassy regimes become amorphous above –60 °C, crystalline domains must be heated above the melt temperature of 60 °C to dissovle—much higher than the temperature at which our experiments were conducted (37 °C). Drug diffusion out of a polymer matrix that is completely in the melt state, immersed in a poor solvent suspension, would lead to collapse of the matrix as depicted in Figure 2. However, the presence of semicrystalline domains acts as a scaffold that inhibits collapse (see Figure 2). The solvent diffuses into the voids left by the drug, resulting in a solvent content that is similar to the amount of drug released, as found in our experiments (Table 3). Note that if water was a good solvent for PCL, we would expect complete particle dissolution (if no semicrystalline domains are present), or a fixed degree of swelling that is independent of drug loading (if semicrystalline domains act as cross-links).

If the drugs examined in this study were hydrophobic, the presence of water in the matrix would not affect their release, since they would prefer to remain within polymer domains. However, both caffeine and nicotine are hydrophilic and considered to be highly soluble in water (see Table 2). Thus, it is likely that the presence of water in the matrix may affect their diffusion and release.

We first calculate the amount of water in the matrix as a function of time. Assuming transport into the matrix is dominated by diffusion, the water content in the matrix, M_w, as a function of time is given by[38]

$$M_w(t) = M_w^{\infty}\left(1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}e^{-D_w n^2\pi^2 t/R^2}\right) \qquad (2)$$

where M_w^{∞} is the maximal water content in the pellet, as listed in Table 3. The diffusion coefficient of water in PCL, D_w, is known to be 2×10^{-7} cm^2/s.[35] Thus, eq 2 has no free parameters and the water content for any system is known in absolute terms as a function of time.

The presence of water in the matrix allows a hydrophilic drug another route for transport: In addition to diffusion via polymeric domains, drug can partition and diffuse through the aqueous phase. Thus, the effective diffusion coefficient of the drug in the polymer–water mixture can be approximated by an average:

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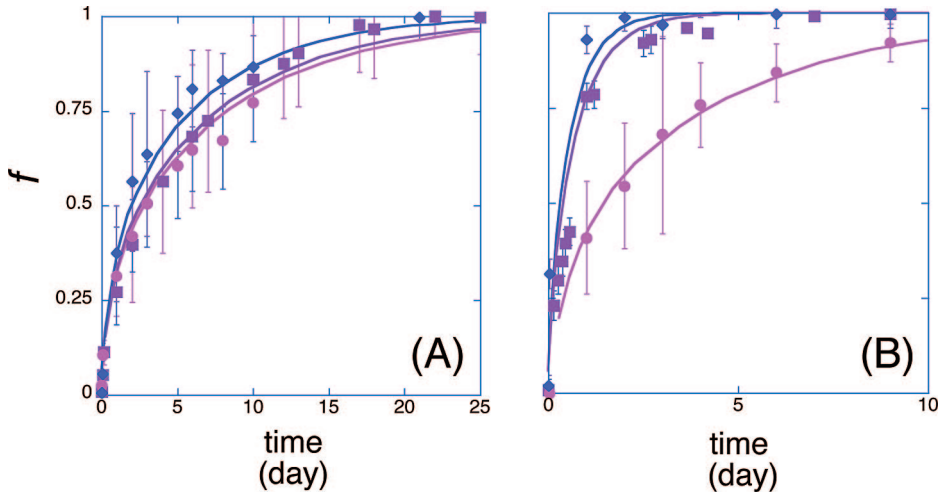

Figure 3. Fitting the release data using our model as set by eqs 1 and 3: (A) caffeine and (B) nicotine. Symbols are as shown in Figure 1. The maximal water content, M_w^∞, was taken from Table 3. The only free fit parameter is the water partition coefficient of caffeine, x_c, found to be 0.006.

$$D_{eff}(t) = D_{d,p} + xM_wD_{d,w} \quad (3)$$

Here, $D_{d,P}$ is the diffusion coefficient of the drug in the polymer and $D_{d,w}$ is the diffusion coefficient in water. x is a partition coefficient that depends on the solubility of the drug in water only, independent of the initial drug loading. $D_{d,w}$ for caffeine is known to be 6.3×10^{-6} cm^2/s, and for nicotine it is 6.0×10^{-6} cm^2/s.[38] Although the diffusion coefficient of either caffeine or nicotine in PCL $D_{d,P}$ is not known, it is reasonable to assume that it is similar for both and of the order of 10^{-8} cm^2/s for both drugs.[39] Thus, the only free fit parameter is x, but once it is fixed for one drug loading it cannot be modified. Substitution of $D_{eff}(t)$ for the diffusion coefficient in eq1 yields the drug release profile.

In Figure 3, we compare the drug release profile as measured experimentally to the predictions of our model (combined eqs 1 and 3). Since the solubility of nicotine in water is approximately 10 times higher than that of caffeine, x_n of nicotine should be about 10 times the value for caffeine. Thus, we have only a single parameter to fit the six release profiles: x_c of caffeine (x_n is taken to be $10x_c$ and M_w^∞ is known from Table 3). As shown in Figure 3A, the three profiles of caffeine release are fit well with $x_c = 0.006$, and the three profiles of nicotine release with $x_n = 0.06$ (Figure 3B).

In conclusion, we find that the release of hydrophilic drugs from PCL matrices is highly sensitive to the presence of water in the matrix: Due to the semicrystalline structure of PCL, drug release is not associated with matrix collapse, but with water transport into the matrix. Drug partitioning and diffusion through the polymer-encapsulated water enhances the rate of drug diffusion, and therefore drug release. We apply a simple diffusion model for the drug, characterized by a time-dependent diffusion coefficient. The model is found to fit our six sets of data well with only one fit parameter, the partition coefficient of caffeine into the polymeric matrix water.

(39) Empirical models suggest that the diffusion coefficient of a molecule through a liquid decreases with the molecular volume of the molecule to the power of 0.5 to 0.6 (see, for example, Welty et al. textbook). The molecular volume of caffeine and nicotine is approximately 10 times that of water (see ref 38). Using the diffusion coefficient of water in PCL and this correlation leads to a diffusion coefficient in PCL that is of order $1 \times 10^{-8} - 5 \times 10^{-8}$ cm^2/s. We used the lower bound in our calculations, but the results are insensitive to the value chosen.

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