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

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ABSTRACT: We examine the release of two highly hydrophilic drugs, nicotine and caffeine, from poly(ε-caprolactone) (PCL) matrices. We find that the dominant mechanism for drug release is drug diffusion through the PCL matrices. As a result, the rate of drug release (defined by the amount of drug released per unit time) decreases exponentially with time. Coating the drug-carrying particles with a drug-free PCL layer significantly changes the release profile: instead of exponential decay, the release rate exhibits a peak whose location (time) and magnitude vary with the diffusion coefficient of the drug in the polymer and the thickness of the coating. As a result, coating may be used to control the release rate and obtain a relatively constant rate over a period of time. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 3149–3156, 2008

Key words: diffusion; swelling; semicrystalline matrix

INTRODUCTION

Interest in polymeric matrices for long-term drug release is driven by the need to ensure chronic patient compliance with prescribed medication regimes,[1–8] where reducing the frequency of drug administration improves outcomes.[9–14] Polymeric drug carriers are also of interest as delivery agents to local target sites such as tissue scaffolds[15] or tumors.[16] While the second application requires micro and nanoscale delivery agents that can be administered intravenously, carriers for the long-term delivery of everyday therapeutic agents may be macroscopic and administered subcutaneously.

Effective long-term drug delivery devices require accurate control of the rate of drug release (mass per unit time) over the period of device activity, to ensure efficacy and eliminate toxicity. The rate of drug release from polymeric carriers has been found to vary greatly with the type of drug.[17–20] Different drugs released from the same matrix, under identical solution conditions, display large differences in their release rate.[17–20] Thus, tailoring the delivery level of a particular drug to fit therapeutic requirements must be achieved by design of the polymer matrix properties.

Long-term release of hydrophobic drugs generally occurs, and thus may be controlled by, through degradation of the polymer matrix.[21–24] Controlling the rate of hydrophilic drug release is more challenging, especially if the matrix is hydrophilic and swells in the buffer solution so that the drug can rapidly diffuse through the swollen regions and ''dump'' into solution. Thus, long-term delivery of hydrophilic drugs is most likely in polymeric carriers composed of relatively hydrophobic and nondegradable, or slowly degrading, matrices.

Poly(ε-caprolactone) (PCL) is a biocompatible polymer of the polyester family that is suitable for implantable or injectable delivery devices.[25–27] PCL is considered ideal for long-term delivery of hydrophilic drugs due to a low degree of swelling in aqueous solutions[28] and slow biodegradation rate via bulk hydrolization of the ester bonds.[25–28] Moreover, due to the lack of acidic degradation products, PCL provides a benign environment for pH-sensitive drugs such as proteins.[27] The release rate of drugs from (pure) PCL matrices was found to depend on the preparation method as well as drug properties and loading.[27] Generally, the release of 20–60% of the initial loading of hydrophilic drugs from PCL was found to take place over a period of hours to several days.[27–32] This stage may be preceded by an

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TABLE I
Characteristics of the PCL Matrices used in this Work

	Manufacturer	M_w (g/mol)	M_n (g/mol)	MP (°C)
PCL-M	Sigma-Aldrich	65,000	42,500	60
PCL-L	Sigma-Aldrich	14,000	10,000	60

initial ''burst'' due to drug adsorption on the particle surface, and/or followed by extremely slow release that may last up to several months.[27]

The mechanism of drug release from PCL matrix has not been clearly determined. It has been suggested that the moderately rapid release rate may be due to drug diffusion through the matrix and leaching into solution. The remainder of the drug is thought to be trapped in crystallized regions,[32] released slowly through the extremely slow matrix degradation process. However, since drug release studies tend to present drug release in terms of the cumulative amount of released drug vs. time, it is difficult to distinguish whether the moderately rapid release stage is, indeed, followed by a slow release one, or to determine the mechanism of release.

In this article, we study quantitatively, the rate of release of two model hydrophilic drugs, caffeine and nicotine, from PCL matrices, *in vitro*. We find that $\sim$ 20% of the caffeine, and $\sim$ 67% of the nicotine, was released within 1 day, while 100% release required 17 and 10 days, respectively. This differs from previous studies that found release of only 30–60% over such periods of time. The release profile of both drugs was shown to follow the profile expected from release via simple diffusion from a uniformly mixed solid particle.[33] The diffusion coefficient of nicotine in PCL, as determined by fitting the release profile to the diffusion model, is found to be $\sim$ ¼ that of water in PCL,[28] as may be expected due to the high MW of the drug. The diffusion rate of caffeine is found to be much slower than that of nicotine, by a factor of $\sim$ 3.5.

The rate of drug release from the PCL particles, as defined by the mass of drug released per unit time, is found to decrease exponentially, as expected from diffusion from a uniformly mixed particle, with a decay rate that is proportional to the diffusion coefficient. Such release profiles cannot be used for drug delivery applications, due to the large variability in rate. Thus, to achieve more uniform release profiles we coat the particles with a layer of drug-free PCL. We find that the coating changes the profile of drug release rate significantly: Rather than exponential decay, we find in nicotine a peak in the rate at about 1 day, followed by a slow decline. In caffeine, the rate of release from the coated particle is nearly constant for $\sim$ 17 days.

MATERIALS AND METHODS

The general procedure used in these experiments has been described elsewhere.[20]

Materials

We use a 50 : 50 mixture, by weight, of low and medium molecular weight PCL (Sigma-Aldrich, Milwaukee, WI) as listed in Table I. The properties of the two drugs are listed in Table II.

Melt mixing

A 60 : 40 mixture of polycaprolactone (PCL) and nicotine or caffeine was placed in an oil bath at 150°C. Using a Teflon® stirrer the viscous material was slowly mixed in a polypropylene cup for thirty minutes. 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 pressing.

Pellet press

To create the pellets, the PCL/drug mixture was softened on a hot plate at 70°C and placed in a 6-mm diameter Teflon®-coated mold. The plate was first pressed at 80°C and 30,000 psi for 30 s and immediately placed in a second press, which operates at room temperature and a pressure of 24,000 psi, until cooled. This procedure was repeated until the pellets reached the density requirement of 1.1 mg/mm^3.

TABLE II
Properties of the Two Drugs used in this Study

	Manufacturer	M_w[a] (g/mol)	Chemical formula[a]	MP[a] (°C)	Measured solubility[b] (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

[a] From Sigma.
[b] Measured in the buffer solution under the same conditions as the release study.

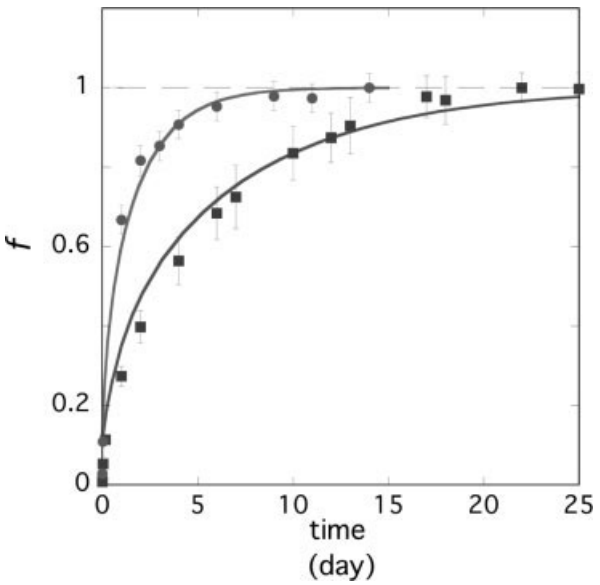

Figure 1 The fraction of drug released, f, as a function of time. Circles denote nicotine, and squares caffeine. The mass of the drug in the polymer pellets was similar (17 ± 0.5 mg), so that f is equivalent to the released mass of drug. We see that all nicotine was released within ~ 10 days, while release of all the caffeine required ~ 17 days. The lines denote a one parameter fit to Eq. (1).

The pellets were weighed and measured by a digital caliper.

UV calibration curve

The concentrations of drug released were measured using an ultraviolet spectrometer. A 0.4 mg/mL solution of either drug in PBS-B 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-B was the lowest concentration.

Coating methods

Three different methods were used to compare the effectiveness of coating the pellets in pure polymer. The first involves dipping in a 10% polymer in acetone solution, following a specific procedure. The pellet was dipped for 1 s and excess polymer was removed by dabbing on a clean Teflon® surface. After waiting for 2 min, the pellet was again dipped and the procedure repeated. They were dried in the hood for an hour and then dipped twice more. After sitting in the hood overnight to evaporate any excess acetone, the pellets were weighed.

The second method utilized an airbrush kit spray gun to apply a 2.5% polymer in acetone solution evenly across the pellets. The pellets were placed in Silly Putty® to keep from shifting. Half of each pellet was sprayed, then the pellets were rotated and the uncoated halves were sprayed. Again, after sitting in the hood overnight, they were weighed to determine the evenness of coating between them.

The third method entailed preparing a film by pressing pure polymer pellets into thin sheets using both the hot and cold presses. The drug-polymer pellets were then wrapped in the thin polymer film and heated to seal the coating. The excess polymer was trimmed to obtain a cylindrical shape and the pellets were weighed for comparison.

In vitro assay

For each study, six to ten pellets of the same type were used. Each pellet was placed in 100 mL of PBS-B 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 the drug load of the pellet dissolved in PBS-B solution. The negative controls were pellets only containing the polymer and no drug.

RESULTS AND DISCUSSION

In Figure 1, we plot the fraction of drug released as a function of time. Since the mass of the drug in all pellets was identical (17 mg), the fraction of drug released is proportional to the mass of drug released. We see that all the nicotine was released after ~ 10 days, while

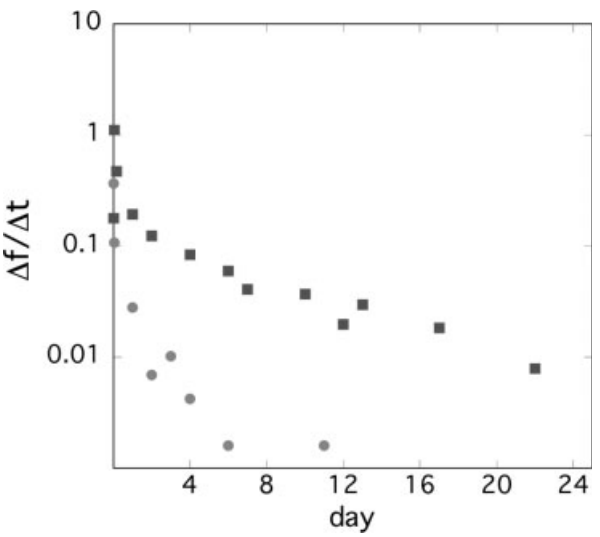

Figure 2 The rate of drug released, $\Delta f/\Delta t$, as a function of time. Symbols are as in Figure 1. $\Delta f/\Delta t$ is in units of 1/day. Since $f = 1$ is equivalent to 17 mg, $\Delta f/\Delta t = 1$ is equal to 17 mg/day. The error bars are not shown for clarity purposes. The average error for nicotine release rate is ± 0.035, and for caffeine ± 0.03.

the caffeine required more than 17 days for full release. This is more clearly illustrated in Figure 2, where we plot the rate of drug released per unit time. Both drugs have an initial, rapid rate of release, which decreases exponentially with time. However, while the rate of nicotine release decreases sharply, the rate of caffeine release decreases in a more moderate manner. It should be noted that, unlike some drug release systems, the initially high rate of release cannot be considered a ''burst'' arising from inhomogeneous drug distribution in drug carriers, but is due to the characteristic profile of drug release in such systems [see Eq. (1) below].

It is interesting to consider some of the other studies of the release of hydrophilic components from PCL matrices. Perez et al.[29] examined the short time release of a hydrophilic and a lipophilic drug from moderately high MW PCL (42,000 g/mol). Perez et al.[29] find that about 30–50% of initial drug loading was released within 2 h, followed by a regime where little or no release occurred. However, due to the short duration of their experiment (8 h) and their presentation (f vs. t), it is possible that slower release may take place over longer periods of time. Jackson et al.[30] studied the release of ribozyme from a low MW PCL (10,000 g/mol), finding that the release occurred over a period of 5–10 days. However, similarly to the Perez et al.[29] results, the maximal degree of ribozyme release was found[30] to be only 30–80% of the initial loading even after 50 days. Sharifpoor and Amsden[32] suggest that in PCL, the relatively rapid release initially is due to diffusion of the drug through the matrix. The remainder of the drug is immobilized, however, within crystalline domains and released only when the matrix degrades, a process that may take months.

In contrast to previous studies,[27–32] we find 100% release of either caffeine of nicotine within 10–20 days. Such complete release is possible, according to the Sharifpoor and Amsden[32] hypothesis, if the PCL matrix underwent enhanced degradation, thereby releasing the drug trapped in crystalline domains. Indeed, it has been shown that drug incorporation can either enhance or inhibit matrix degradation rates.[17–20,27] Thus, it is possible, in principle, that PCL containing 40% nicotine of caffeine may undergo significant degradation over such time scales. To determine whether any polymer degradation occurred over the period of the experiments, we weighed the pellets immediately after all of the drug was released (as determined by UV), and after drying in a vacuum for 8 days. We found no change in the weight of the pellets after drying for 3 days, suggesting that all water was removed within that period of time. The weight of the dry pellets after drying was 62 $\pm$ 4% of the original pellets, confirming that (1) all of the drug was indeed released, and (2) that no significant polymer degradation took place.

Our data clearly demonstrates that the 100% release within a period of $\sim$ 10–20 days is not due to matrix degradation. Thus, we conclude that, unlike previous studies, nicotine and caffeine were not trapped in PCL crystalline domains. This may be attributed to one of two scenarios: (1) differences in pellet formation (where our method suppresses crystallinity), or (2) differences in drug properties (our drugs disrupt crystalline domains or are not miscible in them). The former is unlikely, since our visual observation reveals no change—either swelling or collapse—in the pellet dimensions and geometry throughout the different stages of drug release, water diffusion into the matrix, and drying. This is surprising considering that the drug composes 40% (weight) of the pellets, and suggests that the polymer matrix contains some structural rigidity that cannot be attributed to amorphous fluid domains. This rigidity must be due to the presence of crystalline domains that form a sort of ''scaffold.'' This scaffold prevents the hydrophobic PCL from collapsing when the drug is released, thereby allowing water diffusion into the pellet. It also prevents the pellet collapse when the water is evaporated. Thus, we conclude that our drugs were excluded from the crystalline domains.

Several models have been developed for the release of drugs from nondegradable polymers, accounting for such features as drug binding to the matrix, nonuniform distribution of the drug, or the effect of swelling and water content on the rate of drug diffusion (see, for example, Refs. 17–20). However, we first test the expected release profile based on a classical, simple diffusion model.[33] In this approach, the drug is taken to be uniformly distributed in the pellet initially and the well-stirred solution is considered a perfect sink (namely, no film resistance to mass transfer in the buffer solution). The only release mechanism is that of drug diffusion through the matrix. The fraction of drug released, f, and the normalized rate of release, $\partial f/\partial t$, as a function of time t is[33]

$$f = 1 - \sum_{n=1}^{\infty} \frac{1}{n^2} e^{-Dn^2\pi^2 t/R^2} \tag{1a}$$

$$\frac{df}{dt} = \frac{\pi^2 D}{R^2} \sum_{n=1}^{\infty} e^{-Dn^2\pi^2 t/R^2} \tag{1b}$$

where D is the diffusion coefficient of the drug in the matrix and R the radius of the particle. Note that the fraction of drug released, at any given time, is found in this analysis to be independent of the initial loading, a function of the diffusion coefficient of the drug and the particle dimensions only. Also, it should be recalled that the dosage (mass/time) is

given by *df/dt* multiplied by the initial mass of drug in the pellet.

Fitting our drug release data to Eq. (1) yields an excellent agreement, as shown in Figure 1. Using the characteristic pellet size, 3 mm, for R in Eq. (1) results in diffusion coefficients of 5.06×10^{-8} cm^2/s for nicotine in our PCL matrix, and 1.4×10^{-8} cm^2/s for caffeine. In comparison, Yoon, et al.[28] find that the diffusion coefficient of water in a similar MW PCL (at 37°C) is of order 20×10^{-8}cm^2/s. The fact that the diffusion coefficients of nicotine and caffeine in PCL calculated by the single parameter fit are slower by factors of 4 and 14, respectively, when compared to water, is expected based on the relatively high MW of the two hydrophilic drugs (see Table II). However, it is interesting to note that MW is not the only determinant of the diffusion coefficient: Although the higher MW of the nicotine would suggest a slower diffusion rate than caffeine, the opposite is found.

The successful fit of the release data to the diffusion mechanism equation [Eq. (1)] clearly demonstrates that (a) the dominant mechanism of hydrophilic drug release from PCL is diffusion, and (b) that throughout the experiment the ''infinite sink'' limit (as ensured by keeping the solution concentration well below the drug solubility limit, and a high rate of mixing) was kept. Otherwise, we would expect an effective ''slowing down'' in the release as a function of time due to buildup of drug concentration in the solution. Therefore, the fact that the observed diffusion coefficient of caffeine is slower than nicotine cannot be attributed to its lower solubility is water (see Table II).

As discussed in the Introduction, drug delivery applications require that the drug release rate (which is proportional to *df/dt*) be within a given therapeutic window over a period of time. However, we find that the rate of hydrophilic drug release from of PCL is highly variable (Fig. 2), decreasing exponentially with time [Eq. (1)]. Therefore, constant dosage cannot be maintained.

The sharp decrease in the rate of drug release is due to the fact that, initially, the drug is present in the outer shell of the pellet, and thus has a very small distance to travel until leaching out of the matrix. This process depletes the drug concentration near the boundary with the solution, so that as time increases, so does the distance the drug needs to travel (from within the particle to the solution), as sketched in Figure 3. This trend may be circumvented by designing pellets where the concentration

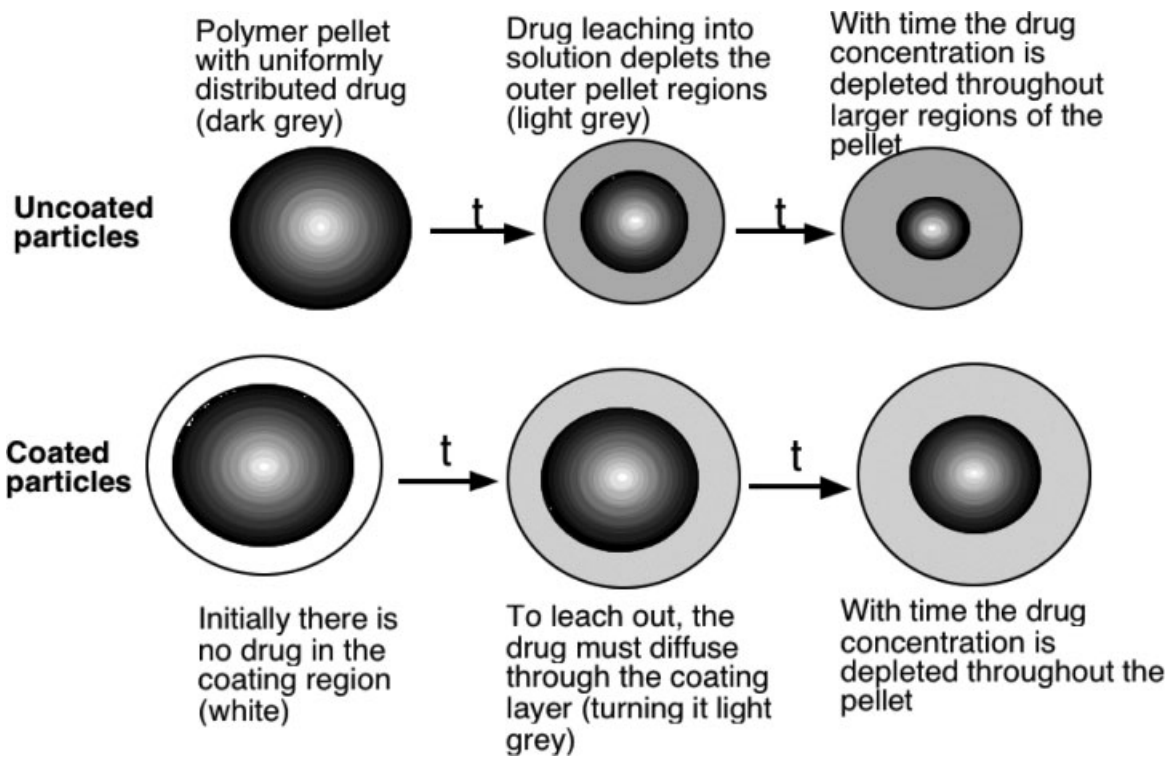

Figure 3 A sketch of drug release from a nondegrading polymer particle. Top: Uncoated particles. Initially (left), the drug (dark) is uniformly distributed in the particle. With time (middle), drug diffusion depletes the concentration from the region near the particle/solution interface. As time increases, the depleted region grows (right). Bottom: Coated particles. Initially, the drug is confined to the inner particle (left) and is excluded from the coating (clear). With time drug diffuses through the coating (middle), giving rise to a depleted region. As time increases, the depleted region grows (right), as in the uncoated particle.

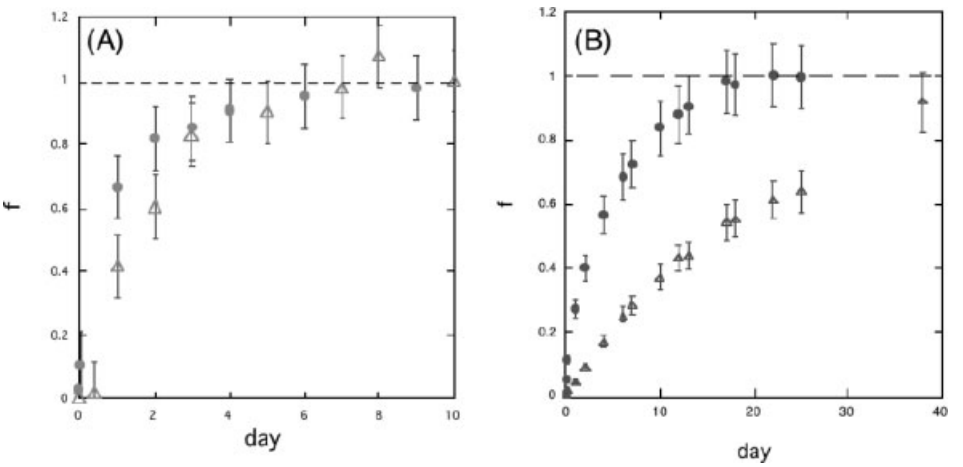

Figure 4 Effect of particle coating on the fraction of released drug. (A) Nicotine and (B) Caffeine. Full symbols denote the uncoated particles, open symbols the coated ones. We see that in nicotine, the coating does not significantly affect the time required to obtain complete release, which remains ~ 10 days. However, in the case of caffeine the coating significantly increases the time required for release, from ~ 17 days in the uncoated to more than 40 days in the coated system.

of drug is higher in the core and lower in the outer pellet regions. However, directly controlling the distribution of drug in a polymer matrix is a complex design issue.

A simpler method to achieve control over the distribution of drug in the polymeric matrix is by coating the drug-containing pellet in a drug-free polymer layer. This design would suppress the initial rapid rate, since the drug must diffuse through the drug-free layer (see Fig. 3) thereby causing a delay. The release rate increases with time, as more drugs diffuses through the coating. However, at some point in time the drug is redistributed throughout the entire pellet + coating, so that the rate of release decays exponentially.

In Figures 4 and 5, we plot the fraction of drug released and the rate of release, respectively, for nicotine and caffeine-containing, film-coated PCL pellets. We see that in the case of nicotine, the film does not significantly affect the time required to achieve maximal release, which remains similar for the coated and uncoated particles [Fig. 4(A)]. However, in the case of caffeine the coating seems to significantly extend the time required for complete release, from ~ 17 days to order 40 days or more [Fig. 4(B)]. Although the time required to obtain 100% release of nicotine is insensitive to the presence of coating, the presence of the coating affects the rate of nicotine release significantly. As shown in Figure 5(A), the release from the coated particles displays an initial delay when there is no drug release, followed by an increase in the rate of release. The rate peaks at ~ 1 day, decreasing thereafter, but in a much more moderate manner than the exponentially decaying profile of the uncoated particle. In caffeine, the release rate seems to follow a different profile, as shown in Figure 5(B). The rate of release remains nearly constant over a period of ~ 17 days, followed by a steady decrease in the release rate.

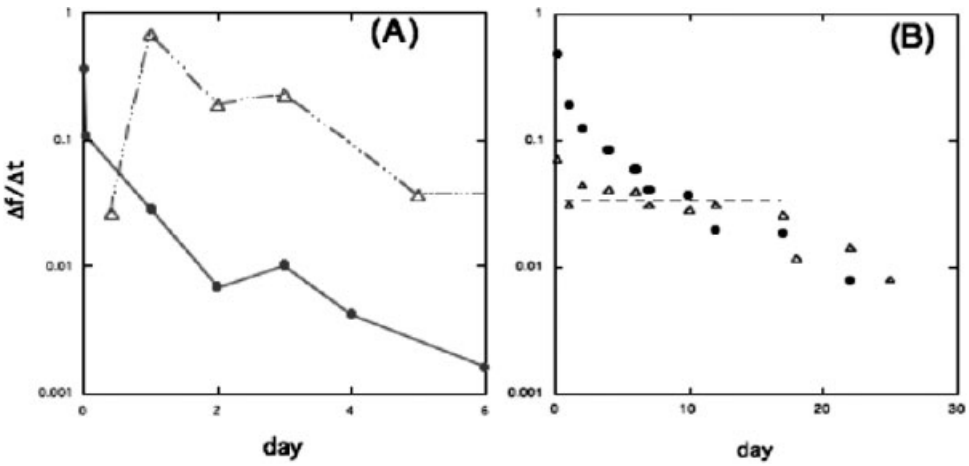

Figure 5 Effect of particle coating on the rate of released drugs. (A) Nicotine, and (B) Caffeine. Symbols are as in Figure 4. The lines in (A) are a guide only.

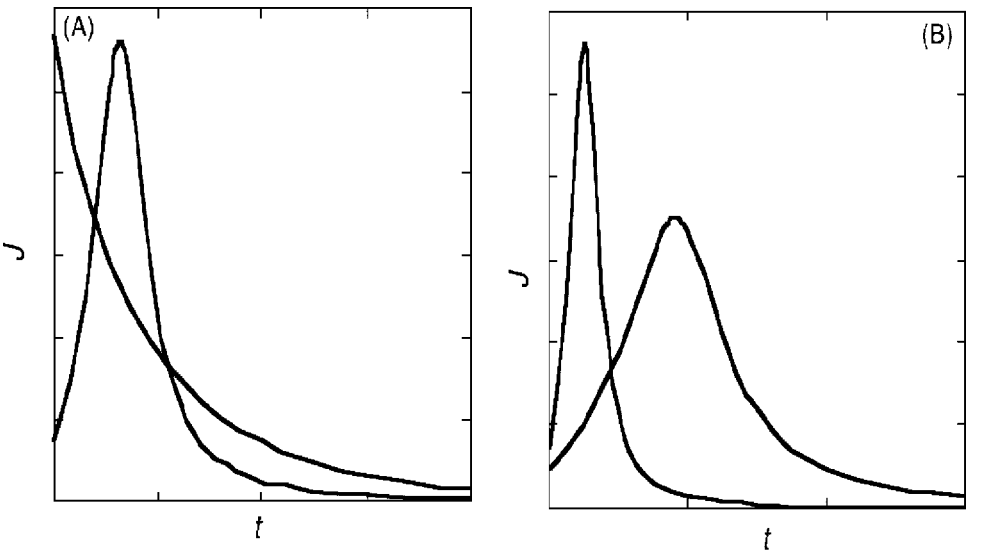

Figure 6 Effect of coating on the rate of drug release (per unit area), J, based on eq. (2). (A) Comparing coated and uncoated particles. The dark line denotes an uncoated particle, where the release rate decays exponentially. The light gray line describes a coated particle with a coating layer thickness that is ¼ the radius of the drug containing particle. (B) Effect of the diffusion coefficient on release rate from coated particles. The light gray line is as in A. The dark line described the rate of release for a particle with identical coating but where the diffusion coefficient of the drug is 3.5 times slower than that on the red line particle. This ratio is similar to the ratio of caffeine and nicotine diffusion rates.

To understand the role of drug-free polymer coating, we develop a diffusion model for a polymer film that initially contains a uniform concentration of drug, encapsulated in a polymer film that is initially polymer free. Note that we cannot use Eq. (1) for the drug-containing region here: Equation 1 assumes that the concentration of drug at the boundary between the particle and the solution is zero (infinite sink), a condition that does not hold for the boundary between the drug-containing and drug-free films. We therefore apply to this system a two-film model, where one film contains a uniform drug concentration and the other has no drug. The boundary conditions are a symmetry BC for the drug-containing particle core, and a sink (concentration equal to zero) for the coating/solution boundary. At the interface between the pellet and the coating we use the condition that the flux is constant (no accumulation at the boundary, since the polymer is the same on both sides of the interface). Also, since the polymer is the same in the coating and in the pellet, so are the diffusion coefficients of the drug in each region, and there is no partition coefficient at the interface. The result is an infinite series whose first term for the flux (rate of release, per unit particle surface area) is

$$J = -D\left.\frac{\partial C}{\partial r}\right|_{r=R} \approx -4C_0D\frac{4C_0De^{-D\pi^2t/R_p^2}\left(2+e^{D\pi^2t/l_c^2}\right)}{R_Pe^{D\pi^2t/R_p^2}\left(2+e^{D\pi^2t/l_c^2}\right)-4e^{D\pi^2t/l_c^2}} \quad (2)$$

Here R_p is the radius of the drug-loaded particle and l_c is the thickness of the coating. C_0 is the initial drug concentration, and D its diffusion coefficient in the polymer. Also, we assumed for simplicity that $R_c \gg l_c$.

In Figure 6(A), we plot the effect of coating film thickness on the rate of release (based on the full series solution). We see that if the coating is thin, the release rate profile resembles that of release from a simple, drug-loaded particle [Eq. (1)], decaying in an exponential manner with time. However, in systems with a finite coating thickness, the release profile displays a peak. This is as expected; initially, the drug must diffuse through the drug-free film leading to a delay and an increase in the flux. However, once the concentration in the core particle begins to deplete, the rate of release decreases. Indeed, this is the profile found for nicotine release from coated particles [Fig. 5(A)]. It is interesting to note that, as observed for nicotine, the overall time required for 100% release (determined by $J \rightarrow 0$) is similar for the uncoated and coated particles.

The magnitude of the peak in J, and the time at which it occurs, depend on the diffusion coefficient of the drug. As shown in Figure 6(B), in systems with rapid diffusion coefficient, the peak is higher and located at low t, while slower-diffusing drugs have a lower peak (that may be taken to be flat, to some extent) located at a longer time. This is in qualitative agreement with the release profile found for caffeine [Fig. 5(B)], although it is unclear why we do not observe an initial delay in this case.

CONCLUSIONS

In this article, we examine the release of two highly hydrophilic drugs, nicotine and caffeine, from PCL matrices. We find that the rate of drug release is dominated, in both cases, by the diffusion of the drugs through the PCL matrix. We do not find any evidence for matrix degradation. Achieving 100% release within 10–20 days suggests that no drugs were sequestered in crystalline matrix domains, possibly due to our mixing method or to specific drug characteristics. Applying a drug-free PCL coating to the particles changes the release rate, as defined by the amount of drug released per unit time: In the uncoated particles, the release rate decays exponentially with a time constant that depends on the diffusion coefficient of the drug in the polymer matrix. However, in coated particles the release rate exhibits a peak, whose location (time) and magnitude depends on the diffusion coefficient and the thickness of the coating. Thus, coating may be used to control the release rate and obtain a relatively constant rate over a period of time.

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