Desorption-Limited Mechanism of Release from Polymer Nanofibers

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This work examines the release of a model water-soluble compound from electrospun polymer nanofiber assemblies. Such release attracts attention in relation to biomedical applications, such as controlled drug delivery. It is also important for stem cell attachment and differentiation on biocompatible electrospun nanofiber scaffolds containing growth factors, which have been encapsulated by means of electrospinning. Typically, the release mechanism has been attributed to solid-state diffusion of the encapsulated compound from the fibers into the surrounding aqueous bath. Under this assumption, a 100% release of the encapsulated compound is expected in a certain (long) time. The present work focuses on certain cases where complete release does not happen, which suggests that solid-state diffusion may not be the primary mechanism at play. We show that in such cases the release rate can be explained by desorption of the embedded compound from nanofibers in the fibers or from the outer surface of the fibers in contact with the water bath. After release, the water-soluble compound rapidly diffuses in water, whereas the release rate is determined by the limiting desorption stage. A model system of Rhodamine 610 chloride fluorescent dye embedded in electrospun monolithic poly(methylmethacrylate) (PMMA) or poly(caprolactone) (PCL) nanofibers, in nanofibers electrospun from PMMA/PCL blends, or in core–shell PMMA/PCL nanofibers is studied. Both the experimental results and theory point at the abovementioned desorption-related mechanism, and the predicted characteristic time, release rate, and effective diffusion coefficient agree fairly well with the experimental data. A practically important outcome of this surface release mechanism is that only the compound on the fiber and pore surfaces can be released, whereas the material encapsulated in the bulk cannot be freed within the time scales characteristic of the present experiments (days to months). Consequently, in such cases, complete release is impossible. We also demonstrate how the release rate can be manipulated by the polymer content and molecular weight affecting nanoporosity and the desorption enthalpy, as well as by the nanofiber structure (monofilic fibers, fibers from polymer blends, and core–shell fibers). In particular, it is shown that, by manipulating the above parameters, release times from tens of hours to months can be attained.

I. Introduction

Critical advances in tissue engineering are expected from composite tissue constructs consisting of multiple cell types. In this context, differentiation of human mesenchymal stem cells (hMSCs) into specific cell lineages can be regulated by the release of appropriate hydrophilic growth factors from nanofiber mats serving as scaffolds for hMSCs. Polymer nanofibers have already been used as scaffolds for chondrocytes and hMSCs for cartilage tissue engineering1–4 however, attempts to understand the mechanism of growth factor release from such nanofibers have been sparse. The physical structure of native extracellular matrix (ECM) has nanoscale texture. The high surface-to-volume ratio of nanofibrous scaffolds and the nanoscale diameter of the fibers seem to provide favorable conditions for cell attachment and growth; cells have been shown to attach to and organize around fibers with diameters smaller than those of the cells.5,6 Other examples of release of hydrophilic compounds from nanofibers in water are related to drugs, such as tetracycline hydrochloride (TCH).7,8 Electrospinning9–14 is a unique process operating at room temperature to form polymer fibers in the diameter range of 102–104 nm. Electrospinning has a distinct feature size advantage over conventional methods of making fibers, such as melt, dry, or wet spinning,15–17 which produce fibers as small as ~105 nm in diameter. Moreover, the making of fibers with conventional techniques frequently involves elevated temperatures (in melt spinning, for example), which may be detrimental not only for the integrity of the polymer but also for the bioactivity of the embedded growth factors. Poly(caprolactone) (PCL), one of the polymers widely used in electrospinning, has been recently used to demonstrate the capability to seed and accommodate hMSCs and support multilineage differentiation.2,3,18 Electrospun nanofibers can be loaded with different admixture molecules and nanoparticles, such as specific proteins acting as growth factors determining the commitment of hMSCs and their differentiation.19,20

References

further differentiation into, for example, cartilage or bone. The rate of hMSC commitment and differentiation toward a specific lineage is determined by the release patterns of growth factors embedded in the electrospun nanoﬁber structures. Release rates of different molecular compounds from electrospun ﬁbers have been studied experimentally. Several groups have previously electrospun biocompatible polymer blends with solutions of proteins or growth factors, so that the latter compounds wind up embedded in the resulting ﬁbers. The growth factors used included human β-nerve growth factor, recombinant human platelet derived growth factor-bb (PDGF-bb), and BMP-2, although the release mechanisms of these compounds have not yet been fully elucidated. Drug and dye release from nanofibers was experimentally studied in several recent publications.

In all these works, nanofibers with encapsulated proteins, growth factors, drug, or dye were fabricated either via the standard electrospinning process (as monolithic ﬁbers) or via co-electrospinning (as core—shell ﬁbers). Release from monolithic nanofibers saturated at various levels including 30—40%, 40—60 wt %, 60%, and 80—90%,. Release rates of 80—90 wt % were achieved when the ﬁbers degraded during the release process. It was shown that the release process does not follow theoretical predictions based on the assumption of solid-state diffusion. The release from core—shell ﬁbers saturated at about 50—60% or 40—80%. Only one set of data for release from core—shell ﬁbers demonstrated nearly complete release, that is, about 90%. However, in that particular case, the drug-free shell totally degraded, thus causing the drug in the core to become fully exposed to the surrounding water. There are some other reports where drug release from core—shell nanofibers was driven by degradation of the carrier rather than by solid-state diffusion. Moreover, in ref 30, an additional polymer, poly(ethylene glycol) (PEG), was blended in the monolithic ﬁbers or shells (in core—shell ﬁbers) together with PCL. When such monolithic or core—shell nanofibers were subjected to the surrounding water, 80—100% release of the embedded proteins or growth factors was achieved when PEG was leached by water, thus creating porosity and in turn enhancing release.

Solid-state diffusion of small- and medium-size molecules inside polymers was studied using molecular dynamics simulations. The predicted values of the diffusion coefﬁcient were of the order of $10^{-6} \text{ to } 10^{-4} \text{ cm}^2/\text{s}$, which are by several orders of magnitude higher than the values expected in drug release from solid-state diffusion alone. The dramatic disagreement of such calculations with the experimental data demonstrated in ref 32 most probably stems from insufﬁcient information available to calculate the intermolecular forces. The inability of the solid-state diffusion theories to explain the data found in the release experiments was clearly recognized in ref 33, where it was argued that retardation due to dissolution of the admixture or to pore interconnectivity and tortuosity must be taken into account to explain the low values of the effective diffusion coefﬁcients and release of less than 100% at the end of very long experiments. The surface area/volume ratio in the experiments of ref 33 was relatively small, and the pore sizes were of the order of $10^{-4} \text{ to } 10^{-5} \text{ nm}$, which led the authors to the assumption that surface-related phenomena (e.g., desorption) could be neglected. This may not be the case when nanofiber mats are the carriers of a released admixture, since such mats have a dramatically higher surface-to-volume ratio. Moreover, nanofibers can accommodate nanoporosity, which should result in a still higher surface-to-volume ratio than is normally thought for nonporous materials.

It is worth mentioning that a vast amount of literature exists on adsorption and desorption in narrow pores and slits (e.g., the recent refs 34—36). These works typically employ numerical methods based on the grand canonical Monte Carlo simulations, molecular dynamics simulations, and continuum-like mesophase models accounting for intermolecular interactions. Their main goal is to predict adsorption/desorption isotherms or condensation patterns. They are not related directly to the release of a solid admixture embedded in a solid which is immersed in a liquid medium, even though they might be considered distinctly kindred to the questions related to controlled release.

The abovementioned studies reporting release saturation well below 100% suggest that solid-state diffusion may not be the leading mechanism of release in many cases. This idea is supported further in the present work by combining experiments and theoretical analysis. Desorption from the nanopore surfaces is put forward as the working release mechanism in such cases. The limiting desorption stage is accompanied by fast diffusion in water ﬁlling the nanopores or being in contact with smooth areas of the nanofiber surface. Based on this revised understanding, variations of polymer molecular weight and concentration in the electrospun solutions are proposed and demonstrated as parameters controlling the desorption process and thus the release rate.

Section II describes the materials used and the experimental methods employed. The experimental results are presented in section III. The physical mechanism of desorption-limited release is introduced in section IV, and the detailed theory is presented in section V. The theoretical predictions are compared with the experimental data and discussed in section VI. Concluding remarks are given in section VII.

II. Materials and Methods

Poly(methylmethacrylate) (PMMA, $M_w = 120, 350, \text{ and } 996 \text{ kDa}$) and poly(caprolactone) (PCL, $M_w = 80 \text{ kDa}$) polymers were purchased from Sigma-Aldrich. Rhodamine 610 chloride dye ($M_w = 479.02 \text{ Da}$), chosen as a model hydrophilic compound, was supplied by Exciton. All the solvents including dichloromethane (MC) and dimethylformamide (DMF) were obtained from Sigma-Aldrich. All of these materials were used without any further processing. A spectroﬂuorometer (Gemini Spectramax by Molecular Devices) was used in ﬂuorescence measurements to quantify the amount of dye present in a solution. Microplates with 24 and 96 wells (Fisher Scientiﬁc) were used for assay analysis.

Nanofibers were electrospun from three different samples of PMMA ($M_w = 120$, 350, and 996 kDa) at concentrations of 24%, 15%, and 15% (wt), respectively, in pure DMF and from PCL ($M_w = 80$ kDa) at concentrations of 11%, 13%, and 15% (wt) in 60/40 DMF/MC (wt). Rhodamine 610 dye and polymers were dissolved in pure DMF or DMF/MC. In 11% PCL solution, the dye content was 0.25 wt %, and in 13% and 15% PCL solutions it was 0.23 wt %. In PMMA (120 kDa) solution, the dye content was 2.34 wt %, in PMMA (350 kDa) solution it was 3.67 wt %, and in PMMA (996 kDa) solution it was 3.15 wt % (all relative to the polymer content). The relative dye concentrations in the PMMA solutions were higher than those in the PCL solutions, because it was found that the release from PMMA fibers is much slower than that from PCL fibers and the dye concentration had to be increased to guarantee a sufficient sensitivity in the experiments with fibers submerged in the release bath (water), as described below. The electrospinning and co-electrospinning setups were similar to those described previously.\(^{9,14,37–40}\) The electrospinning parameters are listed in Table 1. The temperature and relative humidity of the ambient environment were 21–25 °C and 19–23%, respectively. Positive polarity was attached to the needle issuing the polymer solutions. The resulting PCL nanofiber mats containing the dye were collected on a planar grounded electrode. PCL nanofibers in these mats had average cross-sectional diameters in the range 500–700 nm (Table 1) and were arranged on the electrode in a random orientation pattern. PMMA nanofibers with dye were electrospun on a grounded vertically rotating (1150 rpm) wheel collector\(^{37}\) with a metal ribbon over the wheel blade. The resulting PMMA fiber strips were oriented in the direction of the wheel rotation. The average cross-sectional PMMA fiber diameters were 550, 760, and 1750 nm for $M_w = 120$, 350, and 996 kDa, respectively. Nanofibers from PMMA/PCL blends and core–shell fibers were also electrospun on a grounded vertically rotating (1150 rpm) wheel collector.

The as-spun nanofibers were examined under a fluorescence microscope. The obtained red fluorescence images were converted to grayscale without modifying their intensity. The images clearly showed that the dye in the as-spun fibers was distributed uniformly and no dye clusters were visible.

Nanofiber mats and strips were cut in pieces suitable for analyzing dye release. The weight of each piece was determined to evaluate the initial dye mass from the corresponding loading. The PCL and PMMA mat and strip pieces were placed in compartments of a 24-well plate each with 1 mL of deionized water. The well plates were wrapped with aluminum foil to protect the embedded and released dye from degradation due to light, and proper measures were taken to minimize the effect of evaporation of the medium. The well plate was placed on a clinical rotator rotating at 100 rpm. Samples of 100 μL were taken at predetermined time intervals from each well and placed in a 96-well microplate to measure fluorescence, which is proportional to the amount of dye present in a well. All measurements were repeated three times to ensure repeatability.

Prior to the release experiments, the calibration curve for Rhodamine 610 dye was obtained. In subsequent release experiments, only the linear ascendant section of the calibration curve was used in converting the fluorescence intensity to the dye mass concentration.

### III. Experimental Results

The dye release profiles from three different samples of PCL fibers are shown in Figure 1. It is clearly seen that the release from these fibers fully saturates at about 67% for 11 wt % PCL, 50% for 13 wt % PCL, and 32% for 15 wt % PCL in the electrospun solution. A similar dependence of the released amount on the initial polymer concentration in the electrospun solution was reported for core–shell fibers.\(^5\) A possible explanation of

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**Table 1. Electrospinning Parameters and Average Diameters of Fibers**

**Electrospinning of Poly(methylmethacrylate) Nanofibers**

<table>
<thead>
<tr>
<th>no.</th>
<th>$M_w$ (kDa)</th>
<th>conc (%)</th>
<th>flow rate (mL/h)</th>
<th>DC voltage (kV)</th>
<th>electrode spacing (cm)</th>
<th>diameter of fibers (nm)$^a$</th>
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<td>15</td>
<td>0.3</td>
<td>14</td>
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**Electrospinning of Poly(caprolactone) (80 kDa) Nanofibers**

<table>
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<th>electrode spacing (cm)</th>
<th>diameter of fibers (nm)$^a$</th>
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</thead>
<tbody>
<tr>
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<td>1</td>
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<td>14</td>
<td>500</td>
</tr>
<tr>
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<td>1</td>
<td>13.5</td>
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<td>15</td>
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<td>13.5</td>
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**Electrospinning of PMMA/PCL Blends**

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<th>electrode spacing (cm)</th>
<th>diameter of fibers (nm)$^a$</th>
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<td>2</td>
<td>1/9</td>
<td>1</td>
<td>12</td>
<td>10</td>
<td>510</td>
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**Electrospinning of Core (PMMA)/Shell (PCL) Nanofibers**

<table>
<thead>
<tr>
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<th>$M_w$ of the core (kDa)</th>
<th>flow rate (mL/h)</th>
<th>electrode spacing (cm)</th>
<th>DC voltage (kV)</th>
<th>core diameter of fibers (nm)$^b$</th>
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<td>400–1000</td>
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<td>2</td>
<td>996</td>
<td>0.3</td>
<td>12</td>
<td>9</td>
<td>500–1000</td>
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</table>

$^a$ Standard deviations 5% or less. $^b$ The outer shell diameter of the core–shell fibers was about 4000 nm.

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the reduction of the released amount of dye at higher initial polymer concentrations is related to the trend that the fibers fabricated from more concentrated polymer solutions contain less nanoporosity (discussed below). Less dye embedded at the nanopore surfaces of an individual nanofiber then comes in contact with water in the well, thus reducing the amount of the released dye. This explanation is corroborated below by additional experimental data for PMMA nanofibers as well as theory. Note that, in the case of such a relatively low molecular weight polymer as PCL, the release is practically completed in about 90 h (Figure 1).

The release of Rhodamine 610 dye from PMMA nanofibers with three different molecular weights of (i) 120 kDa (24 wt % in solution), (ii) 350 kDa (15 wt % in solution), and (iii) 996 kDa (15 wt % in solution) is depicted in Figure 2. The data clearly indicate the strong effect of molecular weight on the release rate. The lowest molecular weight PMMA (120 kDa) could not be electrospun at 15% because of its low viscoelasticity, which did not allow spinnability. Therefore, it was electrospun at 24 wt %, and hence, the release rate from this sample was affected in this case not only by variation of the molecular weight but also by concentration, as compared to the other two PMMA samples (350 and 996 kDa, both at 15 wt %). From the results for PCL nanofibers (Figure 1), we know that an increase in polymer concentration should reduce the dye release rate. However, in Figure 2, the 120 kDa PMMA sample at 24 wt % revealed a much higher release rate compared to the other two PMMA samples, both electrospun at 15 wt %. Therefore, the effect of the molecular weight on release rate is dramatically stronger than the effect of initial polymer concentration. This could be attributed to the lower nanoporosity of nanofibers produced from higher molecular weight polymers, which decreases the overall desorption of dye molecules from nanofiber surfaces.

The nanoporosity of nanofibers deserves additional discussion. Some groups (e.g., ref 41) studied the surface porosity of polystyrene nanofibers electrospun from solutions in tetrahydrofuran (PS in THF) in humid air and reported the formation of surface pits at humidity levels higher than 25%. This porosity was attributed to the interaction of the water vapor with the polymer solution and was related to the breath figures (solvent-evaporative cooling, which triggers water condensation) and spinodal decomposition (polymer phase separation). The pit diameter increased with polymer molecular weight. As a result of this surface porosity, the surface area of the fibers increased by 30–65%, although no clear trend in the dependence of the area increase on polymer molecular weight was found. In the present work, however, all the fibers were electrospun in an arid environment with humidity of 19–23% where no surface porosity similar to that of ref 41 would be expected. As reported in the latter reference, on the backgrounds of the relatively large surface pits of the order of several hundreds of nanometers (micropores), numerous nanopores of the order of 10 nm (Figure 7 in ref 41) were visible, seemingly unrelated to the ambient humidity. These pores, as well as smaller ones, are the nanopores we consider relevant to the discussion of the results of the present work. Indeed, one should expect that these pores penetrate deep inside the nanofibers, most probably forming an interconnected network with a tremendous surface area much larger than the outer surface and diminishing in number as the molecular weight increases. The reasons for such expectations are the following. The experimental and theoretical results of ref 42 showed that solvent evaporation in electrospinning proceeds mostly via direct permeation of the polymeric matrix comprising the fiber. The process is accompanied by nanoporosity formation, and it should be initiated by the nucleation and bubbling of solvent vapor in the bulk of the polymer solution in the flying fiber. Resistance to such bubbling is provided by the solution viscosity. In concentrated polymeric systems, the viscosity η strongly increases with molecular weight at constant concentration, namely η ∝ $M_w^{3.4}$ (ref 43). In addition, at constant molecular weight, $η ∝ C^{0.4}$, where $C$ is the polymer concentration. Therefore, nucleation and opening of a pore in polymeric systems with higher molecular weights and initial polymer concentrations should be strongly suppressed by increased viscous resistance, similarly to polymer devolatilization. As a result, nanoporosity at higher molecular weights and initial polymer concentrations should be lower.

Vigorously evaporating solvents can cause the formation of hollow fibers and ribbons during the electrospinning process.\textsuperscript{40,45} This was not observed in the present work. Therefore, it is believed that solvent evaporation through the polymer bulk is not extremely vigorous and in all present cases the rate of nanoporosity development is dominated by the matrix viscosity and not by solvent composition.

Scanning electron microscopy (SEM) images of porosity visible on the surface or in a broken cross section of both monolithic (single-phase) electrospun fibers or core–shell co-electrospun fibers were published by several groups (e.g., refs 39 and 41). These images definitely confirm the presence of nanoporosity in the fibers; however, they do not allow estimates of the depth of penetration of the nanopores and their interconnectivity and tortuosity. In addition, these images lack the needed resolution to visualize nanopores of the order of several nanometers in diameter (which are probably the most prevalent nanopores). Therefore, the release rates from nanofibers, which shed light on the presence of nanoporosity and the physical processes taking place at the nanopore surfaces, are of immense value for improved understanding and interpretation of the real role of nanoporosity in many important applications.

In the present study, the nanopore diameters are much smaller than the fiber diameters (~10 nm versus several hundreds nm, respectively). Therefore, on the scale of a nanopore, the curvature of the fiber surface is practically not felt, and the fiber diameter itself has no or little direct effect on the release rate.

The release processes from the PMMA fibers shown in Figure 2 last for about 1400 h, whereas only 0.5–1.4% of the dye has been released. In comparison, PCL fibers released from 32% to 67% of the dye in Figure 1. The temptation to attribute the drastic difference in the release rates between PMMA and PCL to the molecular weight difference should be met with caution. Indeed, the molecular weight of PCL is 80 kDa, which is not much smaller than that of the first of the PMMA samples (120 kDa), whereas the difference in their release rates is much larger. It seems that not only the nanopore surface but also the chemical nature of the nanofiber material (in particular, its binding energy to dye molecules in the presence of water) is important. Before an explanation is attempted, some additional data illustrating the accelerated release by PCL is discussed below.

The observed dramatic difference in the release rates from PMMA and PCL nanofibers (even when their molecular weights are similar) leads to the attempt to control the release rate via electrospinning PMMA/PCL blends. Release profiles from mats electrospun from PMMA/PCL polymer blends are shown in Figure 3. The polymer blends were prepared by dissolving the two polymers in 20/80 wt % MC/DMF solvent. Two electrospun 12 wt % polymer blends contained either 1 part wt PMMA (120 kDa) and 9 parts wt PCL (80 kDa) with 0.35 wt % dye relative to the polymer content, or 1 part wt PMMA (120 kDa) and 1 part PCL (80 kDa) with 0.31 wt % dye relative to the polymer content. Polymer phase separation in the blends occurs in about 24 h after preparation. Therefore, to avoid phase separation, the blend solutions were electrospun immediately after their preparation. It is seen that the increase in the PMMA concentration dramatically decreases the release rate. The release data in Figure 3 clearly indicate that the nanofiber scaffold with a higher concentration of PMMA shows a much slower release compared to that of the lower concentration PMMA nanofiber mat. This confirms that the release rate could be indeed controlled to any desirable level, that is, from a few days to several months, by varying the PMMA/PCL ratio in the electrospun blends. No direct information is available on the physical distribution of the two polymers inside the fibers. Some observations under an optical microscope suggested the formation of fiber sections with a core–shell (PMMA/PCL) structure. However, release data discussed later (Figure 6) suggest that these were monolithic fibers and the polymers in them were mixed on the molecular level rather than forming a dispersed matrix of PMMA in PCL or a core–shell structure.

Both polymers, PCL and PMMA, are biocompatible,\textsuperscript{46,47} although PCL is more appropriate for some types of biological scaffolds. Therefore, it might be more desirable to wrap a PMMA core containing the agent to be released (dye in the present model case) with a PCL shell using core–shell co-electrospinning.\textsuperscript{14,38–40} Also, a combination of the two polymers in the core and shell can be used for controlling the release rate. In Figure 4, release profiles from two core–shell co-electrospun nanofiber mats are shown: (1) core: 24 wt % PMMA (120 kDa) with 0.138 wt % dye relative to the polymer, and shell: 12 wt % PCL (80 kDa) without dye and (2) core: 15 wt % PMMA (996 kDa) with 0.134 wt % dye relative to the polymer, and shell: 12 wt % PCL (80 kDa) without dye. The overall PMMA/PCL mass ratio in the dry core–shell fibers was about (1) 35/65 and (2) 23/77. The release profiles for cases (1) and (2) are located relatively close to each other; the error bars shown demonstrate that the two curves are distinguishable. It is seen that, in these core–shell fibers, the higher molecular weight polymer in case (2) guarantees a slower release rate at $t > 100$ h, even though the overall PCL content in this case is higher. Optical images of some of the largest core–shell fibers used in these experiments are shown in Figure 5. These images show a PMMA core of about 1080 nm in diameter and a PCL shell of about 4340 nm in diameter. A certain amount of blending of PMMA and PCL at the core–shell boundary in the fibers shown in Figure 5 can be expected, since both polymers are co-electrospun in miscible solvents (MC/DMF), which makes the interface less sharp.\textsuperscript{32} Therefore, it is of interest to compare the release profiles of the core–shell


Figure 4. Release profiles for two types of core–shell fibers: (1) 24 wt % PMMA (120 kDa) in the core (with 0.138 wt % dye relative to the polymer) and 12% PCL (80 kDa) in the shell (no dye), and (2) 15 wt % PMMA (996 kDa) in the core (with 0.134 wt % dye relative to the polymer) and 12% PCL (80 kDa) in the shell (no dye). Solvents: core, 60/40 DMF/acetone; shell, DMF. The overall PMMA/PCL mass ratio in the dry core–shell fibers was about 35/65 in (1), and 23/77 in (2).

Figure 5. Optical images of some of the largest (in diameter) PMMA/PCL core–shell nanofibers. On the left, two intersecting fibers are shown; on the right, a part of a single fiber featuring a tortuous core is shown.

Figure 6 shows that not only the polymer concentration (in the electrospun solution), the molecular weight, and the chemical nature of the dye-carrying polymer control the release rate, but also the chemical nature of the polymer in contact with water in the release bath affects the release. In particular, the presence of PCL at the outer surface accelerated the dye release in all cases studied: monolithic, blend, and core–shell fibers. Both PCL and PMMA are basically nonwettable (by water), hydrophobic polymers. However, the ability of PCL to promote the release process could be due to the fact that PCL absorbs water in its nanopores. Water sorption (hydration forces) makes desorption of dye molecules from the wetted surfaces of nanopores easier or even delivers water inside the PMMA nanopores in the core, which could explain the documented acceleration of the release process in the present case in distinction from ref 33, where microscopic protein particles embedded in a polymer matrix dissolved before being released via diffusion through macroscopically large pores filled with water. On the other hand, in the present case of release of the molecular dye dispersion from nanofiber mats, surface phenomena (e.g., desorption from the pore surface) neglected in ref 33 seem to be important and thus should be accounted for. We assume that the overall nanopore surface area in a fiber is significantly larger than the smooth outer surface area of the fiber, which is a plausible approximation for the morphology of electrospun nanofibers.

Consider a nanopore in a nanofiber as sketched in Figure 7. The pore has length \( L \) and cross-sectional radius \( b \). The cross section at \( x = 0 \) corresponds to the fiber surface and represents itself as an opening to a water-filled bath where the fiber is immersed. We assume that in most nanofibers the pores have openings to the outer surface of the fiber and thus are accessible to water from the outside, as the results of ref 42 suggest. A real nanopore can be tortuous rather than straight; however, this should have only a minor effect on the release process outlined below.

The time required for nanopore filling by water is negligibly short compared to the duration of the dye release process. Indeed, according to Washburn’s equation, the time needed to fill the nanopore is \( t_1 = \frac{2L^2}{\mu b \cos \theta} \), where \( \mu \) and \( b \) are the water viscosity and surface tension, respectively, and \( \theta \) is the contact angle (ref 51). Taking for the estimate \( L = 10^{-4} \) cm, \( b = 10^{-6} \) cm, \( \mu = 10^{-2} \) Pa s, \( \sigma = 10^2 \) g/cm/s, and \( \cos \theta \) of the order of 1, we find \( t_1 = 2 \) \( \mu \)s, which is much shorter than the duration of the release processes studied herein (100 h in Figure 1 or 1000 h in Figure 2). Therefore, we model nanopores as being filled with water from the very beginning of the release process. Assume distributed between the two components from the very beginning (curve 4). Therefore, the dye-free pure PCL shell cannot be considered as a diffusion barrier in the given case; on the contrary, it is seen to promote the release process.

IV. Physical Mechanism of Desorption-Limited Release

Rhodamine dye forms nonaggregated (isolated) molecular dispersions in such polymer matrices as PMMA (which was confirmed in the present work using individual fiber images obtained using an optical fluorescence microscope). Therefore, in the present case, dissolution of dye crystals prior to the desorption-driven release stage cannot delay or decelerate the release process. Also, in all present experiments, dye concentrations in polymer solutions were well below the solubility limit (if any). Therefore, the solubility cannot limit the release process in the present case in distinction from ref 33, where microscopic protein particles embedded in a polymer matrix dissolved before being released via diffusion through macroscopically large pores filled with water. On the other hand, in the present case of release of the molecular dye dispersion from nanofiber mats, surface phenomena (e.g., desorption from the pore surface) neglected in ref 33 seem to be important and thus should be accounted for. We assume that the overall nanopore surface area in a fiber is significantly larger than the smooth outer surface area of the fiber, which is a plausible approximation for the morphology of electrospun nanofibers.

Consider a nanopore in a nanofiber as sketched in Figure 7. The pore has length \( L \) and cross-sectional radius \( b \). The cross section at \( x = 0 \) corresponds to the fiber surface and represents itself as an opening to a water-filled bath where the fiber is immersed. We assume that in most nanofibers the pores have openings to the outer surface of the fiber and thus are accessible to water from the outside, as the results of ref 42 suggest. A real nanopore can be tortuous rather than straight; however, this should have only a minor effect on the release process outlined below.

The time required for nanopore filling by water is negligibly short compared to the duration of the dye release process. Indeed, according to Washburn’s equation, the time needed to fill the nanopore is \( t_1 = \frac{2L^2}{\mu b \cos \theta} \), where \( \mu \) and \( b \) are the water viscosity and surface tension, respectively, and \( \theta \) is the contact angle (ref 51). Taking for the estimate \( L = 10^{-4} \) cm, \( b = 10^{-6} \) cm, \( \mu = 10^{-2} \) Pa s, \( \sigma = 10^2 \) g/cm/s, and \( \cos \theta \) of the order of 1, we find \( t_1 = 2 \) \( \mu \)s, which is much shorter than the duration of the release processes studied herein (100 h in Figure 1 or 1000 h in Figure 2). Therefore, we model nanopores as being filled with water from the very beginning of the release process. Assume
Mechanism of Release from Polymer Nanofibers


Figure 6. Comparison of the release profiles from core–shell and blend fiber mats made from the same polymers (PMMA and PCL). Curves 1 and 4 correspond to the data of Figure 3 and show the results for monolithic nanofibers made of polymer blends: (1) 12 wt % polymer blend of PMMA/PCL (1/9 wt) with 0.31 wt % dye relative to the polymer content, and (4) 12 wt % polymer blend of PMMA/PCL (1/1 wt) with 0.31 wt % dye relative to the polymer content. Curves 2 and 3 correspond to the data of Figure 4 and show the results for core–shell fibers: (2) 24 wt % PMMA (120 kDa) in the core (with 0.138 wt % dye relative to the polymer) and 12 wt % PCL (80 kDa) in the shell (no dye), (3) 15 wt % PMMA (996 kDa) in the core (with 0.134 wt % dye relative to the polymer) and 12 wt % PCL (80 kDa) in the shell (no dye).

Figure 7. Schematic of a cylindrical pore (diameter 2b) inside a polymer matrix. The pore is open at x = 0 and closed at x = L.

that the nanopore surface layer contained dye embedded in the polymer matrix when the nanofiber was electrospun and the solvent evaporated. Assume a uniform surface density of dye at the beginning of the release process (t = 0) when the nanofiber was just filled with water. The initial dye surface density is then ρ_w = ρ_o ρ_d/ρ_p, where ρ_o is the average polymer fiber density, 2a is the molecular size, and M_p/M_o is the initial dye/polymer mass ratio in the nanofiber. The surface density of a polymer is ρ_p = ρ_o 2a > ρ_w. It is emphasized that the dimensionality of both ρ_o (and of the surface density of dye at t > 0, ρ_d) and ρ_p is g/cm². Dye desorption from the nanopore surface results in a certain initial bulk concentration of dye in water near the surface c_w at g/cm³ (subscript 0 denotes t = 0). This quantity is proportional to the specific initial dye concentration ρ_d/ρ_p at the nanopore surface, that is, c_w = k(T)ρ_d/ρ_p, where the factor k(T) is given by the Clapeyron-like (or the Arrhenius-like) dependence k(T) = k_0 exp(−E/RT) with the pre-exponential k_0 having the dimensionality g/cm³, E being the desorption enthalpy (or the activation energy), R being the universal gas constant, and T being the absolute temperature. Obviously, at t > 0, a similar expression, c_w = k(T)ρ_d/ρ_p, holds with ρ_d < ρ_0. Since the dye is assumed to be water-soluble (a good model of watersoluble growth factors or drugs), its molecules diffuse in water with a diffusion coefficient D. The release rate from the nanopore is estimated by the mass flux through the opening at x = 0 as J = D c_w d x/L. The total mass of dye to be released is estimated as M = ρ_w L b, since for narrow nanopores with L ≫ b the dye mass at the pore end at x = L is negligibly small compared to that of the lateral surface. In the light of the experimental results described in the previous section, we assume that dye can be released only from the surface layer of the polymer, whereas dye “buried” in the polymer bulk will not be released at all. The characteristic time of the release process is τ_r = GL/L D_eff, where the effective diffusion coefficient is D_eff = D c_w b/ρ_o. Take for the estimate the following realistic values of the parameters: k_0 = 10⁻³ g/cm⁴, ρ_o = 1 g/cm³, b = 10⁻⁶ cm, 2a = 10⁻⁸ cm, E = 52.7 kJ/mol, T = 300 K, and D = 10⁻⁵ cm²/s. Then, D_eff = 10⁻¹⁵ cm²/s. The fact that the value of D_eff is so small compared to the diffusion coefficient of dye in water D is due to the fact that the release process has two stages. The first stage, dye desorption from the nanopore wall, is the limiting stage, whereas the second stage, dye diffusion in water, is relatively fast. The rate of the whole process is dictated by the rate of the limiting stage, and that is the reason for the fact that D_eff/D ≪ 1. For a typical nanopore, L = 10⁻⁴ cm (a tortuous nanopore of that size could be easily accommodated in a typical nanofiber of a cross-sectional diameter of 100 nm and length of several centimeters). Then, τ_r ≈ 10⁷ s, which is 2780 h. This value is of the order of magnitude of a typical duration of the release processes (including some of those studied in the experimental section of the present work). Note that theories of release based on the assumption of solid-state diffusion would attribute D_eff to the solid-state diffusion, since to describe the duration of the experimentally measured process one needs a diffusion coefficient much less than that in water (D = 10⁻⁵ cm²/s). These theories, however, cannot explain the release saturation well below 100% found in many cases. The present approach does provide a detailed physically plausible mechanism of controlled release. It relates D_eff to the basic physical parameters. The present desorption-limited model of release also explains saturation of the release process at levels well below 100% reported in a number of works including the present one and not explained before.

V. Theoretical Analysis

Based on the pore model outlined in the previous section, consider in detail the release process. It is emphasized that the situation we describe resembles to some extent a preparative chromatography (sorption) problem, albeit being totally different from it. The diffusion of dye in water filling the nanopore is described by the following dimensionless equation


\[(52)\text{Ritger, P. L.; Peppas, N. A. J. Controlled Release 1987, 5, 23–36.}\]


\[(57)\text{Guiochon, G.; Felinger, A.; Shirazi, D. G.; Catu, A. M. Fundamentals of Preparative and Nonlinear Chromatography; Elsevier: Amsterdam, 2006.}\]

\[(58)\text{Tikhonov, A. N.; Samarski, A. A. Equations of Mathematical Physics; Dover Publications: New York, 1990.}\]
\[
\frac{D_{\text{eff}} \partial c}{D \partial t} = \frac{\partial^2 c}{\partial x^2} + \frac{1}{r} \frac{\partial}{\partial r} \left( \frac{\partial c}{\partial r} \right) \tag{1}
\]

where \(c\) is the dye concentration in water rendered dimensionless by \(\rho_p\), \(x\) is the axial coordinate in the nanopore rendered dimensionless by its length \(L \) (\(x = 0\) at the pore open exit, \(x = 1\) at the pore end, Figure 7), \(r\) is the radial coordinate in the pore rendered dimensionless by \(L\), and \(t\) is the time rendered dimensionless by the estimated characteristic time of the release process \(\tau_r = L^2 / D_{\text{eff}}\). Since \(D_{\text{eff}} / D \ll 1\), the left-hand side in eq (1) can be neglected and the dye concentration field in the nanopore becomes quasi-steady. The first boundary condition to be enforced is \(c < \infty \) at \(t = 0\). The other boundary and initial conditions will be discussed below. As a result, the quasi-steady concentration field of dye in the nanopore is given by

\[
c(x,r,t) = \frac{A_0'(t)}{2} + B_0'(t)x + \sum_{n=1}^{\infty} I_n(\lambda_n r)[A_n'(t) \cos \lambda_n x + B_n'(t) \sin \lambda_n x] \tag{2}
\]

where we expect a discrete eigenvalue spectrum \(\lambda_n\), since the problem is solved on the finite interval \(0 \leq x \leq 1\) and \(I_n(\cdot)\) is the modified Bessel function. The coefficients \(A_n'\) and \(B_n'\) for \(n \geq 0\) will be found from other conditions discussed below.

The surface concentration of dye at the nanopore surface is governed by the following dimensionless mass balance

\[
\frac{\partial \rho_{\text{ad}}}{\partial t} = - \frac{D_{\text{eff}}}{L^2 a} \frac{\partial c}{\partial r} \bigg|_{r=b/L} \tag{3}
\]

where \(\rho_{\text{ad}}\) is rendered dimensionless by \(\rho_p 2a\). Also, due to the desorption law,

\[
c(1,b/L,t) = \frac{d}{dt} \rho_{\text{ad}} \tag{4}
\]

where the factor \(f\) is given by \(f = (k_d / \rho_p) \exp(-E/RT)\). Equations 3 and 4 form the second boundary condition imposed on the dye concentration field (eq 2) in the nanopore. Combining eqs 3 and 4 and using eq 2, we find

\[
\frac{1}{2} \frac{dA_0'}{dt} + \frac{dB_0'}{dt} x + \sum_{n=1}^{\infty} I_n(\lambda_n b/L)[\frac{dA_n'}{dt} \cos \lambda_n x + \frac{dB_n'}{dt} \sin \lambda_n x] =
\]

\[
- \frac{D_{\text{eff}}}{L^2 a} \lambda_n I_n(\lambda_n b/L)[A_n' \cos \lambda_n x + B_n' \sin \lambda_n x] \tag{5}
\]

Equation 5 shows that the coefficients \(A_n'\) and \(B_n'\) do not depend on time, whereas the other coefficients can be found from the following equations

\[
\frac{dK_n}{dt} = - \frac{D_{\text{eff}}}{L^2 a} \lambda_n I_n(\lambda_n b/L) K_n \tag{6}
\]

where \(K_n\) is either \(A_n'\) or \(B_n'\) \((n \geq 1)\). It is clear that all the modes with large values of \(\lambda_n\) will vanish almost immediately according to eq 6. Also, \(b/L \ll 1\) in the present case. Therefore, we have \(\lambda_n b/L \ll 1\), and thus, \(I_n(\lambda_n b/L) \approx \lambda_n b/2L\), whereas \(I_0(\lambda_n b/L) \approx 1\). Equation 6 then takes the form

\[
\frac{dK_n}{dt} = - \frac{D_{\text{eff}}}{L^2 a} \lambda_n^2 K_n \tag{7}
\]

Note that \(\tau_r = L^2 / |D_{\text{eff}}| = L^2 / [D_{\text{eff}} \rho_p (\rho_{\text{ad}})]\). Also, from eq 4, \(c_{\text{ad}} = f_\rho_{\text{ad}} / 2a\) (dimensional). Therefore, \(D_{\text{eff}} / D = 1\), and the integration of eq 7 yields \(K_n = K_{n0} \exp(-\lambda_n^2 t/2)\). The result for the coefficient \(K_n\) clearly shows that the evolution in time follows the \(\exp(-\text{const} \ t)\) law (with the constant being of the order of \(1\)), where \(t\) is rendered dimensionless by \(\tau_r = L^2 / |D_{\text{eff}}| \gg \tau_{\text{D}}\), which is determined by the rate-limiting stage of dye desorption. The initial values of the coefficients \(K_{n0}\) (either \(A_{n0}'\) or \(B_{n0}'\)) are determined by the initial distribution of the dye surface concentration over the nanopore. Therefore, the initial surface density of dye at \(t = 0\) is given by the Fourier series

\[
\rho_{\text{ad}}(0) = \frac{1}{2\pi} \int_0^{\pi} \sum_{n=1}^{\infty} \left[ A_{n0} \cos \frac{n\pi x}{L} + B_{n0} \sin \frac{n\pi x}{L} \right] \ (8)
\]

where the coefficients, in fact, also appear in the distribution of \(c_{\text{ad}}\) due to eq 4.

The distribution (eq 8) should not be uniform even though dye might be uniformly distributed at the moment when the fiber had been formed. Indeed, immediately (as compared to the release time scale \(\tau_r\) after the nanopore is filled with water), the dye distribution along the surface should accommodate a certain profile with \(\rho_{\text{ad}} = 0\) at \(x = 0\), that is, at the pore exit, where the initial mass flux is effectively infinite (since in the bath \(c = 0\) due to its very large size compared to that of the nanopore). This means that all the coefficients in eq 8 should be zero, except \(B_{n0}' = A_{n0}' = 0\) for \(n = 1, 5, 9, \ldots\). Also, according to eqs 2, 4, and 8, \(A_n' = A_{n0}' = B_{n0}' = 0\), and \(\lambda_n = \pi n / 2\). Therefore, according to eqs 2 and 4, and \(t > 0\) for \(0 \leq x \leq 1\)

\[
\rho_{\text{ad}} = \frac{1}{2\pi} \int_0^{\pi} \sum_{n=1}^{\infty} B_{n0} \exp(-\pi^2 n^2 t/8) \sin(n\pi x/2) \ (9)
\]

Obviously, the modes with \(n > 1\) vanish very rapidly, and the surface density profile of the dye will evolve according to the following dimensional formula

\[
\rho_{\text{ad}} = \rho_{\text{ad0}} \exp\left(-\frac{\pi^2 t}{8 \tau_r}\right) \sin\left(\frac{\pi x}{2L}\right) \ (10)
\]

where we take \(B_{10} = \rho_{\text{ad0}} = \rho_p 2a M_{\text{ad0}} / M_p\). It is interesting to note that, in parallel, via eq 2, we have \(\partial c / \partial x |_{r=b/L} = 0\) which means that we chose the eigenfunctions which do not accommodate dye release from the nanopore bottom. This is immaterial anyway, since the release from the bottom is negligibly small compared to the release from the lateral surface due to the condition \(b/L \ll 1\). In the general case, appropriate eigenfunctions in eq 8 could always be chosen to accommodate dye release at the nanopore bottom \(x = L\).

Equation 10 allows calculation of the mass of dye \(G\) having been released from the nanofibrous material

\[
\frac{G_r}{M_{\text{ad0}}} = \alpha \left[ 1 - \exp\left(-\frac{\pi^2 t}{8 \tau_r}\right) \right] \ (11)
\]

where the nanoporosity factor \(\alpha = M_{\text{ad0}} / (M_{\text{ad0}} + M_{\text{bd0}}) \ll 1\), with \(M_{\text{ad0}}\) and \(M_{\text{bd0}}\) being the initial amount of dye at the nanofiber surfaces (in particular, at the nanopore surfaces) and the initial amount of dye embedded in the fiber bulk, respectively; the total initial amount of dye in the fiber \(M_{\text{ad0}} = M_{\text{ad0}} + M_{\text{bd0}}\). According to eq 11, the release process will saturate at \(\% \) dye release =
α100%, which is less than 100%. The nanoporosity factor α appearing in eq 11 is affected by the nanopore surface area, and thus, it should depend on both the polymer concentration in the electrospun solution and polymer molecular weight. On the contrary, the characteristic time τ_eff depends only on the polymer density ρ_p and the desorption process parameters k_0 and E, which characterize the intermolecular forces binding dye molecules to the polymer surface in the presence of water. Therefore, τ_eff, k_0, and E should be essentially insensitive to the polymer concentration and molecular weight. They should manifest only the chemical nature of the polymer–dye interactions responsible for sorption–desorption processes in the presence of water.

VI. Discussion

Comparison of eq 11 with the experimental data from Figures 1–4 and 6 allows one to establish the parameters of the dye desorption process for different polymers in water and, in particular, to estimate the desorption enthalpy (or the activation energy) E. Two examples of such comparison are shown in Figures 8 and 9.

When the value of τ_eff is established by comparing the experimental data to eq 11 as in Figures 8 and 9, the value of D_eff is found as D_eff = L^2/τ_eff. The value of L was taken as 1000 nm. The values of τ_eff and D_eff obtained are listed in Table 2. The values of τ_eff and D_eff appear to be essentially insensitive to polymer concentration variations among the PCL samples and to polymer molecular weight variations among the PMMA samples. The factor k(T) is then found according to the theoretical relation k(T) = ρ_p 2\alpha D_eff(bD) with the following values of α, b, and D: 2\alpha = 10^{-8} cm, b = 10 nm, and D = 10^{-3} cm^2/s. The values of the polymer density ρ_p for the polymers used and the corresponding values of k(T) are listed in Table 2. From the Clapeyron-like desorption law, the desorption enthalpy E is found as E = −RT ln[k(T)/k_0] with the value of the pre-exponential k_0 taken as k_0 = 10^{-3} g/cm^3 and T = 300 K. The values of the desorption enthalpy E found using this procedure for pure PCL and PMMA nanofibers are also listed in Table 2. It is emphasized that for all three PCL nanofiber samples with different polymer concentrations the value of E is ~37 kJ/mol, whereas for all three PMMA samples with different molecular weights it is ~45 kJ/mol. This manifests that dye desorption from PCL is much easier than that from PMMA. It also manifests that the desorption enthalpy is a function of only intermolecular forces acting in a polymer–dye system in the presence of water, and thus it is independent of polymer concentration or molecular weight. It is emphasized that if dye dissolution were the limiting mechanism of the release process as in ref 33, the release parameters (e.g., E) should be characteristic of the dye alone and should not differ between the polymers. Therefore, different values of E for PCL and PMMA releasing the same Rhodamine 610 dye support that desorption of molecularly dispersed dye from the polymer matrices rather than dye dissolution is the rate-controlling process.

The values of the nanoporosity factor α listed in Table 2 appear to be sensitive to polymer concentration and molecular weight variation. These parameters determine the sample nanoporosity and thus the ultimate release value characterized by α.

It was found that more rigorous shaking on the clinical rotator and a higher overall porosity of the samples (a larger interfiber spacing in the samples) also facilitated dye release, since they enhance water penetration into nanofiber nanopores as well as introduce a convective component which makes desorption easier. The latter is reminiscent of the enhancement of mechanical degradation of polymer macromolecules by stretching, which effectively reduces the activation energy for polymer scission.59–64 Therefore, the values of E in Table 2, in fact, incorporate the effect of convection (resulting from shaking) on the desorption process. This is probably the reason which makes E in Table 2 lower than the value of E = 52.7 kJ/mol used for the estimates in section IV.

The theory described in the previous sections was developed for pure polymers and not for polymer blends or core–shell structures (which might blend near the core–shell interface or

feature individual nanopores penetrating the core and shell together). Therefore, in principle, the theory cannot be directly applied to monolithic nanofibers from polymer blends or core−shell fibers without further generalization. However, it is tempting to find a first estimate of an effective desorption enthalpy in such complex cases by applying the same procedure to the analysis of the corresponding experimental data. The results for E in such complex cases are also presented in Table 2 for comparison. It is instructive to see that, in cases with slower release, the values of E are always higher, which manifests the desorption stage as the limiting one in the release process. To this end, this phenomenological observation points at a possible generalization of the theory based on the same physicochemical principles to more complicated cases of the blend and core−shell fibers.

It is of interest to estimate whether the fiber collection conditions could have had any effect on the nanopore surface area and thus on the dye release rate in the given experiments. Indeed, the PCL nanofiber mats were collected on a planar grounded electrode, whereas all other fibers were collected on a grounded vertically rotating (1150 rpm) wheel collector with a metal ribbon mounted over the wheel blade. The wheel radius Ra was 7.5 cm, and the linear velocity at its edge was about 9 m/s. This velocity is close to the typical velocity values in the electrospun jets, and due to this fact a fast stretching of the jet by the wheel in this case does not happen and significant stress-hardening of individual nanofibers was not observed. To estimate the effect of fiber stretching by the wheel on the surface area of nanopores, consider uniaxial elongation of a fiber with a stretching ratio λ. It is easy to show that the surface area of a nanopore inclined by an angle θ to the stretching axis changes by the factor of (λ sin² θ + λ⁻² cos² θ)⁻¹/₂ sin² θ + λ² cos² θ)⁻¹/₂. In particular, the axially oriented pores (θ = 0°) will experience a decrease of their surface area by the factor of λ⁻¹/₂, whereas the radially oriented pores (θ = 90°) will experience a decrease in their surface area by the factor of λ⁻¹/₂. The largest value of λ in the additional stretching due to the rotating wheel is given by λmax = [(Ra/H) + 1]² − (Ra/H)²)½, where H is the distance from the nozzle to the wheel top edge. In the present case, Ra = 7.5 cm, H = 12 cm, and λmax = 1.5. Therefore, the surface area of the axially oriented pores will increase by the factor of 1.22, whereas the surface area of the radially oriented pores will decrease by the factor of 0.9. For the pores with the intermediate orientation, the largest increase of the surface area is of about 1.25. All these values are close to 1. Therefore, the variation of the pore surface area due to the additional stretching by the wheel is insignificant, and the drastic difference between the release rates from the PCL fibers (electrospun on the grounded plate) and the PMMA ones (electrospun on the wheel) is unaffected by the wheel stretching.

<table>
<thead>
<tr>
<th>Fiber Systems Studied</th>
<th>τ (h)</th>
<th>Deq (cm²/s)</th>
<th>ρp (g/cm³)</th>
<th>k(T) (g/cm³)</th>
<th>E (kJ/mol)</th>
<th>α</th>
</tr>
</thead>
<tbody>
<tr>
<td>11% PCL</td>
<td>11.86</td>
<td>2.34 × 10⁻¹³</td>
<td>1.14</td>
<td>2.67 × 10⁻¹⁰</td>
<td>37.752</td>
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<td>1.14</td>
<td>3.08 × 10⁻¹⁰</td>
<td>37.396</td>
<td>0.496</td>
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<td>37.264</td>
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</tr>
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<td>PMMA (Mw = 120 kDa)</td>
<td>308.43</td>
<td>9.01 × 10⁻¹⁵</td>
<td>1.18</td>
<td>1.06 × 10⁻¹¹</td>
<td>45.703</td>
<td>0.0144</td>
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<td>PMMA (Mw = 350 kDa)</td>
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<td>1.25 × 10⁻¹¹</td>
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<td>PMMA (Mw = 996 kDa)</td>
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<td>1.13 × 10⁻¹⁴</td>
<td>1.18</td>
<td>1.33 × 10⁻¹¹</td>
<td>45.237</td>
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<td>PMMA/PCL blend (1/9 wt)</td>
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<td>3.37 × 10⁻¹¹</td>
<td>42.918</td>
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<td>PMMA/PCL blend (1/1 wt)</td>
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<td>7.70 × 10⁻¹²</td>
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<td>core−shell PMMA (350 kDa)/PCL</td>
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<td>3.64 × 10⁻¹¹</td>
<td>42.725</td>
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<td>core−shell PMMA (996 kDa)/PCL</td>
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<td>1.16</td>
<td>4.42 × 10⁻¹¹</td>
<td>42.236</td>
<td>0.203</td>
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</table>

VII. Concluding Remarks

The present experiments showed that 100% release of dye encapsulated in polymer nanofibers is not attained in the case of the effectively nondegradable (on the time scales of the present experiments) PCL and PMMA nanofibers (PCL degradation takes about 2 years). The release process is hindered in nanofibers formed from more concentrated polymer solutions and in polymers with higher molecular weights. In both cases, it is believed that denser nanofibers with reduced nanoporosity are formed. These findings hint that the primary release mechanism in such cases may not be related to solid-state diffusion of the dye in the polymer matrix. Instead, desorption from the nanopore surfaces is put forward as the rate-limiting stage of the dye release mechanism from these nanofiber samples. The dye release is subsequently followed by fast diffusion in water, which fills the nanofibers. This two-stage release process is fully substantiated by the proposed theory and corroborated by the present experimental data. In particular, the desorption enthalpy E and nanoporosity factor α for PCL and PMMA of different concentrations and molecular weights were determined. It was shown that the values of E depend only on polymer−dye intermolecular interactions in the presence of water and are insensitive to the polymer concentration in the electrospun solution or the polymer molecular weight. The result that for the same dye the value of E differed for different polymer matrices is consistent with the hypothesis that the limiting stage is desorption characteristic of molecular dye dispersions in polymer matrices, rather than dissolution of the admixture agglomerates studied earlier. It was also shown that the values of the nanoporosity factor α are determined by polymer concentration in the electrospun solution and polymer molecular weight, both of which are responsible for nanoporosity. The duration of the release process is fully controlled by the value of the desorption enthalpy E, whereas the ultimate release level is controlled by α. Based on this understanding, variations of polymer molecular weight and concentration in the electrospun solutions (using different polymers, their blends, or core−shell structures) are proposed and demonstrated as tools to control nanofiber nanoporosity and the dye desorption process, and ultimately the release rate. The pessimistic conclusion that the desorption-limited release mechanism does not allow complete release of the embedded compound (on practical time scales) is accompanied by the optimistic view that nanofibers could be very good carriers for drugs, proteins, and growth factors, since they have a very large specific surface area and thus can facilitate the highest possible release.

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