Membrane-encased polymer millirods for sustained release of 5-fluorouracil

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Received 10 November 2001; revised 26 November 2001; accepted 26 November 2001

Abstract: This article describes the design and development of a novel membrane-encased polymer millirod for the sustained release of an anticancer drug, 5-fluorouracil (5-FU). The millirod consists of two functional compartments: (1) an inner 5-FU-loaded monolithic millirod as the drug depot, and (2) an outer NaCl-impregnated polymer membrane to control the release rate of 5-FU. The inner millirod is fabricated by a compression-heat molding procedure to permit the entrapment of 5-FU particles in the poly(D,L-lactide-*co*-glycolide) (PLGA) matrix. The drug loading density is controlled at 30 w/w% to achieve a burst release of 5-FU (>90% of the drug are released within 48 h) from the monolithic millirod. The NaCl-impregnated PLGA membrane is generated by solvent casting and is then wrapped over the monolithic millirod to produce the membrane-encased millirod. Scanning electron microscopy shows that dissolution of NaCl particles produces a semipermeable polymer membrane to provide a sustained release of 5-FU. The membrane thickness and the density of NaCl particles inside the membrane are useful parameters to control the release kinetics of 5-FU. Under the experimental conditions in this study, sustained release of 5-FU [rates between 0.1 and 0.4 mg/(day · cm of millirod)] is achieved for 2 to 5 weeks in phosphate-buffered saline (pH 7.4) at 37°C. Results from this study demonstrate that membrane-encased polymer millirods provide controllable sustained release kinetics for applications in intratumoral drug delivery. © 2002 Wiley Periodicals, Inc. J Biomed Mater Res 61: 203–211, 2002

Key words: controlled release drug delivery; poly(D,L-lactide-*co*-glycolide); 5-fluorouracil; intratumoral drug delivery

INTRODUCTION

Liver cancer is one of the most lethal forms of cancer. Current treatment of liver cancer includes surgical resection, systemic or regional chemotherapy, arterial embolization, cryotherapy and radiation therapy.[1] Although surgical resection has been considered the potentially curative option, only a small number of patients with hepatic tumors are surgical candidates due to factors such as age and poor general health. The large number of unresectable tumor cases demonstrates the necessity to develop a minimally invasive technique for the local tumor destruction. Recent studies have shown that image-guided radiofrequency (RF) thermal ablation provides an effective, minimally invasive method to treat malignant hepatic tumors.[2–5] As a percutaneous procedure, RF ablation is carried out under image guidance to place a needle electrode directly inside the tumor and introduce heat to destroy the tumor tissue. This procedure only requires local anesthesia, and although patients stay overnight at the hospital, it potentially can be an outpatient procedure. Current studies have shown, however, that tumor recurrence frequently occurs at the ablation boundary due to the inability to achieve a sufficient therapeutic margin in the hepatic parenchyma adjacent to the treated tumors.[4–7] The abundant blood flow acts as a heat sump, and consequently, the cancer cells at the normal liver–tumor tissue boundary are difficult to be destroyed with RF ablation alone. The long-term goal of our research is to develop a local drug therapy following RF ablation to deliver anticancer drugs directly to the ablated tumor tissues to eliminate the remaining viable cancer cells and prevent tumor recurrence. Compared to systemic chemotherapy, this intratumoral drug delivery approach can potentially improve the clinical efficacy of drugs while minimizing their undesirable systemic toxic effects.

We conceptualize the design of a cylindrical millirod (diameter: 1.6 mm, length: 10 mm) as a drug delivery device for intratumoral drug delivery applications. This geometry permits the direct implantation of the millirod inside the tumor tissues by a modified

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Contract grant sponsor: Whitaker Foundation; contract grant number: RG-99-0342

14-gauge tissue biopsy needle under image-guided procedures. In a previous publication, we reported the fabrication of polymer millirods from poly(D,L-lactide-*co*-glycolide) (PLGA) polymer using a compression–heat molding procedure.[8] Experimental results demonstrate that this procedure produced PLGA millirods with reproducible release profiles and adequate mechanical strength for implantation. Further studies showed that these monolithic millirods gave burst release kinetics where majority of the entrapped agent (>90%) were released in the first 2 days.[8] For many anticancer drugs, sustained release is more desirable than burst release to maintain the drug concentration for a prolonged period of time to assure the drug efficacy.[9–12] In the current work, we report the development of a membrane-encased polymer millirod to permit the sustained release of an anticancer drug, 5-fluorouracil (5-FU). 5-FU is a commonly used drug for liver tumors,[13–15] and it is a suicide inhibitor to thymidylate synthase, a key enzyme involved in the conversion of dUMP to dTMP. Results from this study show the sustained release of 5-FU at rates between 0.1 and 0.4 mg/(day · cm of millirod) for 2 to 5 weeks at 37°C. The release rate can be freely controlled by the membrane structure (e.g., membrane thickness) and composition (e.g., density of impregnated NaCl particles).

MATERIALS AND METHODS

Materials

Poly(D,L-lactide-*co*-glycolide) (lactide: glycolide = 1:1, MW 50,000 Da, inherent viscosity 0.65 dL/g) was purchased from Birmingham Polymers, Inc. (Birmingham, AL). 5-Fluorouracil was purchased from Sigma (St. Louis, MO). Sodium chloride (NaCl), phosphate-buffered saline (PBS) and methylene chloride were obtained from Fisher Scientific (Pittsburgh, PA). PLGA microspheres (size ~5 μm) were produced by a single emulsion procedure.[8]

Preparation of 5-FU-loaded, monolithic PLGA millirods

The monolithic millirods containing 10, 20, and 30 w/w% 5-FU were fabricated by a compression-heat molding procedure described in a previous publication.[8] Briefly, 5-FU powder and PLGA microspheres were weighed separately according to the final loading densities of 5-FU in the millirods. The two components were placed in a plastic tube and physically mixed by vortex for 10 min. The mixture was placed into a Teflon tube (i.d. 1.6 mm) and then the Telfon tube was placed inside a stainless steel mold. The mold was put inside an iso-temp oven at 90°C (Fisher Model 282A, set point accuracy <2°C) for 2 h to allow the annealing of PLGA polymer. Compression pressure of 4.6 MPa was applied during the annealing process by copper weight. The monolithic millirods with 30 w/w% 5-FU were further used to fabricate the membrane-encased millirods.

Preparation of NaCl-impregnated PLGA films

A solvent casting method was used to prepare PLGA membranes containing NaCl particles. First, NaCl particles with size distribution between 90–150 μm were selected by sieves, and the size of the particles was verified by SEM. The NaCl particles were then mixed together with PLGA polymer according to designed ratios, and methylene chloride was added into the mixture. The volume of methylene chloride was measured so that the concentration of PLGA was 200 mg/mL. The suspension was vigorously vortexed to disperse NaCl particles inside viscous PLGA solution homogenously. The suspension was immediately poured into a Teflon dish (5 cm in diameter) and allowed to dry at room temperature for 48 h and then under high vacuum for another 48 h. After drying, the NaCl-impregnated PLGA film was peeled off the Teflon dish by forceps, and the thickness of the membrane was measured by a micrometer at 10 different locations and the average thickness was calculated. The membrane thickness was controlled by using different volumes of PLGA polymer suspension on the same Teflon dish.

Preparation of membrane-encased PLGA millirods

Membrane-encased PLGA millirods were obtained by wrapping the monolithic millirods (30 w/w% 5-FU) with NaCl-impregnated PLGA films. The conjunction of the PLGA film was annealed by compression with a heated stainless-steel forceps. Both ends of the membrane-encased PLGA millirods were sealed by dipping the ends into 400 mg/mL PLGA solution in methylene chloride. The millirods were then dried for 24 h in the air followed by another 24 h under vacuum. The same procedure was repeated for millirods with different membrane structure and composition (Table I).

SEM analysis

Scanning electron microscopy (SEM, JEOL model 840) was used to study the morphology of the monolithic and membrane-encased PLGA millirods. Both the outer surface and the cross-section of the millirods were examined. Before SEM analysis, the sample was mounted on the aluminum stub by double-sided tape and sputter coated with Pd (thickness 10 nm). SEM analysis was carried out at an accelerating voltage of 20 kV.

TABLE I
Structural Composition and Release Properties of Different Membrane-Encased Millirods

Millirod Code	Inner Millirod 5-FU% (w/w)	Outer Membrane NaCl% (w/w)	Membrane Thickness (μm)[a]	$t_{1/2}$ (days)[b]
FU-1	30	10	209 ± 13	24
FU-2	30	20	191 ± 14	18
FU-3	30	30	206 ± 17	10
FU-4	30	50	215 ± 20	6.0
FU-5	30	50	137 ± 18	4.1

[a]The standard deviation was obtained from 10 measurements.
[b]$t_{1/2}$corresponds to the time when 50% 5-FU is released.

In vitro release study

The release study was carried out in PBS buffer (pH = 7.4) at 37°C. Each millirod was placed in a glass vial containing 10 mL PBS buffer. The sample vials were placed in an orbital shaker (C24 model, New Brunswick Scientific) with a rotating speed of 100 rpm. At each time point, the solution was removed for UV measurement and 10 mL of fresh PBS solution was added. The concentration of released 5-FU in PBS buffer was determined at its maximum adsorption wavelength of 266.1 nm by an Hitachi U3210 UV-Vis spectrophotometer. The extinction coefficient of 5-FU at this wavelength was measured to be 46.1 mL/(cm · mg). The release study for monolithic millirods with 10, 20, and 30 w/w% 5-FU was carried out for 7 days, while for the membrane-encased millirods, release study continued until all of the 5-FU was released.

RESULTS

Characterization of monolithic millirods with different loading density of 5-FU

Figure 1 illustrates the release profiles of monolithic millirods with 10, 20, and 30 w/w% loading density of 5-FU. All three compositions showed typical diffusion-based release kinetics at the early release phase (t < 40 h). At closer examination, millirods with different loading density of 5-FU showed different release percentage when reaching the slow release or plateau phase. For example, at 80 h, almost 95% of the incorporated 5-FU was released from the 30 w/w% millirods while only 45 and 25% of 5-FU were released from the 20 and 10 w/w% millirods, respectively. In addition, the drug release rates decreased dramatically in the plateau phase compared to the initial phase for all the millirods despite significant amount of 5-FU still remained inside 10 and 20 w/w% millirods.

To understand the mechanism of 5-FU release from the millirods, we used SEM to characterize the microstructure of the 30 and 10 w/w% millirods. Figure 2(a) and (b) shows the morphology of outer surface and cross-section of 30 w/w% 5-FU millirod after 2 days of release study in PBS buffer, respectively. At this time, more than 90% of the 5-FU was released from the PLGA millirod. The outer surface appears to be rough, and contains holes as a result of dissolution of 5-FU particles at the millirod surface [Fig. 2(a)]. Examination of the cross-section shows that dissolution of 5-FU particles led to the formation of empty interconnecting pores and channels [Fig. 2(b)] in the PLGA matrix. These results are consistent with the high percentage of 5-FU release (>90%), and indicate that 30 w/w% loading of 5-FU is sufficiently high to generate a continuous 5-FU phase inside the PLGA matrix.

Figures 2(c) and (d) show the morphology of outer surface and cross-section of 10 w/w% millirod after 2 days of release, respectively. The surface of 10 w/w% millirod [Fig. 2(c)] appears to be smoother and less porous than that of 30 w/w% millirod [Fig. 2(a)]. Furthermore, no interconnecting channels were observed in the cross-section image. Empty pores induced by leaching of 5-FU particles were located closely to the surface of the millirod [Fig. 2(d)]. These results are

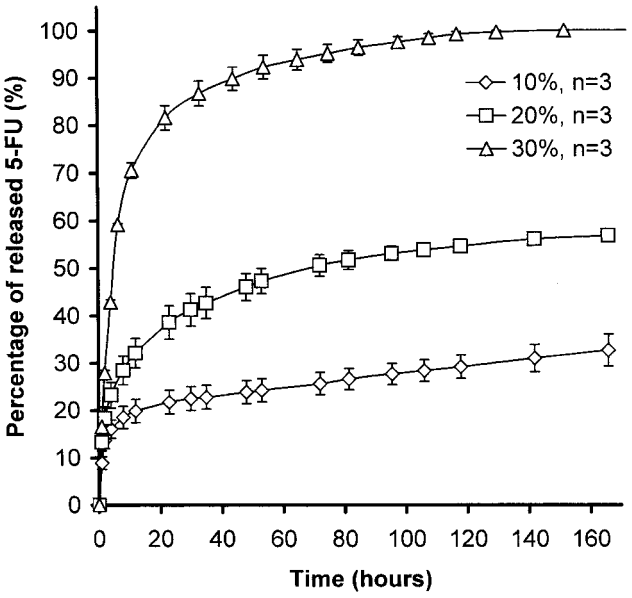

Figure 1. Release profiles of monolithic millirods with 10, 20, and 30 w/w% loading density of 5-FU. The release studies were carried out in PBS buffer at 37°C. The error bars were measured from triplicate samples.

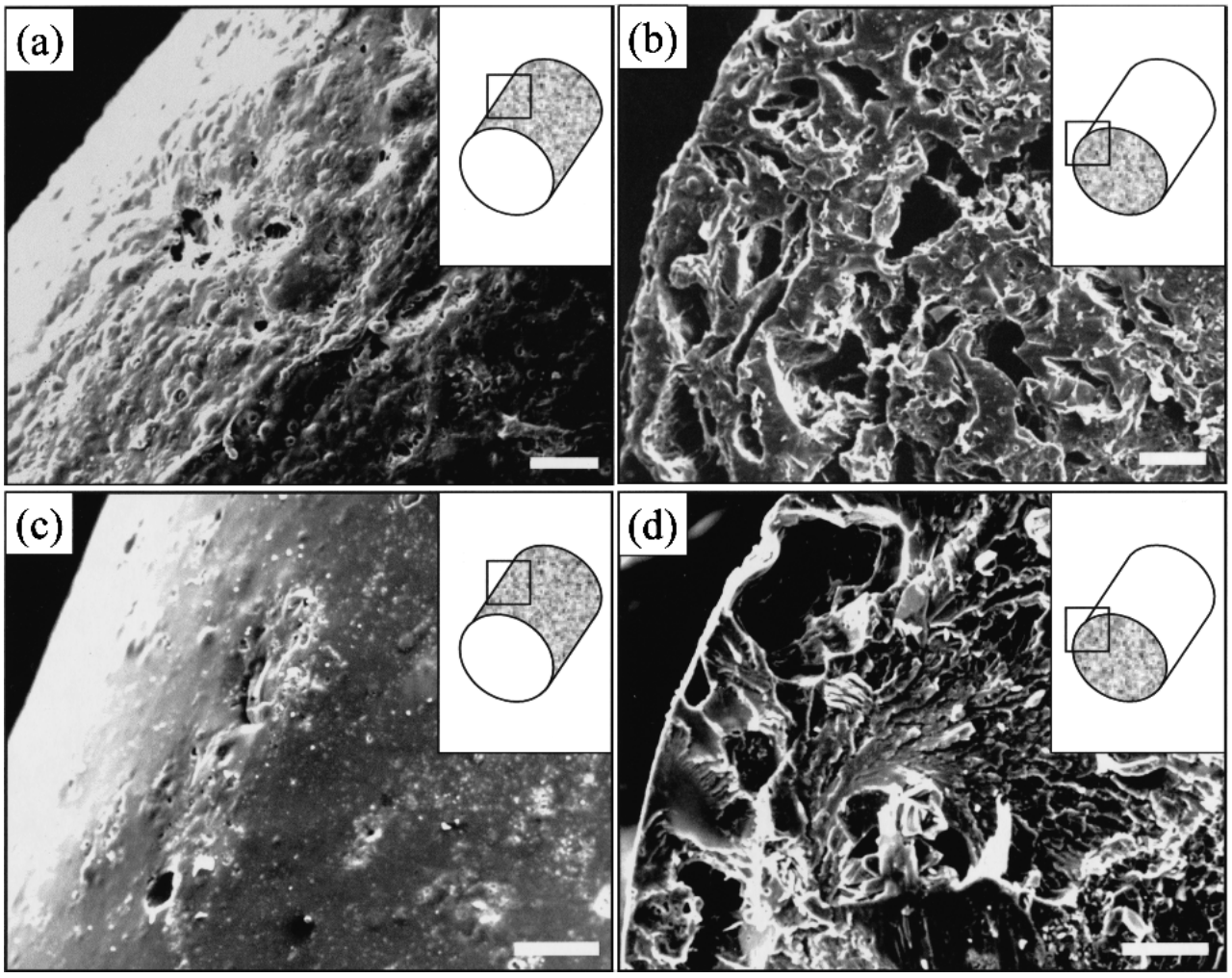

Figure 2. SEM analysis of the microstructures of 10 and 30 w/w% monolithic millirods after 2 days *in vitro* release study: (a) 30 w/w% millirod, side surface; (b) 30 w/w% millirod, cross-section; (c) 10 w/w% millirod, side surface; (d) 10 w/w% millirod, cross-section. The scale bars are 100 μm for all the images.

consistent with the release study in which majority of 5-FU (~80%) still remained inside the 10 w/w% millirod after 2 days (Fig. 1).

Surface analysis of NaCl-impregnated PLGA membrane

We used a solvent-casting method to produce the NaCl-impregnated PLGA membrane. In this study, we fixed the size distribution of NaCl particles (90–150 μm) and varied two parameters in NaCl density and film thickness to control the membrane permeability. We used SEM to analyze the particle dispersion and pore formation in the PLGA film. Figure 3(a) shows the surface and cross-section (inset) of 50 w/w% NaCl-impregnated PLGA membrane before hydration. The SEM analysis shows that NaCl particles were embedded inside the PLGA matrix, and the dispersion of NaCl particles was homogenous. The thickness of the membrane was measured to be 137 ± 18 μm. The cross-section image [Fig. 3(a), inset] shows that NaCl particles almost bridged the two opposite surfaces of the membrane, which is consistent with the size distribution of the NaCl particle (90–150 μm). Figure 3(b) shows the surface and cross-section (inset) of the same membrane after 48 h of hydration study in PBS buffer. The results clearly demonstrate that NaCl particles were leached out from the PLGA membrane, leaving empty pores across the membrane. The porous membrane became a semipermeable barrier that can be used to control the release kinetics of drugs from a burst release device.

Release study of membrane-encased millirods

Table I lists five types of membrane-encased millirods with different membrane properties. In these

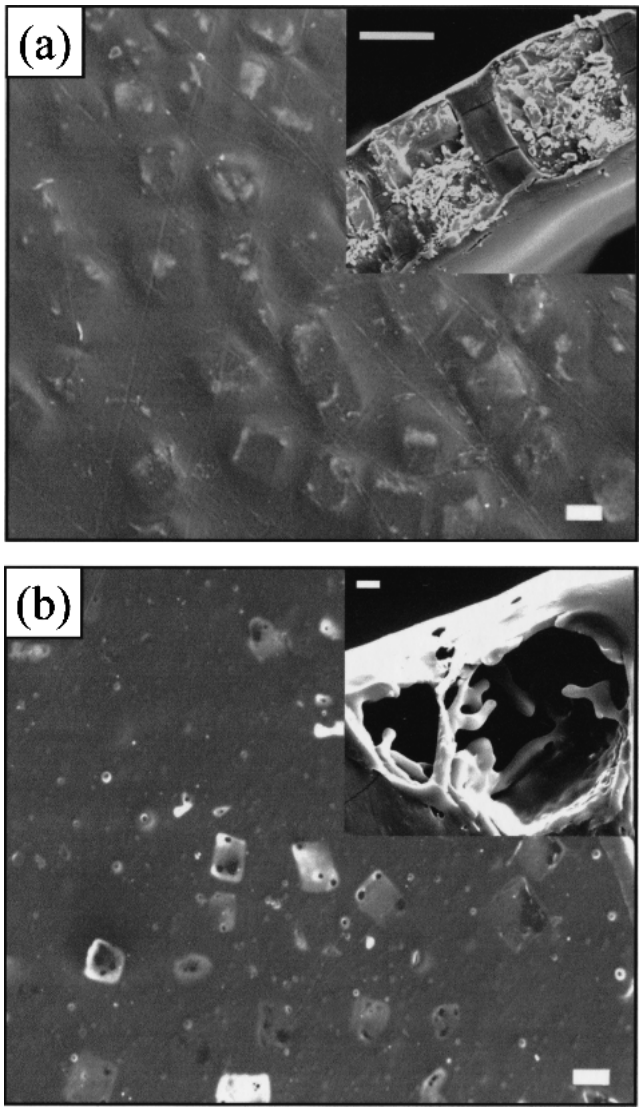

Figure 3. SEM analysis of the morphology of NaCl-impregnated PLGA membrane. The NaCl loading percentage is 50 w/w% and the membrane thickness is 137 ± 18 μm. (a) Surface morphology before the hydration study. (b) Surface morphology after 48 h of hydration study. The inset in each figure shows the cross-section of the membrane. The scale bar is 10 μm in Figure 3(b) inset and 100 μm in all the other images.

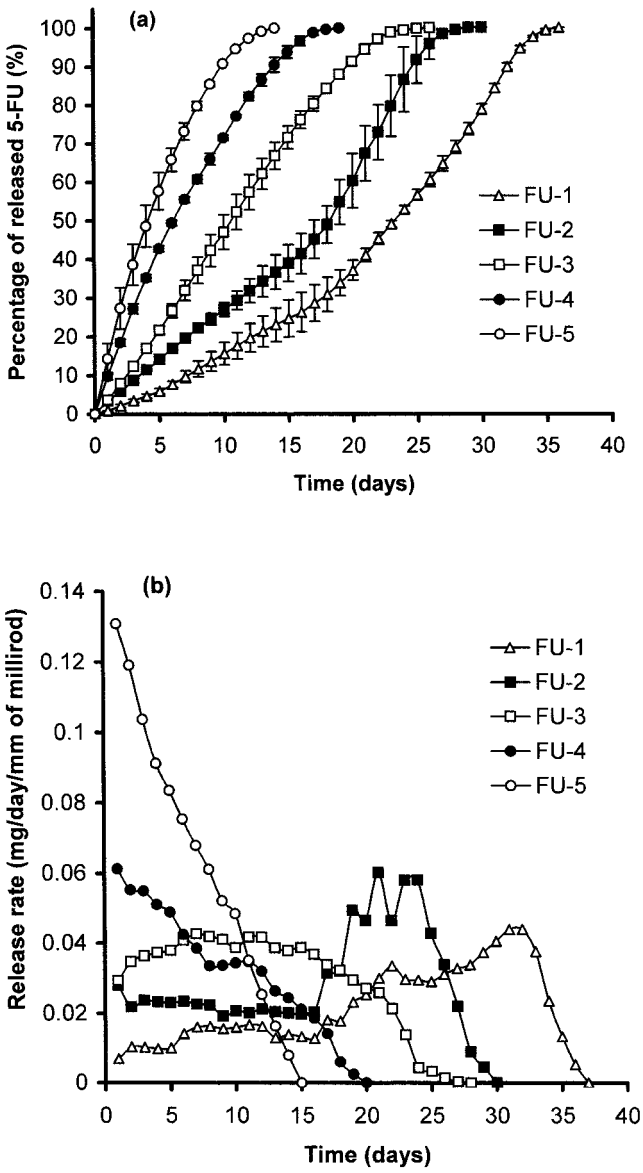

Figure 4. Cumulative release (a) and rate profiles (b) of membrane-encased millirods. The structural composition for each type of millirod is listed in Table I. The error bars in Figure 4(a) were measured from triplicate samples. For clarity of presentation, the error bars were not shown in Figure 4(b).

membrane-encased devices, we chose 30 w/w% monolithic millirods as the inner millirods. As shown in Figure 1, 30 w/w% millirods gave burst release kinetics where more than 90% of 5-FU was released in the first 2 days. PLGA membranes with different NaCl loading and membrane thickness were used to control the release rate from the polymer millirods. The NaCl loading density in the membrane varies from 10 to 50 w/w% and the membrane thickness from 137 ± 18 to 215 ± 20 μm (Table I).

Figure 4(a) shows the cumulative percentage of released 5-FU over time for different membrane-encased millirods. Compared to monolithic millirods, the membrane-encased millirods clearly demonstrate the sustained release kinetics. For example, the time for the release of 50% 5-FU ($t_{1/2}$) is 5 h for the 30 w/w% monolithic millirods (Fig. 1). In comparison, the values of $t_{1/2}$ are 4, 6, 10, 18, and 24 days for FU-5, FU-4, FU-3, FU-2, and FU-1 millirods, respectively. Depending on the use of different membranes, 20 to 120 times of sustained release was achieved compared to the monolithic device. Moreover, the sustained release kinetics can be controlled by the membrane properties. In a series of control experiments, we discovered that increasing the loading density of NaCl in the membrane while maintaining approximately the same

membrane thickness (e.g., from FU-1 to FU-4) led to decreased values of $t_{1/2}$ and faster release kinetics. Meanwhile, increasing the membrane thickness while maintaining the same NaCl loading density (e.g., from FU-5 to FU-4) led to increased values of $t_{1/2}$ and slower release kinetics (Table I). Closer examination of the release curves also shows that the FU-1 and FU-2 millirods displayed two-phase release profiles where the release rates increased at approximately day 17.

To quantify the rate profiles of different membrane-encased millirods, we plotted the release rates of 5-FU over time [Fig. 4(b)]. Results show that the drug release rates of FU-5 and FU-4 millirods kept decreasing over time. The release rate of FU-5 millirods was approximately 0.13 mg/(day · mm of millirod) at the beginning of the release study, and decreased to 0.05 mg/(day · mm of millirod) after 10 days when more than 90% of 5-FU was released. For FU-4 millirods, the initial release rate was approximately 0.06 mg/(day · mm of millirod) and the rate decreased to 0.025 mg/(day · mm of millirod) after 15 days when 90% 5-FU was released. In contrast, the release rate of FU-3 millirods was maintained in the range of 0.03 to 0.045 mg/(day · mm of millirod) in the first 20 days, and the device almost worked as a zero-order release device to deliver majority of the drug dosage (>90%).

Consistent with the observation in Figure 4(a), the rate profiles of FU-1 and FU-2 millirods displayed two distinguished phases of drug release. Before day 17, both millirods behave similarly to a zero-order release device. In this earlier phase, the release rates of FU-1 and FU-2 millirods were 0.010–>0.016 and 0.020–>0.025 mg/(day · mm of millirod), respectively. However, the release rates of both types of millirods increased in the later phase before 90% of the drug dosage was released. More specificly, the release rates of FU-2 millirods were elevated from 0.020 at day 16 to 0.060 mg/(day · mm of millirod) at day 21. Similarly, the release rates of FU-1 millirods increased continuously from 0.012 at day 16 to 0.045 mg/(day · mm of millirod) at day 32.

SEM analysis of FU-2 millirods

To gain insight on the two-phase release kinetics, we used SEM to analyze the microstructure of the FU-2 millirods at different times during the release study. Figure 5 shows the cross-sections of the FU-2 millirods before release, 2 and 18 days after release in the PBS buffer. Figure 5(a) demonstrates the two-compartment structure of the membrane-encased millirods: the NaCl-impregnated outer membrane and the inner monolithic millirod. SEM image after 2 days of release study [Fig. 5(b)] shows that the NaCl particles were leached out from the outer membrane and the membrane became porous. A small portion of 5-FU that was close to the membrane was also released. However, the extent of release was significantly smaller than that of the 30 w/w% monolithic millirod after the same time period [Fig. 2(b)]. This is

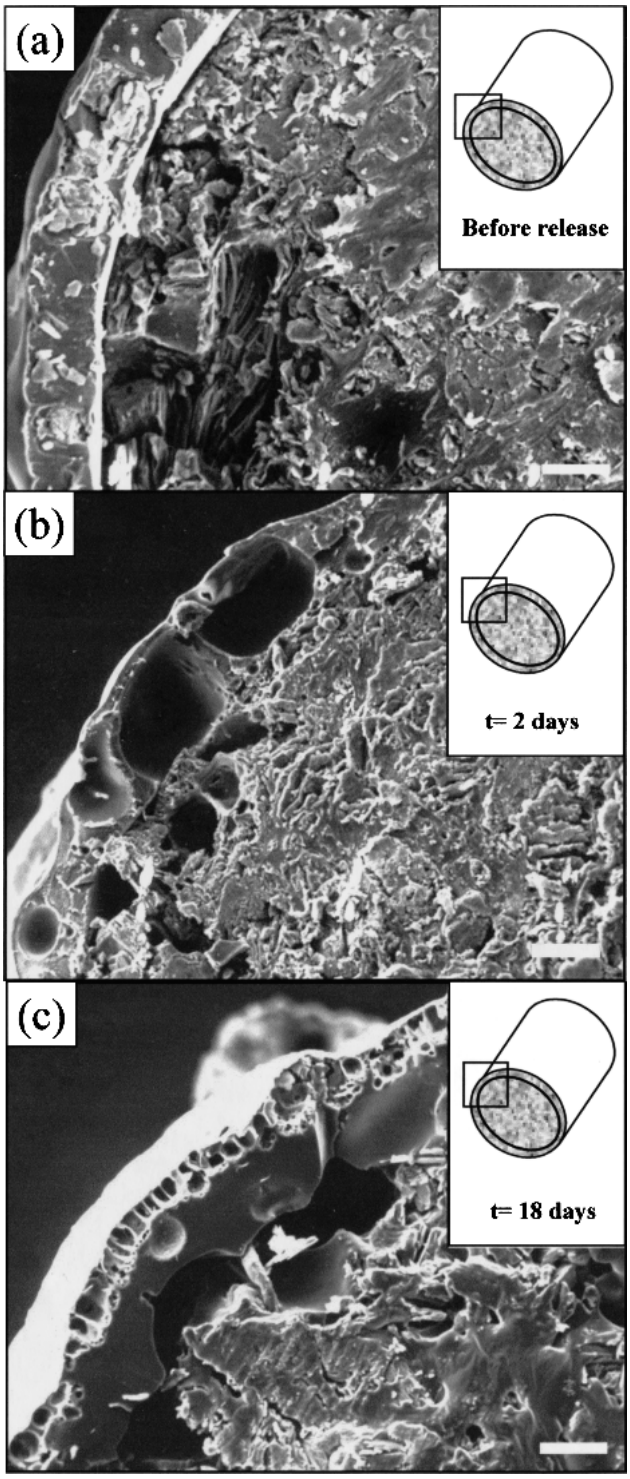

Figure 5. SEM analysis of the cross-section of FU-2 millirods before release study (a), 2 days (b), and 18 days (c) after release study in PBS buffer. The scale bars are 100 μm in all the images.

consistent with the release data that only 10% of 5-FU was released from the FU-2 millirod, while over 90% was released from the monolithic millirod after 2 days. After 18 days of release, SEM analysis shows obvious signs of polymer degradation in the outer membrane [Fig. 5(c)]. Small pores were uniformly observed at the outer surface of the PLGA membrane. Because the size of these pores (10–20 μm in diameter) is significantly smaller than the NaCl particles, we believe that they are the result of polymer degradation and dissolution, which is consistent with the degradation studies of PLGA films reported by Mikos' lab.[16,17] For FU-2 millirods, formation of micropores leads to an increase in membrane permeability as well as the release rate in the second release phase as observed in Figure 4(b).

DISCUSSION

Studies on the monolithic millirods (Fig. 1) demonstrate that varying the 5-FU loading density in the polymer matrix only provides limited control over the release kinetics of the drug. In all three conditions, burst release of 5-FU was observed in the first day followed by a plateau phase where the release rates were dramatically decreased in the following week. The observed release profiles are consistent with a percolation theory used in diffusion-controlled drug release systems.[18,19] In this theory, a percolation threshold exists in a binary system consisting of a drug and polymer matrix. The percolation threshold corresponds to a critical drug loading density that ensures the formation of a continuous drug phase inside the polymer matrix. Below this value the incorporated drug phase is isolated and surrounded by the insoluble polymer matrix, which leads to an incomplete release; above this value the drug phase forms interconnected channels and results in a complete release. Based on the release profiles of 10, 20, and 30 w/w% 5-FU millirods in Figure 1, we infer that the percolation threshold of 5-FU/PLGA binary system is between 20–30 w/w%. This is supported by the SEM analysis where 30 w/w% millirods showed interconnected channels after 2 days of drug release [Fig. 2(b)] while in 10 w/w% millirods, only drug particles with direct contact to the millirod surface were released [Fig. 2(d)].

There are multiple challenges that limit the use of monolithic millirods to control the release kinetics of 5-FU. First, sustained release of drugs over several weeks is difficult to achieve. After the initial burst release in the first 2 days, drug release reaches a plateau phase and little 5-FU is released in the following days (Fig. 1). Second, there are limited parameters in a monolithic device to control the release kinetics. Although drug loading density directly affects the release rates in the burst phase, it does not provide an accurate control of release rates in the plateau phase. Third, when the drug loading density is below the percolation threshold, "dose dumping" of the remaining 5-FU in the polymer matrix may occur as a result of bulk degradation behavior of PLGA.[20] In this case, water-soluble excipient molecules (e.g., glucose) can be incorporated into the devices to increase matrix porosity for a complete release, however, the release kinetics will resemble those of 30 w/w% millirods instead of a sustained release profile. Due to the above limitations, new designs of polymer millirods are necessary to permit an accurate control of the release properties of 5-FU.

Here we report the design and development of a novel membrane-encased polymer millirod to sustain the release of 5-FU for 2–5 weeks. This device consists of two modular components: a monolithic millirod that supplies 5-FU based on a predetermined drug dosage, and a polymer membrane that controls the release rates. This design is similar to the reservoir type of controlled release systems.[21] In the membrane-encased millirod, a monolithic millirod with a burst and complete release of 5-FU is necessary as the drug depot. Here we chose the 30 w/w% monolithic millirod (>90% 5-FU were released in less than 2 days; Fig. 1) in the proof-of-principle studies. Under the circumstance when the drug dosage is below the percolation threshold, an excipient molecule such as NaCl or glucose can be introduced to achieve the burst and complete release kinetics from the monolithic millirod.

Results from this study demonstrate that membrane-encased millirods are much more versatile and effective to control the drug release kinetics than the monolithic millirods. In a series of experiments [Fig. 4(a)], we showed that a sustained release of 5-FU has been achieved from 2 (FU-5 millirod) to 5 weeks (FU-1 millirod). Moreover, the duration and rate of drug release can be controlled by varying the permeation properties of the PLGA membrane. In this study, we controlled the membrane permeability by varying the membrane thickness and porosity (NaCl loading density) (Table I). Thinner membrane and higher NaCl loading lead to faster release of 5-FU. The ability to control the rate and duration of drug release from polymer millirods is essential for intratumoral drug delivery applications to thermoablated tumors. Drug release rate controls the amount of drug released into the tumor tissue per unit time, which subsequently dictates the drug concentration distribution profiles in the ablated tissue. Depending on the ablation size and drug transport properties in the normal and ablated tissues, an optimal drug release rate exists to permit the reaching of drug concentration at the ablation boundary to the therapeutic level.

Several observations on the release properties of the membrane-encased millirods indicate the necessity for

further optimization of these devices. First, millirods FU-1 and FU-2 showed an increase in release rates after 16 days of approximately zero-order release of 5-FU [Fig. 4(b)]. This is a result of the increase in membrane permeability due to PLGA degradation as supported by SEM analysis [Fig. 5(c)]. To circumvent this problem, a slower degrading polymer [e.g., poly(L-lactic acid), half-weight degradation time is 10–40 weeks depending on molecular weight][22] can be used to replace PLGA (3 weeks).[17] It should be noted, however, that a maximum time duration exists for any degradable polymers as membrane materials to maintain the controlled-release profiles. Second, the release rates of millirods FU-4 and FU-5 decreased throughout most of the release studies. We believe that the decreased release rates reflect the decrease in concentration gradient of 5-FU across the PLGA membrane over time. In a reservoir type of delivery device, zero-order release is achieved by maintaining drug concentration inside the membrane at its solubility limit (for 5-FU, it is 12 mg/mL).[21] In faster release systems (such as millirods FU-4 and FU-5), this may be difficult to achieve depending on the dissolution rate of 5-FU particles and the drug diffusion rate from inside the PLGA matrix to the inner surface of the PLGA membrane. In this regard, a water-soluble polymer (e.g., dextran) can be blended inside the monolithic millirods to facilitate the dissolution and diffusion of 5-FU. Third, in addition to NaCl particles, other porogen materials can also be used to control the membrane permeability. NaCl particles are simple and inexpensive materials that permit easy control over the porosity and pore size in the PLGA membrane. In applications where high ionic concentrations are not desirable, other organic-based materials (e.g., glucose particles, polyethylene glycol polymer) can be used to control the membrane permeability and the drug release rate from the membrane-encased millirods. Current work is in progress to explore these strategies to optimize the millirod development.

CONCLUSIONS

A membrane-encased polymer millirod was successfully developed to provide a sustained release of anticancer drugs. The design consists of two modular components: a monolithic millirod as a drug depot to provide a predetermined drug dosage, and a semipermeable polymer membrane to control the release rates. Compared to monolithic devices, membrane-encased millirods provide a much more methodical approach to control the release kinetics. In a series of experiments, membrane thickness and porosity were systematically varied to sustain the release of 5-FU over 2–5 weeks at controllable release rates. In addition to 5-FU, the membrane-encased millirod should also permit the controlled delivery of other types of antitumor agents or a combination of multiple agents simultaneously. The availability of this technology opens many future opportunities in the image-guided, minimally invasive treatment of cancer.

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