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A study of drug release from homogeneous PLGA microstructures

Ghanashyam Acharya^{a,b}, Crystal S. Shin^{a,b}, Kumar Vedantham^{a,b}, Matthew McDermott^c, Thomas Rish^{a,b}, Keith Hansen^{a,b}, Yourong Fu^c, Kinam Park^{a,b,c,*}

^a Department of Biomedical Engineering, Purdue University, West Lafayette, IN 47907, USA

^b Department of Pharmaceutics, Purdue University, West Lafayette, IN 47907, USA

^c Akina, Inc., West Lafayette, IN 47906, USA

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ABSTRACT

The hydrogel template method was used to fabricate homogeneous drug–PLGA microparticles. Four drugs (felodipine, risperidone, progesterone, and paclitaxel) were loaded into the PLGA particles with the homogeneous size of 10 μm , 20 μm , and 50 μm . The drug loading into the PLGA microparticles was 50% and higher.

The felodipine–PLGA microstructures of four different sizes showed that the drug release kinetics is dependent on the total surface area available for drug release. The smaller the particle size, the release rate was faster. Two types of microparticles (10 μm diameter and 10 μm height, and 50 μm diameter and 5 μm height) showed zero-order release and complete release was observed within 2 weeks. The release rate, however, was not exactly proportional to the surface area. Different drugs which were loaded into the same PLGA formulation showed different release profiles. The main difference was on the initial burst release. The overall release profile seems to be similar for different drugs, if the release profile is adjusted to eliminate the burst release. The initial burst release appears to be inversely related to the water-solubility of a drug, i.e., the lower the water-solubility of a drug, the higher the burst release.

The hydrogel template method allowed preparation of homogeneous particles with predefined sizes with high drug loading. It allowed study on the effect of size and shape on the drug release kinetics. With the microparticles of homogeneous size and shape, the drug release kinetics can be projected based on the size of microparticles and water-solubility of a drug. The ability of making homogeneous particles is expected to provide better prediction and reproducibility of the drug release property of a given formulation.

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1. Introduction

Fabrication of homogeneous nano/micro particles of predefined size and shape with high drug contents and controllable release kinetics has been the focus of current drug delivery research [1]. Quite often, the drug delivery platforms of choice have been liposomes, polymeric micelles, polymeric solid particles, and lipid nanocarriers [2–8]. These platforms, especially solid particles, yield polydisperse particles with sizes that usually span a wide range and with a tendency of aggregation [9]. They also have rather low drug loading capacity and high burst release [10,11]. Naturally, current efforts in developing drug delivery systems have focused on controlling the particle size, shape, drug loading capacity, and drug release kinetics.

A number of new methods have been developed for fabrication of homogeneous nano/micro structures. Those nanofabrication techni-

ques include nanoimprint lithography [12], soft lithography [13], step and flash imprint lithography [14,15], microcontact hot printing [16], particle replication in nonwetting templates (PRINT) [17,18], continuous flow-lithography [19], and electrohydrodynamic cospinning [20]. Recently, we have developed a new nanofabrication method based on the hydrogel template strategy for fabrication of particles specifically designed for drug delivery [21].

The hydrogel template approach was used to prepare homogeneous PLGA microparticles with different dimensions. For long-term drug delivery, a drug is usually loaded into microparticles made of biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA). Understanding the drug release kinetics from drug-containing PLGA microparticles is important for designing microparticles with predictable release kinetics. Most of the drug release studies have been done using drug–PLGA microparticles with polydisperse particle sizes, and thus, the observed drug release is the average release from a mixture of different particle sizes. In this study, homogeneous microparticles were prepared to examine the effect of the particle size on the drug release kinetics. The particles were loaded with four different drugs with the drug loading of 50% or higher.

* Corresponding author. Purdue University, Weldon School of Biomedical Engineering, 206 S. Martin Jischke Drive, West Lafayette, IN 47907-2032, USA. Tel.: +1 765 494 7759.

E-mail address: kpark@purdue.edu (K. Park).

2. Materials and methods

2.1. Materials

Gelatin (from porcine skin, Type A, 300 bloom) was purchased from Sigma (St. Louis, MO, USA). Poly(lactic-co-glycolic acid) (PLGA, lactic acid:glycolic acid = 50:50) of different molecular weights (MW 36,000, IV 0.7 dl/g; MW 65,000, IV 0.82 dl/g; MW 112,000, IV 1.3 dl/g) were purchased from Lactel (Pelham, AL). Felodipine (FDP), paclitaxel (PTX), progesterone (PRG), and risperidone (RSP) were purchased from Sigma.

2.2. Fabrication of a silicon wafer master template by photolithography

A silicon wafer was spin coated with SU8 2025 photoresist (Microchem, MA) at 2000 rpm for 30 s followed by baking at 95 °C for 3 min. The photoresist coated silicon wafer was exposed to UV radiation through a mask containing a circular pattern for 12 s. The diameter of circles was varied from 10 µm to 50 µm, and the height of the pillars was also varied from 5 µm to 50 µm. After exposure, the silicon wafer was post baked at 95 °C for 3 min followed by development in SU-8 developer for 2 min. The silicon wafer was rinsed with isopropanol and dried with nitrogen gas.

2.3. Fabrication of drug-containing PLGA microcylinders

The four drugs loaded into microparticles were FDP, PTX, PRG, and RSP. The diameters of the microparticles prepared were 10, 20, and 50 µm. The height of the particles was either 5 µm to make microdiscs or 50 µm to make microcylinders. For notation, the microcylinder with 50 µm diameter and 50 µm height containing FDP is described as FDP-50/50. The microdisc of the same drug with 5 µm height is, thus, FDP-50/5. The overall process of making microparticles is described in Fig. 1.

2.3.1. Fabrication of hydrogel templates

A clear gelatin solution (30% w/v in aqueous solution, 10 ml) at 50–55 °C was transferred with a pipette onto a silicon master template (3" diameter) containing circular pillars (e.g., of 50 µm diameter and 50 µm height). The gelatin solution was evenly spread to form a thin film completely covering the master template and cooled to 4 °C for 5 min by keeping it in a refrigerator. Cooling resulted in formation of a gelatin template which was subsequently peeled away from the master template. The obtained gelatin template contained circular wells (e.g., of 50 µm diameter and 50 µm depth). The gelatin template was examined under a bright field reflectance microscope to confirm its structural integrity. The preliminary experiment suggested that a solution of 30% gelatin resulted in templates which were elastic and mechanically strong enough for further processing.

2.3.2. Filling of the hydrogel templates with drug-PLGA solution

The wells in a hydrogel template were filled with a drug and PLGA dissolved in methylene chloride (CH₂Cl₂). The concentration of the

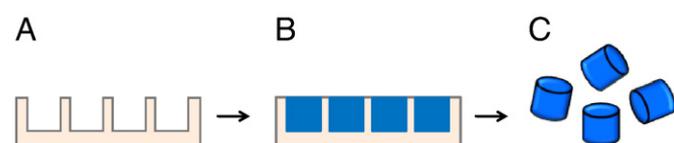


Fig. 1. Schematic diagram showing the fabrication of homogeneous drug-PLGA microparticles using the hydrogel template method. (A) A hydrogel template with wells is formed from the silicon wafer master template. (B) The wells in the hydrogel template are filled with drug-PLGA in organic solvent and then dried. (C) The drug-PLGA particles are obtained by simply dissolving the hydrogel template in aqueous solution.

drug-PLGA was 20% w/v in CH₂Cl₂ for all four drugs. The weight ratio of drug:PLGA was 50:50 for FDP, PRG, and RSP, and 65:35 for PTX.

Hydrogel templates were filled with drug-PLGA by transferring 200 µl of drug-PLGA solution in CH₂Cl₂, and evenly spreading it. Then, the templates were left at room temperature to evaporate the solvent. The drug-filled hydrogel templates were examined by bright field and fluorescence microscopy.

2.3.3. Collection of drug-PLGA microparticles from hydrogel templates

A batch of 10 hydrogel templates filled with drug-PLGA were dissolved in a 100 ml beaker containing 50 ml of Nanopure water at 40 °C and gently shaken for 2 min to completely dissolve the templates. This step resulted in complete release of the free microparticles into the solution. The solution was transferred into conical tubes (15 ml) and centrifuged for 5 min (Eppendorf Centrifuge 5804, Rotor A-4-44, at 4500×g). The pellet obtained upon centrifugation was freeze dried and stored in a refrigerator. This pellet, upon resuspension in 1 ml of Nanopure water, formed a suspension of free and isolated microparticles.

2.3.4. Characterization of drug-PLGA microparticles

The drug-containing microparticles were visualized by a bright field and confocal fluorescence microscope (Olympus Spinning Disc Confocal Imaging Microscope BX61-DSU, Center Valley, PA) which is equipped with Intelligent Imaging Innovations Slide Book 4.0 software for automated Z-stack and 3-D image analysis.

2.3.5. Measurement of size distribution

Microparticle size distribution was measured on a Microtrac S3500 particle size analyzer equipped with Microtrac Flex Version 10.3.3 software (Microtrac Inc., Largo, FL). Suspensions of FDP microstructures (1 mg/ml in water) were used as analysis samples.

2.4. In vitro drug release experiments

In a typical experiment, the drug-loaded microparticles were separately weighed into three 10 ml glass vials, and 5 ml of PBS/Tween-20 (pH 7.4) release medium was transferred into each vial. These vials were kept in an orbital shaker maintained at 37 °C with constant agitation. At 24-h time intervals 5 ml of the release medium was withdrawn from the vials and replaced with the same amount of the fresh medium. Thus collected samples were transferred into glass vials and stored in the refrigerator. Sampling of the release medium was continued for 3 weeks.

Each sample was filtered through a 0.5 µm syringe filter and subjected to HPLC analysis on a Hitachi LaChrom-7000 HPLC. The analytical column was X-Terra C-18 (250 mm x 4.6 mm) from Waters. The system was equipped with autosampler, in line degasser, and column oven set at room temperature. The mobile phase was a mixture of methanol (90%) and ammonium acetate (10%, pH 7), used after filtration through 0.22 µm membrane filter. Injection volume was 65 µl, the flow rate was 1.0 ml/min and the pressure was 1200 mm.

The total amount of a drug loaded into microparticles was determined by dissolving an accurately weighed amount of the microparticles in 1 ml CH₂Cl₂, followed by addition of methanol (9 ml). The precipitated PLGA was removed by centrifugation. The clear solution was rotary evaporated and the solid formed was redissolved in the mobile phase (10 ml). An aliquot of this solution was filtered through a 0.5 µm syringe filter, analyzed by HPLC, and was compared with the standard curve to quantify the content.

3. Results and discussion

Homogeneous drug-PLGA microparticles of predefined dimensions were prepared using the hydrogel template method. The

felodipine (FDP)-loaded microparticles prepared in four different sizes: FDP-10/10; FDP-20/20; FDP-50/50; and FDP-50/5. In addition, PLGA microparticles loaded with progesterone (PRG-50/50), paclitaxel (PTX-20/20), and risperidone (RSP-50/50; RSP-20/20) were also fabricated. Fig. 2 shows an example of the microcylinders prepared by the hydrogel template. The figure shows a gelatin template before (Fig. 2-A) and after (Fig. 2-B) filling with FDP, and homogenous FDP-loaded PLGA microcylinders obtained after dissolving the gelatin template (Fig. 2-C). FDP itself is fluorescent, and thus, the micro-particles can be easily visualized by fluorescence imaging (Fig. 2-D).

The size distribution of FDP microstructures was analyzed by dynamic light scattering studies. Suspension of FDP microstructures in water (1 mg/ml) were used for the analysis. Dynamic light scattering studies of FDP microstructures revealed a tight size distribution (Fig. 3). FDP-50/5 microdiscs showed a single peak at 44 μm (96%) demonstrating a homogeneous size distribution. In the case of FDP-50/50 microcylinders, three peaks were observed at 62 μm (9%), 52 μm (67%), and 44 μm (24%). For microcylinders of FDP-20/20, the major peak was at 22 μm (45%) with smaller peaks at 19 μm (11%), 26 μm (33%), and 31 μm (8%) respectively. The size distribution profile of FDP-10/10 microcylinders contained a major peak at 11 μm (48%) followed by smaller peaks at 9 μm (26%) and 13 μm (22%), respectively. The size distribution of all microstructures is much narrower around the intended target size than the microspheres prepared by the conventional emulsion methods.

While FDP-50/5 in a disk shape shows a highly homogeneous size distribution with a single peak, other microstructures in the cylinder shape show additional sizes around the intended size. The presence of smaller peaks around the major peak indicates that the microcylinders are not as homogeneous as the microscopic images present. This may be due to the presence of minor differences in the microstructure. For example, when the cavities of a hydrogel template are filled with drug-PLGA solution to form microcylinders, the cavities may not be filled completely, or the height of the center may decrease a little bit due to drying to form a concave top. Also, it is equally possible that some cavities may be filled with excess drug-PLGA solution resulting in elevated height, and these factors may result in minor peaks around the main peak size for the microcylinders. This explanation is reasonable, because the size distribution is similar for all three microcylinders of 10/10, 20/20, and 50/50. The homogeneous distribution of 50/5 also makes sense, because making the disk

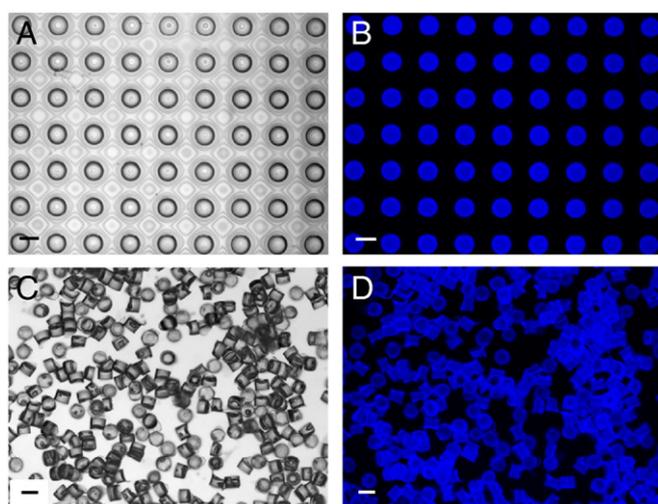


Fig. 2. Fabrication of felodipine (FDP)-loaded PLGA microcylinders, FDP-50/50. (A) Bright field image of a gelatin template; (B) fluorescence image of the gelatin template filled with FDP-PLGA; and (C) and (D) bright field and fluorescence images of individual FDP-PLGA microparticles obtained by dissolving the gelatin template (scale bars correspond to 50 μm).

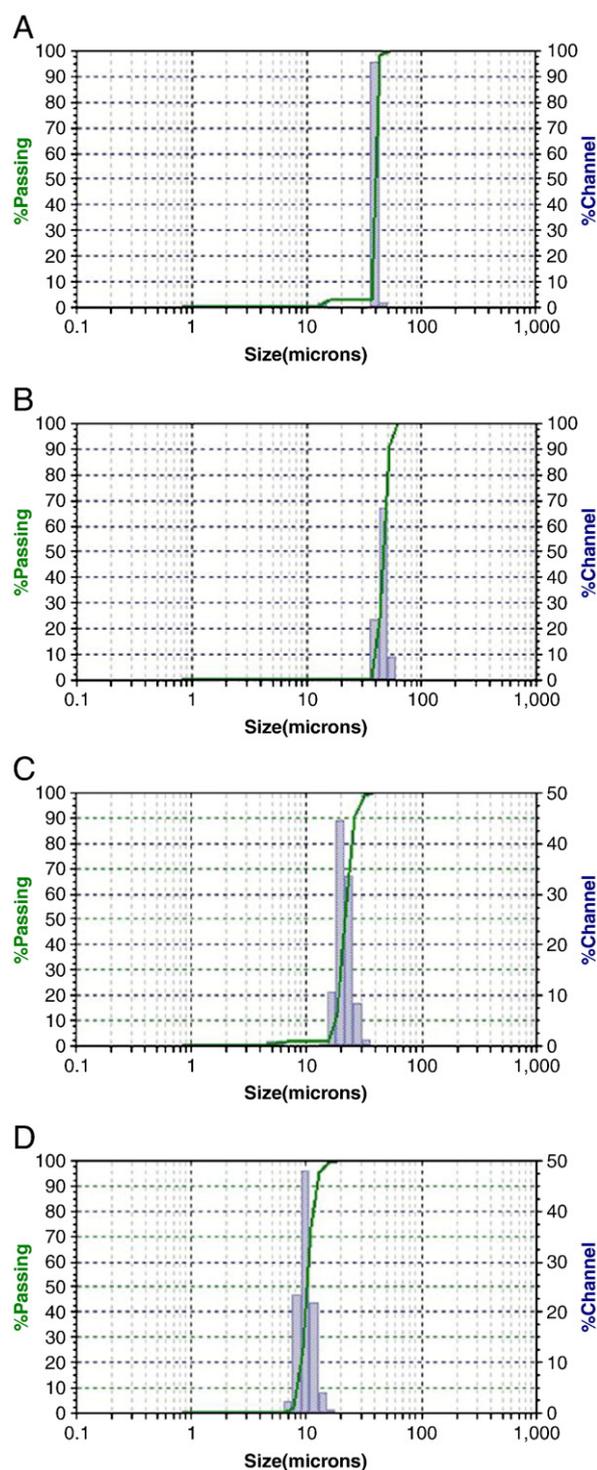


Fig. 3. Size distribution analysis of FDP microstructures. Dynamic light scattering profiles of FDP-50/5 microdiscs (A), FDP-50/50 microcylinders (B), FDP-20/20 microcylinders (C), and FDP-10/10 microcylinders (D).

shape structure does not require filling the cavities of the template only once. Naturally, the final size is highly homogeneous.

FDP release from PLGA microparticles of different dimensions was examined, and the release profiles are shown in Fig. 4. As shown in the figure, the FDP release kinetics from FDP-50/5 (50 μm disk) and FDP-10/10 (10 μm cylinder) were almost the same. The FDP release from FDP-20/20 was slower than 50/5 and 10/10, and the release from FDP-50/50 was the slowest. Fig. 4-B shows the release kinetics using the cumulative percent release. The data in Fig. 4 are interesting in a few

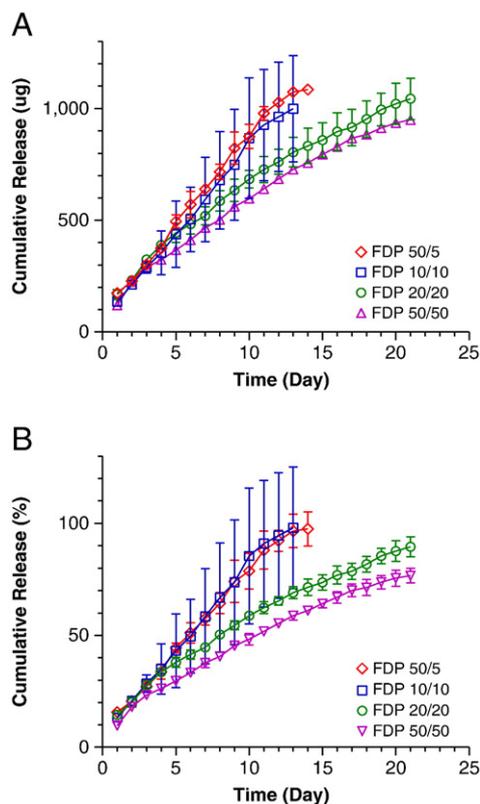


Fig. 4. Release profiles in the cumulative amount (A) and in percent (B) of felodipine (FDP) from PLGA microparticles of four different dimensions (FDP-10/10; FDP-20/20; FDP-50/50; and FDP-50/5). The content of FDP in the microparticles was 50 % (w/w). (n = 3).

ways. First, the initial burst release is only about 10% for all formulations, as one can find out by extrapolating the linear portion of the release profiles to time zero. Considering the fact that the drug loading was 50% of the total mass, it is rather interesting to observe only such a low burst release. Most of the microparticulate formulations, commonly prepared by the emulsion methods, result in the initial burst release around 30–50% [10,11]. The burst release is mainly due to the accumulation of a loaded drug at the surface of microparticles, and this is most prominent when microparticles are prepared by the conventional emulsion methods. Second, the drug release is almost zero-order for FDP-50/5 and 10/10, and the release profiles of the other two formulations (FDP-20/20 and 50/50) also show the zero-order release for the first half of the release period, after which a slight decrease in the release rate was observed. Thus, it appears that as the particle size is 10 μm or less, the zero-order release can be obtained. It is noted that the error bars for FDP-10/10 is much larger than that for FDP-50/5, suggesting that the microdisc structure may be more reproducible in the release profile. Overall, the release profiles of FDP-20/20 and 50/50 are still very good, as it can release the drug continuously at a rate without significant changes.

The total amount of FDP used in the release study was the same for all four formulations, and the PLGA formulations were prepared under

the same processing condition. Thus, the major factor affecting the drug release kinetics is expected to be the particle dimension. Since the particles with different dimensions have different surface areas, and thus, the total surface areas available for drug release. The ratios of the relative total surface area were calculated, as shown in Table 1. The order of the total surface area available for drug release was FDP-10/10 > 50/5 > 20/20 > 50/50. The total surface area for FDP-50/5 is 80% of that for FDP-10/10. Thus, it is understandable to observe the same release kinetics for both within the experimental error in Fig. 4. Also understandable is the faster release of FDP from FDP-20/20 than from FDP-50/50. The release rate, however, was not exactly proportional to the surface area. For example, the drug release rate for FDP-10/10 is only 50% larger than that for FDP-20/20, although 100% increase is expected. The increase is even much less than expected between FDP-10/10 and 50/50. Thus, while the surface area is an important factor determining the drug release kinetics, it does not seem to be the only factor. Because all microparticles were prepared under the same condition for the same drug, it is not clear what additional factors may affect the drug release kinetics at this point.

The effect of drug properties on the release kinetics was examined using three more drugs. PLGA microcylinders were prepared containing progesterone (PRG), risperidone (RSP), and paclitaxel (PTX). The sizes prepared were 20 μm (for FDP, RSP, and PTX) and 50 μm (for PRG, FDP, and RSP). The structure, molecular weight, and water-solubility of each drug are listed in Table 2. Molecular weights are similar, except for PTX. The water-solubility of FDP and RSP are orders of magnitude higher than that of PRG and PTX.

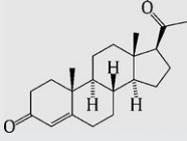
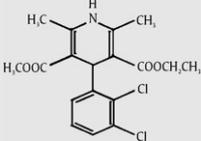
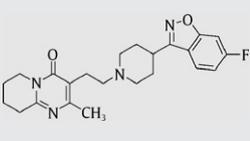
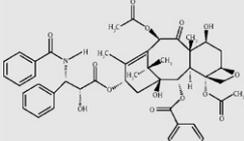
Drug release profiles of four drugs in two different formulations are shown in Fig. 5. Fig. 5-A shows the release of FDP, RSP, and PRG from 50 μm cylinders. Both PRG and FDP show initial burst release of 10–20%, but a delayed release was observed with RSP. The delayed release, sometimes called time-lag, is not common for drug release from matrix systems, especially microparticles prepared by the double emulsion methods [27]. Haloperidol, with the water-solubility of 130 μg/ml, also showed a lag time, but its PLGA formulation was prepared in the film form first and subsequently pressed into pellets [28], making it rather difficult to compare with our system. The lag time for RSP-50/50 is about 2 days. Table 2 shows that RSP has higher water-solubility than the other three drugs used in the study. Despite such higher water-solubility, the release was delayed. The drug release kinetics, i.e., the slope of the steady state release, is similar for PRG and FDP. The only difference is the higher burst release by PRG. Fig. 5-B shows the release profiles of FDP, RSP, and PTX. The initial burst release is most prominent with PTX, which has the lowest water-solubility. The PTX loading was 65% as compared with other drugs, but even if this higher drug loading is considered, the initial burst release is still very significant. The drug release occurred faster from the 20 μm particles (Fig. 5-B) than from the 50 μm particles, as expected. Also, the drug release rate decreases at a later period of the release.

It is interesting to notice that the rank order of the initial burst release (PTX > PRG > FDP > RIP) is inversely related to the water-solubility of the drug. In other words, the initial burst release is related to the hydrophobicity of the drug. This is in a sense understandable. When the solvent is dried to form solid drug/PLGA particles, drug molecules migrate with the solvent to the surface, and

Table 1
Calculation of the relative total surface areas of the four microparticle structures used for the felodipine (FDP) release studies.

Microparticles	Particle dimensions (d μm × h μm)	Particle volume (μm ³)	Relative particle volume	Relative particle #/unit vol	Particle surface area (μm ²)	Relative total surface area (μm ²)	Relative surface area
FDP-10/10	10 × 10	785	1	125	471	58,875	1
FDP-50/5	50 × 5	9812	12.5	10	4710	47,100	0.8
FDP-20/20	20 × 20	6280	8	15.6	1884	29,390	0.5
FDP-50/50	50 × 50	98,125	125	1	11,775	11,775	0.2

Table 2
Molecular structures, molecular weights, and aqueous solubilities of four drugs.

Name	Progesterone	Felodipine	Risperidone	Paclitaxel
Chemical structure				
Mol. wt.	314.5 g/mol	384.3 g/mol	410.5 g/mol	853.9 g/mol
Water-solubility (reference)	15.2 µg/ml [22]	110 µg/ml [23]	216 µg/ml [24]	0.3 µg/ml [25,26]
Drug:PLGA ratio	50:50	50:50	50:50	65:35
Microparticles	PRG-50/50	FDP-20/20, FDP-50/50	RSP-20/20, RSP-50/50	PTX-20/20

the extent of the drug migration is expected to be higher for more hydrophobic drugs, resulting in higher accumulation at the surface, which in turn results in higher burst release. This also explains, at least in part, the delayed release of RSP which has the highest water-solubility, or the lowest hydrophobicity. Because of its low hydrophobicity, RSP does not migrate to the surface as the solvent does during the drying process.

The drug release from polymer matrices is known to depend on at least three factors, such as the surface area, diffusion coefficient and concentration gradient of a drug. Because the drug loading was similar (50% for FDP, RSP, and PRG, and 65% for PTX), and the molecular weights of the drugs are not widely apart, except for PTX, we can assume that the concentration gradient for each drug is comparable. Fig. 5 shows that the steady state drug release rates (i.e., the slopes) are about the same for all drugs, except for slightly higher release rate of RSP followed by the lag time. Thus, the surface area, the concentration gradient, and the

diffusion coefficient of each drug are comparable, i.e., not different by orders of magnitude. The release data collectively suggest that the drug release from the PLGA formulations can be adjusted by controlling the size of the microparticles. The larger the particle size, the slower and longer release of a drug. For zero-order release, the microparticles in the disc shape (e.g., FDP-50/5) is preferred rather than in the cylinder shape (e.g., FDP-10/10), because the former shows the smaller standard deviation in the release data. The extent of the initial burst release seems to be inversely related to the water-solubility of a drug. With the microparticles of homogeneous size and shape, the drug release kinetics can be projected based on the size of microparticles and water-solubility of a drug. Controlling the microparticle size will also provide better prediction and reproducibility of the drug release property of a given formulation. Further studies on the effect of microparticle size and shape using more drugs are expected to provide information on a priori prediction of the drug release kinetics.

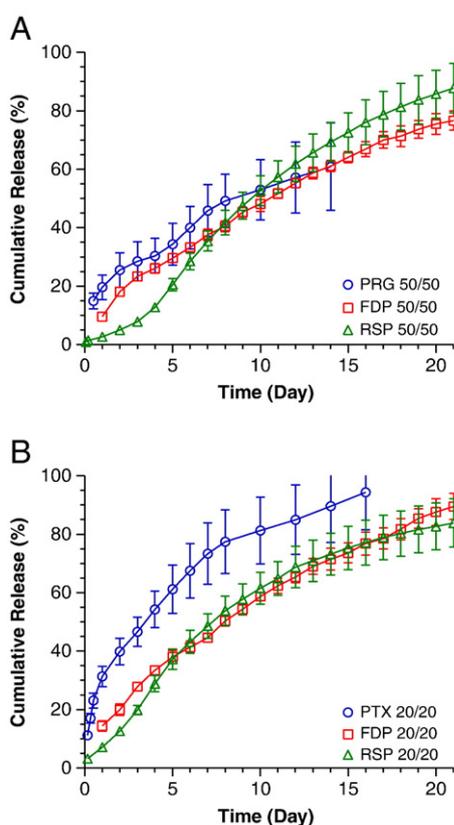


Fig. 5. Comparative release profiles of different drugs from drug-PLGA microparticles: (A) release profiles of felodipine (FDP), risperidone (RSP), and progesterone (PRG) from 50 µm microcylinders (50/50). (B) Release profiles of FDP, RSP, and PTX from 20 µm cylinders (20/20). The amount of drug in the microparticles was 50 % (w/w). ($n=3$).

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