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Control of cilostazol release kinetics and direction from a stent using a reservoir-based design

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Abstract: Sustained release formulations of a potent antithrombotic drug, cilostazol, in poly-(lactic acid-*co*-glycolic acid) (PLGA) matrices were created for luminal release from a novel drug-eluting stent utilizing reservoirs (RES TECHNOLOGY™). The crystallinity of cilostazol and the morphology of the cilostazol/polymer matrix in the stent reservoirs were examined by cross-polarized optical microscopy and differential scanning calorimetry. An *in vitro* method was developed to study release kinetics of various cilostazol formulations and to examine correlation with *in vivo* release. Formulation parameters such as drug-to-polymer ratio and the use of a polymer barrier on the abluminal surface of the drug/polymer matrix were found to be effective in modulating drug release rate. Cilostazol/$PLGA_{75/25}$ in the weight ratio of 50/50 to 70/30 displayed first-order release kinetics for the majority of the drug load. Addition of an abluminal polymer barrier slowed cilostazol release rate when compared to the bidirectional reservoir design. Excellent correlation between cilostazol *in vivo* release profile from stents in a porcine coronary artery model and that measured *in vitro* in a modified USP-7 apparatus suggests that the *in vitro* release system is capable of predicting *in vivo* release of cilostazol from stent reservoirs. © 2012 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 100B: 603–610, 2012.

Key Words: drug-eluting stent, cilostazol, release kinetics, thromboresistance, RES TECHNOLOGY™ platform

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INTRODUCTION

Despite dramatic improvements in percutaneous coronary intervention (PCI) associated with the use of drug-eluting stents (DES),[1–3] there is still a need to reduce the high rates of stent thrombosis and restenosis associated with higher risk patients, such as those with diabetes and acute myocardial infarction. To this end, the development of new DES with improved safety and efficacy profiles continues, aided by experience with novel therapeutic and improved stent platforms.

Cilostazol ((6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone; Pletal®) is a potent, direct-acting antiplatelet and vasodilator agent that is currently approved for treatment of intermittent claudication in patients with peripheral vascular disease.[4–6] Its mechanism of action involves inhibition of cyclic adenosine monophosphate-specific (cAMP) phosphodiesterase III in target tissues. The antiplatelet activity of cilostazol results from its ability to increase platelet cAMP levels and to decrease intracellular calcium and glycoprotein (GP) IIb/IIIa receptor activation.[7–9] Cilostazol may provide additional therapeutic benefit in the context of PCI by inhibiting smooth muscle cell proliferation and inflammation, as well as by improving endothelial function.[9,10]

The therapeutic benefits of cilostazol in the setting of PCI are supported by clinical trials in patients with diabetes or long lesions showing that systemic administration of cilostazol with DES further reduces luminal narrowing, compared to treatment with DES alone, leading to further significant reductions in restenosis rates that are sustained after two years.[11–13] Randomized clinical trials and meta-analyses indicate that addition of cilostazol to systemic antiplatelet therapy with aspirin and clopidogrel, following coronary stenting with DES or bare metal stents, leads to better patient outcomes than use of aspirin and clopidogrel alone, especially in patients with high-risk profiles.[14–19] Comparison of data from a large registry showed that triple therapy with cilostazol, aspirin, and clopidogrel, compared to aspirin and clopidogrel alone, significantly reduced 12-month risk of stent thrombosis and myocardial infarction after DES implantation.[20] These studies provide a rationale for local delivery of cilostazol from a stent in conjunction with

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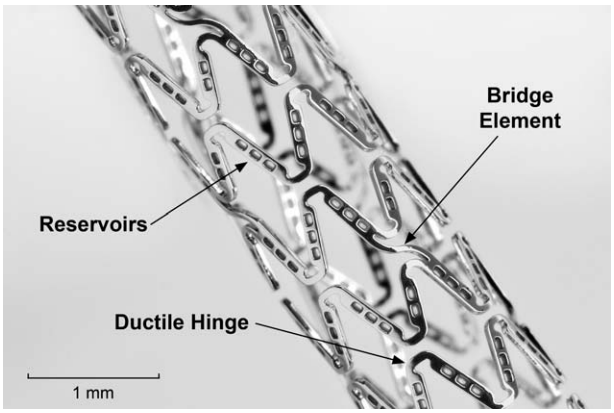

FIGURE 1. RES TECHNOLOGY™ stent platform showing major design features.

systemic use of dual antiplatelet therapy (DAPT) for a greater margin of safety against stent thrombosis without additional bleeding risk from systemic cilostazol administration, as well as eliminating the problem of medication compliance.

The RES TECHNOLOGY™ Platform is a new stent design that provides an alternative to conformal stent coatings for local drug delivery (Figure 1). Instead of using a non-degradable polymer coating for drug release, it uses discrete reservoirs and a bioabsorbable poly-(lactic acid-*co*-glycolic acid) (PLGA) polymer matrix, or inlay, for drug delivery. PLGA has been used in a wide range of approved biomedical applications, including absorbable sutures, orthopedic devices, and controlled drug-delivery implants.[21,22] It degrades *in vivo* by hydrolysis of ester linkages to lactic acid and glycolic acid residues that are subsequently metabolized via the Krebs cycle to carbon dioxide and water.[23,24] The reservoir-based design platform eliminates the risk of idiosyncratic reactions to permanent polymer coatings that may play a role in late stent thrombosis.[25] More importantly, the reservoir-based design makes it possible to release more than one drug from a stent with independent release kinetics and directional control for each drug. The platform has demonstrated its effectiveness in the RESELUTION-1 clinical trial with the NEVO™ Sirolimus-eluting Coronary Stent.[26,27]

The potential to elute a potent antithrombotic agent like cilostazol from the luminal surface of a stent to mitigate the problem of stent thrombosis while independently co-eluting sirolimus from the abluminal surface (Figure 2) could represent an important advance in vascular therapy with DES, particularly in the treatment of high-risk patients. The main objectives of this study are to: (1) develop a stent utilizing the reservoir-based design with controlled luminal delivery of cilostazol, (2) examine the cilostazol/PLGA formulation parameters that affect cilostazol release kinetics and duration, and (3) demonstrate *in vitro-in vivo* correlation of cilostazol elution.

EXPERIMENTAL

Preparation of cilostazol filled stents

Cilostazol (mw 368.47, 99.59% pure, Haori Pharma-Chem Inc., Edison, NJ) and poly-(lactic acid-*co*-glycolic acid) polymer (Durect Corp., Cupertino, CA) were solubilized using dimethyl sulfoxide (DMSO, Sigma). Filling solutions contained various weight proportions of cilostazol and PLGA in the range of 50/50 to 70/30 (w/w). RES TECHNOLOGY™ stents were made of cobalt-chromium alloy (L-605) with reservoirs arranged uniformly along the stent struts. The reservoir filling process used a high speed, optically-guided, piezoelectric injection system to load a drug-polymer-solvent formulation into each reservoir. A series of reservoir filling and drying steps was carried out until all the inlays were deposited and the desired total drug content was obtained. Inlay designs with varying cilostazol/PLGA ratios were prepared for evaluation of release kinetics (RK). Each filled reservoir contained the same solid inlay composition. DES was prepared using two different reservoir designs. Stents of the first design were made using only a single drug-polymer inlay composition comprising cilostazol and PLGA, called a "monolithic" design. The second design, called an "abluminal barrier" design, was made by depositing the cilostazol-PLGA inlay and covering it with an abluminal-side layer comprising PLGA alone. Polymer inlay deposits were prepared with PLGA that had a lactide to glycolide molar ratio of 75:25 (inherent viscosity 0.68 dL/g) or 50:50 (inherent viscosity 0.38 dL/g).

Optical microscopy

The polymer/drug filled reservoirs were observed using an optical microscope (Keyence Digital Microscope model VHX-500) equipped with polarizers. The polarizers were fully crossed to observe birefringence to determine morphological features of the reservoirs.

Thermal analysis

A Mettler Toledo DSC 822 differential scanning calorimeter (DSC) was used to analyze pure drug substance and drug-polymer formulations for their respective crystallinity, drug-polymer miscibility, and potential interactions. Drug and stent formulation samples were compacted and crimped into 40 μL aluminum DSC pans and tested at a heating rate of 10°C/min.

Determination of cilostazol *in vitro* release kinetic profile

The release medium used for drug RK profile evaluation was phosphate buffered saline (PBS, Sigma P-5368) containing 4% (wt/v) bovine serum albumin (BSA, Albumin Bovine Serum Fraction V, Sigma A-9647) and 0.02% sodium azide (NaN_3, Sigma) as a bacteriostat. Drug release kinetics from

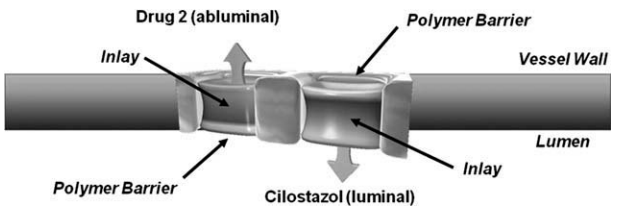

FIGURE 2. Schematic representation of dual drug inlay design in a reservoir-based stent.

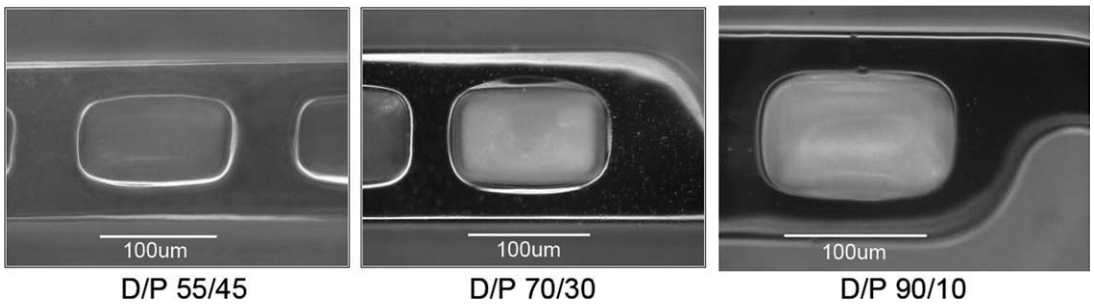

FIGURE 3. Optical micrographs of cilostazol-PLGA blends at various D/P ratios (×800).

stents was determined using a Varian USP-7 apparatus (Model Vankel Bio-Dis #7) with an agitation rate of 5 dips/minute and a bath temperature of 37°C. Release media (15 mL) were changed at predetermined intervals to maintain infinite sink conditions. At selected time periods, the amount of cilostazol released into the media was assayed by HPLC. HPLC analysis was performed on an Agilent Model 1100 equipped with an auto-sampler and a Phenomenex Luna C18(2) column (RP, 3u, 4.6 × 100 mm). Cilostazol content was measured by UV detection at 258 nm. HPLC samples were prepared with the following protocol: an aliquot (1 mL) of release medium from each time point was transferred to a vial, 1 mL of acetonitrile was added and the mixture was sonicated for 15 minutes. The resultant protein precipitate was separated by centrifugation (Eppendorf 5413 C) at 14,000 rpm for 10 minutes and then 1 mL of supernatant fluid was withdrawn and assayed for cilostazol by HPLC. After the final RK time point, the cilostazol remaining in the stent was assayed by extracting the stent with 1 mL of acetonitrile. The drug mass-balance was calculated as the sum drug released + drug remaining on stent compared to the average initial drug measured on separate stent samples. At least three stents were assayed at each time point to construct the RK profile curve (cumulative percent cilostazol released vs. time) for a particular stent formulation. All stents were sterilized prior to RK profile determination.

Determination of cilostazol *in vivo* release kinetic profile

Cilostazol-eluting stents (3.0 × 17 mm) were mounted on balloon catheters, sterilized and implanted in coronary arteries (1–3 stents/pig) of 11–16-week-old Yorkshire swine (30–43 kg) under fluoroscopic guidance. Pigs were anesthetized and quantitative coronary angiography (Medis QCA-CMS 6.0 system) was used to facilitate stent deployment at a balloon:artery ratio of 1.05–1.15:1. An initial heparin bolus (~400 U/kg, IV) was administered to achieve an activated clotting time of >300 seconds. Oral antiplatelet therapy consisting of aspirin (325 mg) and clopidogrel (300 mg loading dose + 75 mg maintenance dose) was administered daily until animals were euthanized. Stents were explanted at 1, 3, 8, 14, and 30 days postimplantation to establish the RK profile.

Stented arteries were harvested intact and stored at −70°C. Subsequently, stents were brought to room temperature and the surrounding arterial tissue was carefully dissected away. Cilostazol was extracted from the stents using acetonitrile, and HPLC was used to determine the cilostazol content. The mean drug content of unimplanted stents was used as the initial drug loading dose. Explanted stents were assayed for drug at each time point and the amount of cilostazol released was calculated by difference; these values were used to construct the cumulative drug release versus time RK profile.

All animals utilized were cared for according to policies and principals established by the Animal Welfare Act and NIH Guide for Care and Use of Laboratory Animals.

RESULTS AND DISCUSSION

Cilostazol morphology in reservoir matrix

The morphology of cilostazol/$PLGA_{75:25}$ inside stent reservoirs containing drug-polymer (D/P) ratios of 55/45, 70/30, and 90/10 (w/w) were determined using cross-polarized optical microscopy. There does not appear to be any macro-phase separation between the drug and polymer, and crystalline drug domains appear to be uniformly dispersed in the polymer matrix over this range of D/P ratio (Figure 3). It should be noted that the resolution of optical microscopy (800×) is not high enough to quantify the dispersion (e.g., phase size) of the drug in the polymer matrix. Figure 4 shows the first heat differential scanning calorimetry (DSC) scans of as-received cilostazol, cilostazol precipitated from DMSO by drying, and cilostazol/PLGA in a filled stent reservoir. The first heat DSC scan of the as-received drug shows

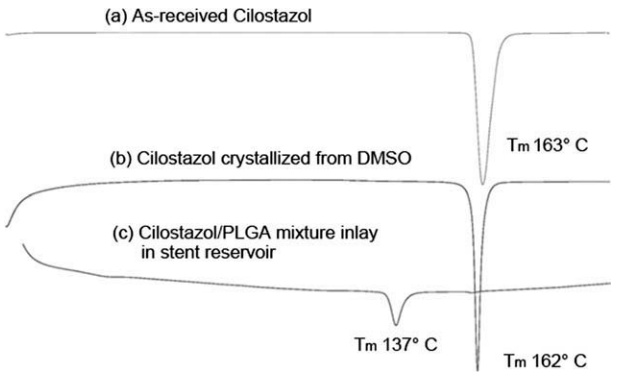

FIGURE 4. DSC Thermograms (first heat): (a) as-received cilostazol; (b) cilostazol crystallized from DMSO; and (c) cilostazol/PLGA 75:25 mixture inlay in stent reservoir.

a large crystalline melting endotherm with an onset temperature of 158°C and a peak melting temperature of 163°C. When cilostazol is dissolved and precipitated from DMSO, the crystalline structure is preserved and the melting endotherm is observed at the same temperature, but the melting transition is sharper compared to the as-received cilostazol. For the drug-polymer formulation in a filled stent, the endotherm is smaller with an onset temperature at 134°C and peak at 137°C. Form A is the polymorphic structure of as-received cilostazol and crystallized cilostazol from DMSO as it melted at about 162°C. Form B is the polymorphic structure of cilostazol in the drug-polymer formulation, as the melting point was about 137°C. These observations correspond with previously reported literature values determined by DSC and X-ray diffraction patterns.[28]

Development of a release medium for cilostazol-eluting stents

When conducting *in vitro* drug elution measurements, the release medium had to provide infinite sink conditions for each time period to ensure that drug release would not be artificially limited. Cilostazol is reported to be 95–98% protein bound in blood, principally to serum albumin.[29] Thus, we added 4% bovine serum albumin (BSA) to phosphate buffered saline (PBS) release medium to mimic *in vivo* conditions. The solubility of cilostazol (2.9 μg/mL in 0.01*M* phosphate buffered saline at 37°C) was increased to 38 μg/mL in PBS containing 4% BSA at 37°C. Use of PBS-BSA as the release medium reduced the volume required to maintain sink conditions to 15 mL and provided cilostazol release kinetic profiles that generally correlated to those observed *in vivo.*

Directional release control of cilostazol from stent

In most DES, the drug is contained in a conformal strut coating covering the entire metal surface. When the stent is deployed in an artery, the drug is released in all directions: luminally (toward the vessel lumen and bloodstream), abluminally (toward the vessel wall) and from the sides of the stent struts. In a stent with reservoirs, drug release can occur only from the luminal or abluminal surfaces of the reservoir inlay. Conceptually, in the "monolithic" design where the stent reservoirs contain a single drug-polymer inlay composition, cilostazol is available from both reservoir surfaces and can elute in both the luminal and abluminal direction at similar rates (i.e., bidirectional release). In the "abluminal barrier" design, reservoirs are initially filled with a drug-polymer composition followed by an overlying layer of polymer on the abluminal side. Compared to the luminal surface, the abluminal surface polymer inlay serves as barrier to drug elution, so initial drug release will be greater in the luminal direction. The drug/polymer matrix of each reservoir serves as the depot for sustained drug release over time. Since the drug needs to cross an additional polymer barrier on the abluminal surface, the bulk of drug transport and diffusion from the reservoir would be directed toward the luminal surface. Effectively, cilostazol elution in both the initial and sustained time phases would favor luminal release.

To evaluate the ability to control the release direction of cilostazol from stents, reservoirs were filled using both monolithic and abluminal barrier inlay designs for comparison of *in vitro* elution profiles. The monolithic design loaded reservoirs with a cilostazol/PLGA matrix consisting of a D/P ratio of 50/50 (w/w), using a total cilostazol dose of 285 μg on a 3.5 mm × 17 mm stent. The abluminal barrier design loaded the same initial drug/polymer matrix as the monolithic design, with a D/P ratio of 50/50 w/w. However, an additional layer of PLGA was deposited on the abluminal surface to cover the drug-matrix in the reservoir. Thus, the bulk of the reservoir inlay was identical to the bidirectional design, but the composition of the abluminal surface was predominantly PLGA. In both designs, the drug matrix polymer and the barrier polymer was $PLGA_{75:25}$ (inherent viscosity, IV = 0.68 dL/g). The average thickness of drug-polymer matrix was about 65–75 μm and the average thickness of the abluminal polymer barrier was about 15 μm.

Cilostazol *in vitro* release kinetic profiles in PBS-4% BSA media were determined at 37°C for stent samples of both reservoir designs and the average RK profiles are shown in Figure 5. At the same total drug dose, the elution rate for the abluminal barrier design was substantially slower than the monolithic reservoir design. The observed effect is consistent with the attenuation of abluminal cilostazol release by the polymer barrier, leading to cilostazol release predominantly from the luminal side and an overall slower release rate compared to the monolithic design. Given the desired antithrombotic function of cilostazol, sustained release of cilostazol from the luminal side would be the favored cilostazol formulation for this stent.

The Higuchi analysis[30] of various cilostazol release curves gave plots for both reservoir designs that were linear for about 80% of total drug release, indicating that the majority of cilostazol release is diffusion controlled and the $PLGA_{75:25}$ matrix does not change over a 30- or 50-day

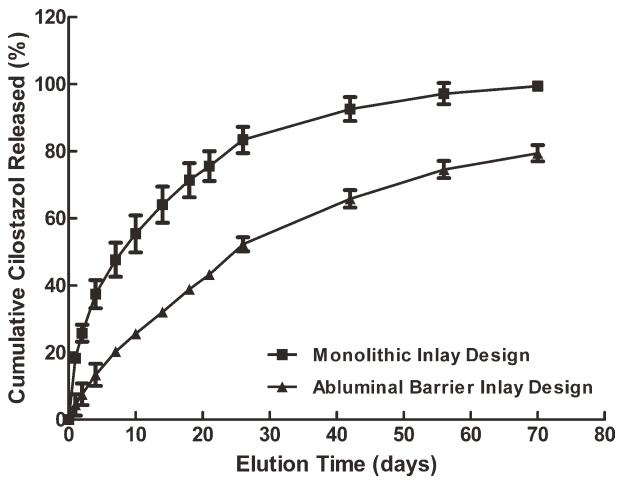

FIGURE 5. Cilostazol release kinetic profiles for monolithic (bidirectional) vs. abluminal barrier (unidirectional) inlay design stents (D/P 50/50–PLGA75:25 system).

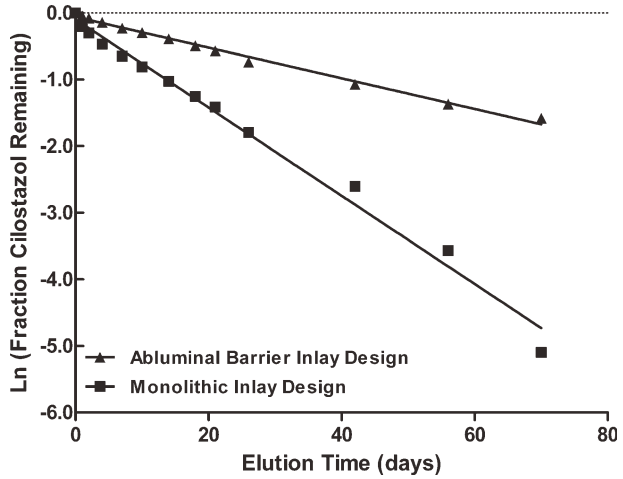

FIGURE 6. Cilostazol release rate plots for monolithic (bidirectional) vs. abluminal barrier (unidirectional) inlay design stents (D/P 50/50–PLGA75:25 system).

elution period for monolithic or abluminal barrier designs, respectively. Additionally, the elution rate constants were determined as shown in Figure 6. The plots were found to be linear over the first 80% of the release duration, indicating that for both stent inlay designs, cilostazol release followed first-order release kinetics. The rate constant for the first-order elution was 0.0245 d^{-1} ($r^2 = 0.996$) and 0.0604 d^{-1} ($r^2 = 0.996$) for the abluminal barrier and monolithic design stents, respectively. The ratio of first-order release rate constants from the bidirectional release reservoir design to that of the predominantly luminal direction release design was about 2.5, supporting the hypothesis that a polymer barrier can attenuate the abluminal release rate and create a substantially luminal releasing stent. Thus, incorporation of a polymer barrier on the abluminal side of the reservoir reduced the cilostazol elution rate by about 50% compared to a monolithic design. These observations are consistent with a unique capability of a stent using the reservoir-based design to modulate the direction of cilostazol release predominantly toward the vessel lumen.

Photomicrographs of the luminal and abluminal reservoir surfaces of a filled reservoir at D/P of 55/45 for initial stents and stents after 30 days elution were taken. Under cross-polarized microscopy, the luminal surface showed some crystalline dispersed drug, while the abluminal surface shows only amorphous polymer. After 30 days, about 65% of the cilostazol had eluted and the luminal surface was eroded, while the abluminal surface was intact with some minor swelling of the PLGA evident.

Effect of cilostazol/PLGA ratio (D/P ratio) on *in vitro* release kinetics

The effect of the ratio of cilostazol to PLGA (D/P) on the *in vitro* release profile was examined for stents with the abluminal barrier design. Stent reservoirs were filled with either a D/P of 70/30 or 55/45 w/w mixture of cilostazol/PLGA in the drug matrix, followed by a pure PLGA abluminal-side layer. Additionally, the effect of the lactide to glycolide molar ratio (L:G) in PLGA on release kinetics was evaluated using either $PLGA_{75:25}$ or $PLGA_{50:50}$ for both the drug-matrix and polymer barrier inlays.

The effect of D/P ratio on *in vitro* RK profile in stents prepared entirely (i.e., both drug-matrix and barrier inlays) with $PLGA_{75:25}$ (IV = 0.68 dL/g) is presented in Figure 7. Increasing the cilostazol content from 55% to 70% resulted in both an acceleration of the cilostazol release rate and a shortening of the release duration as measured by the time to elute >90% of the drug from the stent. While delivery of 90% of the cilostazol dose required 28 days for the D/P 55/45 mixture, stents prepared with the D/P 70/30 matrix mixture eluted the same proportion in only seven days. D/P ratio therefore represents a formulation parameter that can be used to modulate drug delivery duration over a relatively wide time interval. Higuchi plots were linear for stents prepared at both D/P ratios and cilostazol appeared to be released by a diffusion-controlled mechanism for over 80% of the RK profile suggesting minimal change occurred to the $PLGA_{75:25}$ matrix while the drug elutes. The increase in release rate that occurred as the D/P ratio was increased from 55/45 to 70/30 was not due to an initial burst of drug or a change in release mechanism. Cilostazol elution maintained first-order behavior for at least 80% of the eluted dose in both cases as shown in Figure 8. The first order rate constant was sensitive to D/P in the range examined, increasing from 0.123 d^{-1} ($r^2 = 0.997$) at a D/P ratio of 55/45 to 0.362 d^{-1} ($r^2 = 0.995$) at a D/P ratio of 70/30. Thus, the use of $PLGA_{75:25}$ allows effective modulation of the cilostazol release rate from the stent in a first-order, diffusion-controlled process.

For comparison, the effect of D/P ratio on the *in vitro* release profile of stents prepared entirely (i.e., both drug-matrix and abluminal barrier inlays) with $PLGA_{50:50}$ (IV = 0.38 dL/g) is presented in Figure 9. Identical barrier designs as for $PLGA_{75:25}$ were prepared with the same drug-matrix D/P ratios of 55/45 and 70/30. Increasing the cilostazol proportion in the drug matrix deposits from 55%

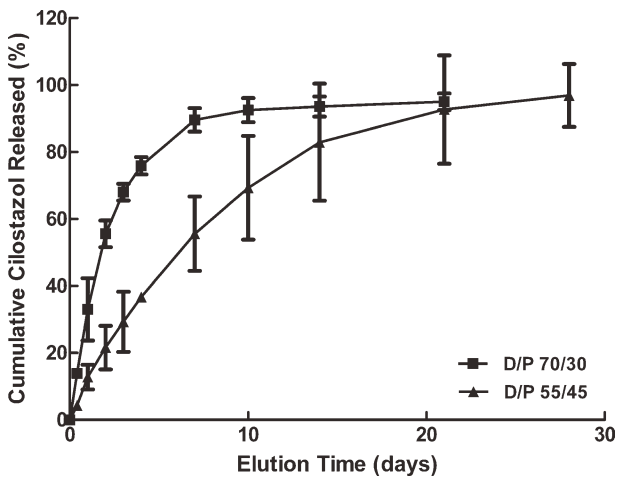

FIGURE 7. Effect of D/P ratio on cilostazol release kinetic profile: PLGA75:25 drug-matrix with PLGA75:25 abluminal barrier.

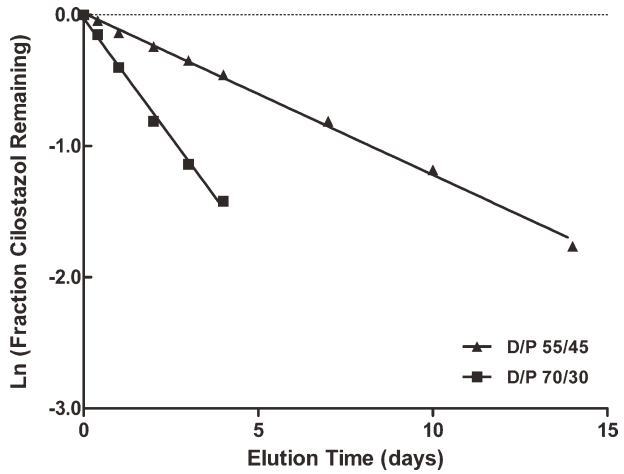

FIGURE 8. Effect of D/P ratio on cilostazol release rate: PLGA75:25 drug-matrix with PLGA75:25 abluminal barrier.

to 70% again resulted in an acceleration of the initial drug elution rate, but in contrast to $PLGA_{75:25}$, the total elution duration remained similar at about 28 days for both D/P ratios using $PLGA_{50:50}$. However, there was a notable change in the overall shape of the release profile from a first-order curve with $PLGA_{75:25}$ to a sigmoidal shaped curve using $PLGA_{50:50}$. Following an initial period of 2–4 days, where the rate followed first-order kinetics, the release rate slowed. After about 14 days, the rate increased again and continued until all drug was released. The post-14-day rate acceleration was greater for the D/P 55/45 reservoir formulation such that the overall release time was nearly identical to the D/P 70/30 formulation. Similar sigmoidal release profiles have been observed previously in the release of paclitaxel from PLGA filled stents[31] and of ciprofloxacin from $PLGA_{50:50}$ filled stents.[32]

The observed reduction in initial elution rate that creates the sigmoidal profile for the $PLGA_{50:50}$ formulation is hypothesized to be due to polymer swelling resulting from water ingress and subsequent constriction of surface accessible pores,[33] effectively reducing the surface area for drug elution. Hydrolysis of the more labile glycolide ester linkages that are present at a higher concentration in $PLGA_{50:50}$ has been reported to result in a faster water ingress rate than for $PLGA_{75:25}$.[34] The observed late stage rate acceleration would be consistent with a bulk erosion degradation mechanism for PLGA.[35,36] The same sequence of events is operative for both the D/P 70/30- and 55/45-based systems; coincidently, the overall time to complete drug release is nearly identical, despite a faster initial rate for the higher D/P ratio system.

In the $PLGA_{50:50}$-based system, a linear Higuchi relation was observed only for the first four days of elution (~12% cilostazol release) for the D/P 55/45 system and only the first two days (~28% cilostazol release) for the D/P 70/30 system. The deviation from linearity in the Higuchi plot after the initial 2–4-day elution period is postulated to reflect a change in the PLGA matrix, presumably due to matrix swelling and pore closure. In the high drug-percentage D/P 70/30 system, drug elution was more rapid in the initial stage of release (initial stage first-order elution rate constant was 0.16 d^{-1} ($r^2 = 0.972$)) than for the lower D/P 55/45 ratio system (0.03 d^{-1} ($r^2 = 0.955$)) (see Figure 10), and there was no linear relation in the Higuchi plot thereafter in the total 28 days of release. Cilostazol releases more rapidly from the polymer matrix in the 70/30 D/P inlay, and a larger polymer surface area therefore becomes available for water ingress. Swelling and possible pore closure can occur earlier in the elution profile with resultant reduction in the elution rate constant. The final stage increase in elution rate that characterizes the sigmoidal release profile begins at about the same time in both systems (after about 14 days), but the D/P 70/30 achieves a greater cumulative release and the "second burst" drug release is thus comparatively smaller. This observation is consistent with a nonspecific hydrolytic degradation of the PLGA 50:50 common

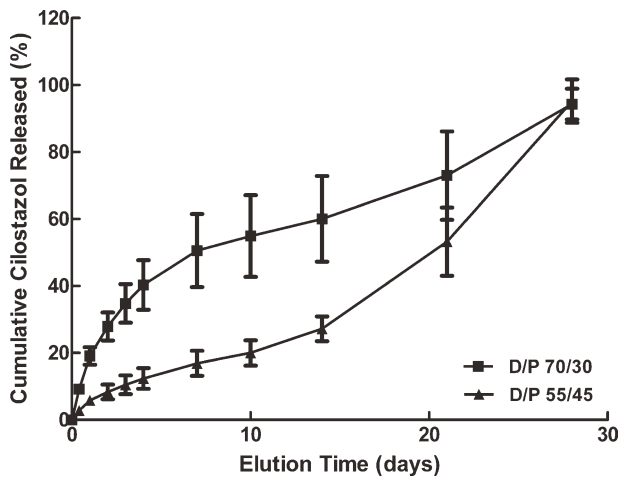

FIGURE 9. Effect of D/P ratio on cilostazol release kinetic profile: PLGA50:50 drug-matrix with PLGA50:50 abluminal barrier.

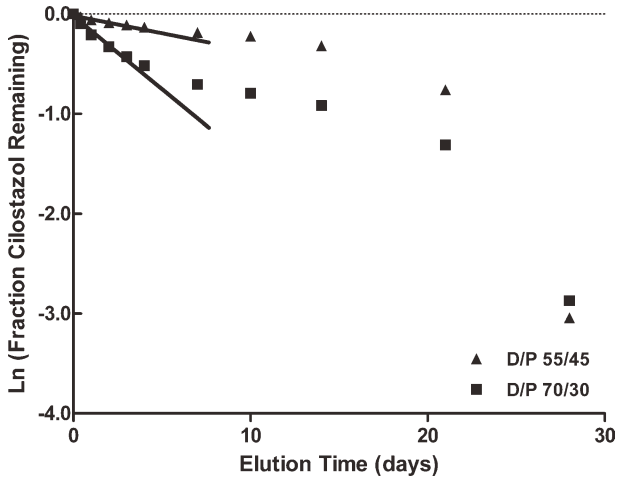

FIGURE 10. Effect of D/P ratio on cilostazol release rate: PLGA50:50 drug-matrix with PLGA50:50 abluminal barrier.

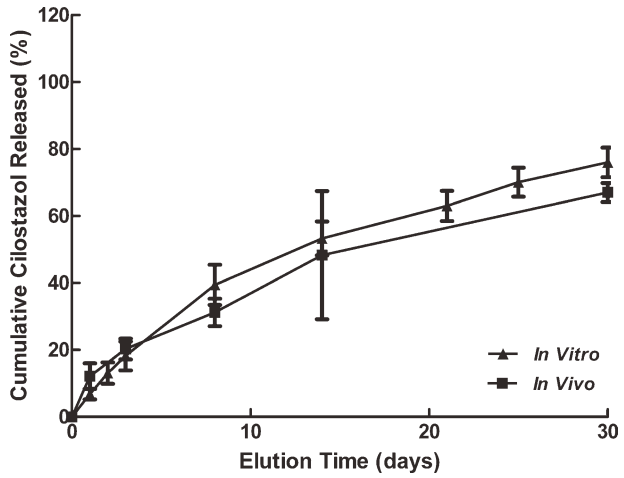

FIGURE 11. Cilostazol kinetic release profiles: *in vitro–in vivo* correlation (IVIVC).

to both systems and suggests that polymer matrices at both D/P ratios have fully hydrated.

In vitro-in vivo correlation for cilostazol RK for abluminal barrier design stents

The release kinetics of stents that contained a drug-matrix of cilostazol/$PLGA_{75:25}$ at a D/P ratio of 55/45 and an abluminal barrier of $PLGA_{75:25}$ were determined *in vitro* in PBS-4% BSA media using a USP-7 apparatus and *in vivo* at various times of implantation in a standard porcine coronary artery model. The results shown in Figure 11 suggest that there is an excellent correlation between the *in vitro* and *in vivo* RK profiles for cilostazol over 30 days. Cilostazol release (about 65–75% of total drug) over the first 30 days followed first-rate release kinetics, almost superimposable on the *in vitro* curve obtained in real time from the PBS-BSA medium in a USP-7 apparatus. This *in vitro-in vivo* correlation (IV-IVC) suggests that the PBS-BSA release system appears to be capable of predicting the *in vivo* release profiles of cilostazol/PLGA formulations in reservoir-based stents.

CONCLUSIONS

The RES TECHNOLOGY™ Platform (reservoir-based design) provides a novel stent configuration to expand the therapeutic potential of drug-eluting stents by making it possible to deliver drugs with directional control. Results from the current study showed that changes in the reservoir inlay design (monolithic or abluminal barrier) and the drug-matrix D/P ratio were effective in modulating the RK profile of cilostazol by altering the rate and duration of elution from the stent. An inlay design comprised cilostazol and PLGA 75:25 as the drug delivery matrix and an abluminal barrier comprised of $PLGA_{75:25}$ or $PLGA_{50:50}$ was shown to provide a predominantly luminal release of drug by a diffusion-controlled mechanism that followed first-order release kinetics. By controlling the cilostazol/PLGA ratio in the drug matrix inlays, the overall duration of release could be controlled over a range of 7–60 days.

In stents using $PLGA_{75:25}$ for both the drug matrix and barrier polymer, the *in vitro* release profile was shown to follow first-order release kinetics via a diffusion-controlled mechanism for over 80% of the eluted dose. For analogous $PLGA_{50:50}$-based inlays, however, *in vitro* cilostazol release followed first order kinetics for only the first 20–40% of the loaded dose and the Higuchi relation became non-linear, suggesting that the $PLGA_{50:50}$ matrix hydrated and swelled to a larger degree during cilostazol release in the intermediate period. The use of $PLGA_{50:50}$ produced a more complex sigmoidal-shaped release profile. Based on the more rapid degradation of $PLGA_{50:50}$ compared to $PLGA_{75:25}$, stent inlays prepared with the former polymer showed a late accelerated phase of cilostazol release which is consistent with polymer bulk erosion.

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