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A novel accelerated in vitro release method for biodegradable coating of drug eluting stents: Insight to the drug release mechanisms

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ABSTRACT

The major objective of the present study was to develop an accelerated in vitro release method for everolimus/poly(lactic-co-glycolic acid) (PLGA) biodegradable DES that reflects and discriminates between many different sources of variations in the manufacturing process by introducing organic solvents in the release medium. To get further insight into the underlying drug release mechanisms, alongside release studies, the surface changes of the coated stents and the molecular weight changes of the polymer upon immersion in the selected release media were examined by scanning electron microscopy and size exclusion chromatography. The incorporation of acetonitrile in the release medium resulted in an increase in the drug release rate due to an increment in total porosity of the matrices. The developed method reflected and discriminated between different sources of variations in the manufacturing process and correlated with the real-time release. Over 80% of everolimus release occurred within 24 h. The molecular and gravimetric weights of PLGA remained unchanged throughout the dissolution period, suggesting that the polymer does not undergo degradation through cleavage of its backbone ester linkages. It is likely that the drug release occurred mainly through its diffusion. The method can be employed as a rapid quality control test during development or commercial manufacturing.

1. Introduction

The localized drug delivery from drug-eluting stents (DESs) has been shown to be quite effective and accepted as one of the most promising treatment methods for preventing restenosis after stenting procedures (Beijk and Piek, 2007; Biondi-Zoccai et al., 2008; García-García et al., 2006; Kipshidze et al., 2005; Laroia and Laroia, 2004; Maeng et al., 2008; Moussa et al., 2004; Pendyala et al., 2008; Ramcharitar and Serruys, 2008; Rastogi and Stavchansky, 2008; Roiron et al., 2006; Sheiban et al., 2008). DESs ensure maximum delivery of the pharmacological agent(s) directly to the target site, since they are in immediate contact with the coronary artery wall. This results in therapeutically effective drug concentrations in the surrounding tissues with a minimal systemic release of the drug and thus, negligible risk of systemic toxicity (Tesfamariam, 2007, 2008; Vetrovec et al., 2006; Wiemer et al., 2008).

Drugs that have been successful in inhibiting restenosis include immunosuppressants sirolimus, everolimus and ABT-578 and the antiproliferative paclitaxel (Altman and Scazziota, 2003; Chapman and Perry, 2004; Nashan, 2002; Pascual, 2006; Patel and Kobashigawa, 2006; Versaci et al., 2002). The polymers used to deliver the drug can be biodurable such as poly-*N*-butyl methacrylate, polyethylene-vinyl acetate, styrene–isobutylene–styrene and phosphorylcholine methacrylate or biodegradable such as polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid) (PLGA) and polyanhydrides (Acharya and Park, 2006; Cristescu et al., 2007; Gunatillake et al., 2006; Hnojewyj et al., 2008; Kumar et al., 2002; Serruys et al., 2005; Varshney et al., 2007). Major interest in this area has focused on aliphatic polyesters such as polylactide-co-glycolides and their homopolymers due to the favorable toxicology of their degradation products (Middleton and Tipton, 2000). Within the body, the lactide/glycolide polymer chains are cleaved by hydrolysis to form natural metabolites (lactic and glycolic acids), which are eliminated from the body through the citric acid cycle primarily as CO_2 and H_2O. The drug compounds are mixed in the polymer matrix and gradually become released as the polymer is dissolved in the tissue (Acharya and Park, 2006; Zackrisson et al., 1995). The polymeric coating on a DES is designed to sustain appropriate drug release kinetics in order to deliver the therapeutic dose of the drug for the required time interval at the treatment site.

An estimation of the real-time release rate is critical for characterization of the DES dosage forms. The process, however, consumes significant time spanning weeks or months for sustained release of

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these dosage forms. This is disadvantageous in early research, and therefore not conducive for efficient management of product development. An accelerated (short-term) in vitro release method would be helpful for a rapid assessment of the formulation and processing variables (Zackrisson et al., 1995). Also, the accelerated in vitro release methods are desirable for the quality control, particularly in the establishment of specifications for releasing product batches. There are few literature reports on accelerated drug release testing from PLGA microspheres and other delivery devices (Agrawal et al., 1997; Alexis, 2005; Aso et al., 1994; Lindström et al., 1996; Makino et al., 1986; Shameem et al., 1999). The accelerated drug release from PLGA has been achieved by the increase in polymer degradation rate via acid or alkali catalyzed hydrolysis, addition of surfactants to enhance drug diffusion, or increase in temperature, which enhances polymer mobility and therefore drug diffusion. Of the various parameters (temperature, ionic strength, pH, enzymes, surfactants and agitation rate) that can be altered, the easiest way to achieve accelerated release has been reported to be an increase in temperature (Faisant et al., 2006). Although increased temperature appears to be a suitable method for accelerating the drug release/degradation of the polymer, concerns still remain, since the drug and the components of the medium are likely to undergo degradation under this stress condition employed.

The major objective of the present study was to develop an accelerated in vitro release method for everolimus/PLGA biodegradable DES that reflects and discriminates between many different sources of variations in the manufacturing process by introducing organic solvents in the release medium.

2. Materials and methods

2.1. Chemicals

All chemicals were at least analytical grade. HPLC grade acetonitrile (ACN) was obtained from Fisher Scientific (Somerville, NJ, USA). The 10% Tween20 (polyethylene glycol sorbitan monolaurate solution), sodium acetate, ammonium acetate, butylated hydroxytoluene (BHT) and porcine serum were purchased from Sigma–Aldrich (St. Louis, MO, USA). Acetic acid was obtained from J.T. Baker (Phillipsburg, NJ, USA). HPLC grade water was prepared by purifying demineralized water in a Milli-Q filtration system (Millipore, Bedford, MA, USA). The reference standard for everolimus was purchased from Novartis (Basel, Switzerland). The polystyrene standards were obtained from Polymer Laboratories (Fluka, Sigma–Aldrich, St. Louis, MO, USA).

2.2. In vitro release studies

The in vitro release studies were conducted using a USP apparatus7 (Reciprocating Disk/Stent Holder) 12-row system (Varian, CA, USA). Everolimus/PLGA 75/25 stents were loaded on the stent holders designed to prevent the stent from touching the side of the tubes and dipped in 8 ml release medium at 37 ± 0.5 °C. The medium was changed by advancing the apparatus to the next row of tubes containing fresh medium. Several release media containing different surfactants, surfactant concentrations and buffer concentrations were investigated. Agitation was determined in dips per min (dpm). During all the in vitro release studies, the agitation rate and temperature were maintained constant at 5 dpm and 37 °C, respectively. At the end of each dipping time interval, the samples were transferred into HPLC vials and analyzed for everolimus by reversed phase-high performance liquid chromatography (RP-HPLC) (Kamberi et al., 2008). After the last time point, the stents were separately transferred into 1 ml volumetric flasks containing 1 ml of 0.02% BHT/ACN solution, and the flasks were sonicated for 30 min at room temperature. The extracted solutions were transferred into HPLC vials and analyzed for the residual of everolimus.

For the long-term in vitro release study, the porcine serum with 0.1% sodium azide was selected as a "biorelevant" medium to simulate the in vivo condition, and the everolimus release was determined from the residual of everolimus on the stent.

2.3. Determination of molecular weight by gel permeation chromatography (GPC)

The molecular weight (Mw) of polymer matrices at time 0 (T_0) and each pre-determined dipping time interval prior to the medium change was determined by GPC using a Water series HPLC system (Waters Technologies, Inc., Palo Alto, CA, USA) provided with a binary pump, a thermostatted autosampler, a thermostatted column compartment, and a refractive index detector maintained at 37 °C. The data were collected and analyzed using Empower Software (Waters Technologies, Inc.). A Polymer Laboratories PGGel Mixed-D column (7.5 mm ID × 300 mm, 5 μm; Mw range, 200–400.000 Da) maintained at 50 °C served as stationary phase. The final chromatographic conditions involved an isocratic elution, with 0.1% lithium chloride in dimethyl acetamide (DMAC) as a mobile phase using a flow rate of 0.5 ml/min. The injection volume was 30 μl and the run time 35 min. The Mw was calculated from calibration curves obtained for polystyrene standards (Mw range, 3.5–320 kDa). The stents were dissolved in 0.3 ml of DMAC by shaking (150 motions/min) at room temperature for 2 h. To minimize possible contamination from plastic materials glass equipments (vials and syringes) were used. Weight average molecular masses were calculated based on polystyrene standards (319,000, 75,000, 23,800, 9580, and 3460 Da). The calibration was performed with every experiment. All the measurements were conducted in triplicates and the mean values and standard deviations reported.

2.4. Scanning electron microscopy (SEM)

The SEM studies were conducted on stents prior to and after exposure to the release media to observe surface morphology changes. The stents exposed to the release media were rinsed three times with water and padded dry with paper towel. All the stents were examined using a Hitachi S-4300 field emission scanning electron microscope (Hitachi Scientific Instruments, Mountain View, CA, USA). Images were taken of the coating surface at 40× and 300× magnifications (accelerating voltage of 10 kV).

2.5. Mass loss study

The stents were carefully weighed at T_0. After each pre-determined dipping time interval, three stents were rinsed with distilled water and dried for 72 h in a vacuum oven to a constant weight. The percentage mass remaining was calculated by the formula shown below:

$$\text{Percent mass remaining} = \frac{m_d}{m_i} \times 100\%$$

where m_i: initial mass of the stent; m_d: mass of the stent after dipping time interval.

2.6. Electron beam (E-beam) irradiation

E-beam irradiation was performed by employing a SureBeam® On-Site System (Kenneth et al., 2000). In brief, the stents were exposed to the irradiation field by passing under the scan horn.

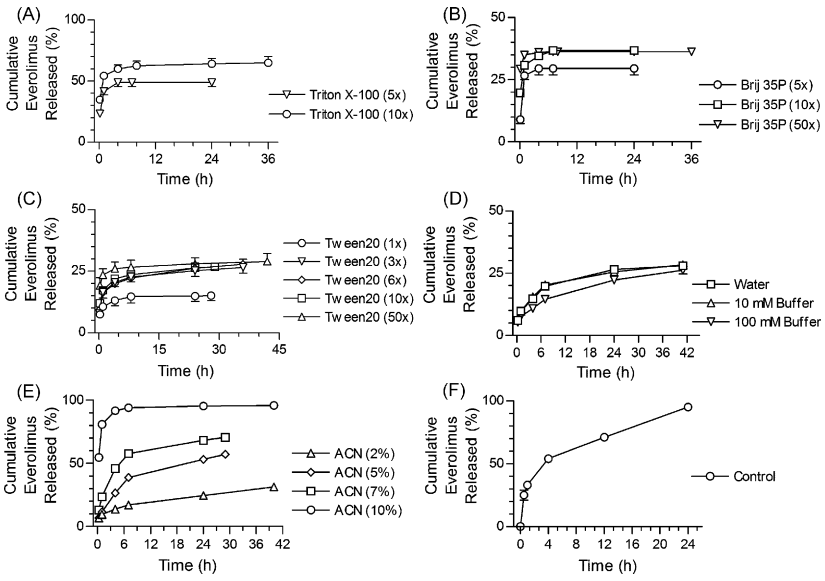

Fig. 1. The cumulative release rate profiles of everolimus in the media of deliberate variation in composition: (A) Triton X-100, (B) Brij 35P, (C) Tween20, (D) Buffer, and (E) acetonitrile concentration; (F) final conditions (7% (v/v) ACN at 0.5, 1, 4, and 12 h and 10% at 24 h in 0.4% Tween20 and 10 mM sodium acetate (pH 5.0)). Data represent mean and S.D. for $n = 12$.

The operating parameters (conveyor speed and scan height) were set accordingly to achieve the final dose delivery of 25, 45, or 60 kGy. The absorbed dose was measured by a Far West Radiochromic dosimetry film at the reference monitoring position. The quantity of radiation energy imparted per unit mass of the stent is referred as absorbed dose in gray (Gy).

2.7. Statistics

The comparison of in vitro release profiles was performed using the similarity factor, f2 (Moore and Flanner, 1996). The compared profiles were considered equivalent when f2 value of 50 or greater (50–100) was obtained.

3. Results and discussion

The choice of a suitable release medium is an important aspect in the in vitro release method development. Factors such as adequate solubility of everolimus in the in vitro release media to ensure 'sink' conditions under experimental conditions throughout the period of study, stability of the drug in the media and the media components during the entire period of study, as well as the economy for use were considered important aspects of the development phase of the method. During the initial stage of this work, several release media containing different nonionic surfactants, surfactants concentrations and buffer concentrations were investigated. Since nonionic surfactants generally have smaller critical micelle concentration (CMC) values than ionic surfactants and are known to be good solubilizers of hydrophobic substances such as everolimus, Brij 35P (tricosaethylene gliol dodecylether), Tween20 and Triton X-100 were selected (Cort et al., 2002; Lee et al., 2005).

The effect of media composition on the release rate of everolimus is shown in Fig. 1, where the cumulative percentage of drug 'released' into each release medium is plotted as a function of time. The in vitro release profiles of everolimus showed that an increase in the percentage of surfactant resulted in an increase in the release rate of everolimus (Fig. 1A–C). It is well known that the surfactant lowers the interfacial tension between the product and the release medium, allowing for a more rapid and possibly more complete penetration of the release medium into matrix (Makino et al., 1986). At higher surfactant concentrations, a greater amount of surfactant is incorporated into the matrix, which results in greater wetting/solubilization of the drug, and consequently increasing the drug release rate from the matrix (Jamzad and Fassihi, 2006; Nokhodchi et al., 2008, 2002).

Fig. 1D shows the effects of the concentration of the sodium acetate buffer on the release rate of everolimus. At 100 mM buffer concentration, only a slightly slower release occurred, compared to both the 10 mM buffer and the non-buffered systems. The calculated similarity factor f2 (values ranged from 70 to 97) indicates that the release rate profile of everolimus in the non-buffered system and 10 mM buffer is not different from the profile in the 100 mM sodium acetate buffer (pH 5.0), indicating that the buffer strength did not significantly influence the release profiles. This can be explained by the fact that everolimus is a neutral molecule, and as such its interaction with the acid end groups of PLGA is not impacted by the increase in the ionic strength of the release medium (Shameem et al., 1999). The slight decrease of everolimus release when increasing the buffer concentration from 10 to 100 mM might be attributable to the promotion of hydrophobic interactions at the higher salt level (Regnier, 1983). Judging by the cumulative percent release profiles, approximately 10–50% of the drug is released at a relatively rapid rate during the first hours, followed by slower or no release over the next 20 h. There was no observable increase in the rate or extent of everolimus release after 24 h with all the tested release media. Overall, the initial fast release rate is commonly ascribed to the drug detachment from the polymer surface, while the later slow release results from the sustained drug release from the inner layer. Neither of these release media compositions ensured at least 80% of everolimus release at the last time point, which is recommended as a specification for the accelerated release (FDA, 2008).

On the bases of the preliminary studies (Fig. 1E), a release medium containing 7% (v/v) ACN at 0.5, 1, 4 and 12 h and 10% at 24 h in 0.4% Tween20 and 10 mM sodium acetate (pH 5.0) was selected as especially suited for our application and employed in all other studies (Fig. 1F).

To get further insight into the underlying drug release mechanisms, alongside release studies, the SEM and GPC were used. The

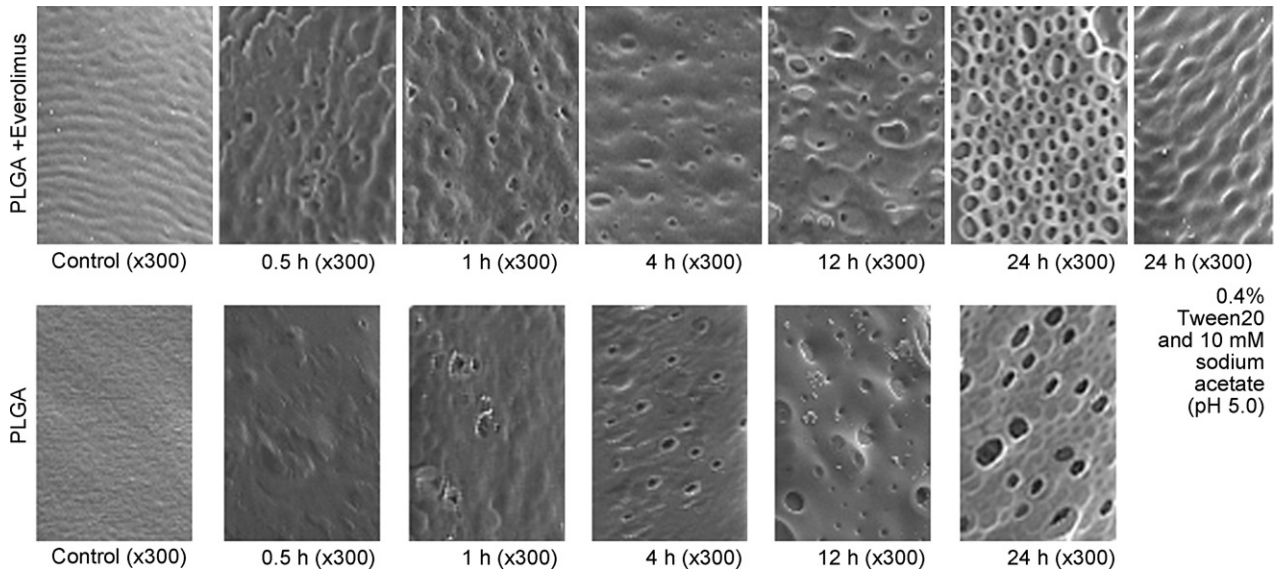

Fig. 2. The SEM images of the surface morphology of PLGA + everolimus/PLGA alone stents prior to (control) and after exposure to the release medium (7% (v/v) ACN at 0.5, 1, 4, and 12 h and 10% at 24 h in 0.4% Tween20 and 10 mM sodium acetate (pH 5.0)) overtime, or after 24-h exposure to 0.4% Tween20 and 10 mM sodium acetate (pH 5.0).

changes of the surface morphology of the PLGA alone/PLGA plus everolimus coated stents along with the molecular weight changes of the polymer upon stent immersion in the selected release media were examined. In addition, the changes of the gravimetric weight at the end of each test period were investigated. The SEM images are shown in Fig. 2. The control stents showed a smooth, nonporous surface. The polymer alone/polymer plus drug coated stents immersed in the release media for 0.5 and 1 h appeared to swell with a rougher surface, yet retaining their morphology, while the stents immersed in the release media for 4, 12, and 24 h exhibited an incrementally porous surface. However, no pores were observed on the surface of stents immersed in medium containing 0.4% Tween20 and 10 mM sodium acetate (pH 5.0) only (Fig. 2), no matter of the extent of the immersion time. Comparison of SEM images of polymer plus drug coated stents with those of polymer alone coated stents after exposure to the release medium overtime revealed an increased pore surface area/diameters and the number of total pores on the drug coated stents *vs*. polymer alone coated stents as the drug release progresses (Fig. 2). Therefore, it is speculated that the increased porosity of the stents with an increasing in the immersion time in the release media is attributed to the presence of ACN and the voids left behind by the released drug. ACN is well known for its swelling property, and it is likely that its presence in the medium produces a sufficient swelling of the polymer, which leads in the creation of pores (Chiu et al., 1995; Oh et al., 1999; Shi et al., 2006; Wise, 1995). The formation of these pores on the other hand gives transport pathway to the drug and facilitates its diffusion through the polymeric coating, leading to persistent enhanced release of everolimus throughout the 24-h dissolution period. The consistently circular shape of the pores created throughout the stent may be advantageous as well, allowing for a more precise control of the everolimus release over porosity.

The GPC and gravimetric weight mass loss data indicate that the polymer does not undergo degradation (hydrolytic or biodegradation) through cleavage of its backbone ester linkages. The molecular weight and gravimetric weight of PLGA remained unchanged throughout the 24-h dissolution period (Mw at T_0 and 24 h, ~96,000 Da; % mass remaining at 24 h, ~101%), suggesting that the everolimus release occurred mainly through its diffusion through the matrix pores formed due to the presence of ACN in the dissolution medium and the drug solubilization.

To demonstrate that the method is discriminative (i.e., sensitive to product quality in terms of release characteristics), everolimus/PLGA 75/25 coated stents were subjected to increasing levels of E-beam sterilization energy doses (25, 45, and 60 kGy) and the in vitro release profiles compared. As shown in Fig. 3, the dissolution profiles of the everolimus stents sterilized with 45 and 60 kGy are significantly different from that of the stent sterilized with 25-kGy dose (f2 values ranged from 23 to 40). In addition, to ensure that the method can detect the influence of critical manufacturing variables and differentiate between the different degrees of product performance, the coating parameters such as atomization pressure and stent-to-nozzle distance were modified. A comparison of drug release profiles obtained using the nominal manufacturing conditions (spray coater atomization pressure, 15 psi; stent-to-nozzle distance, 2.5 mm; and irradiation, 25 kGy) to that obtained using the modified manufacturing conditions (spray coater atomization pressure, 6.5 psi; stent-to-nozzle distance, 9.5 mm; and irradiation, 25 kGy) is shown in Fig. 4. The significantly different release profiles observed among products from different manufacturing variables (f2 = 40) indicate that the developed in vitro release method has enough discriminatory power to resolve manufacturing differences.

Importantly, the comparison of everolimus release profiles obtained at different days by different operators and different instruments indicated no discrepancies in the results (f2 values

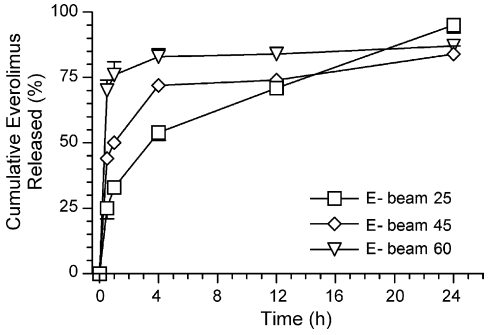

Fig. 3. The cumulative release rate profiles of everolimus from the stents e-beamed with varying sterilization dosages. Data represent mean and S.D. for $n = 12$.

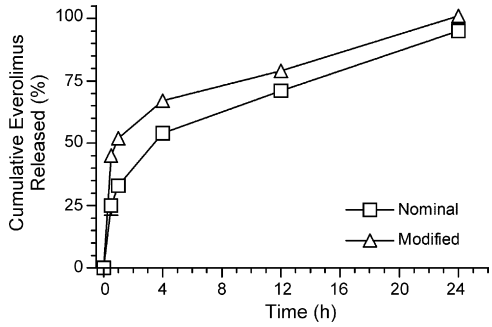

Fig. 4. The cumulative release rate profiles of everolimus under nominal (spray coater atomization pressure, 15 psi; stent-to-nozzle distance, 2.5 mm; and irradiation, 25 kGy) and modified (spray coater atomization pressure, 6.5 psi; stent-to-nozzle distance, 9.5 mm; and irradiation, 25 kGy) manufacturing conditions. Data represent mean and S.D. for $n = 12$.

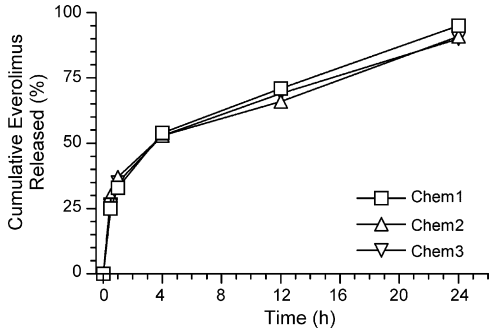

Fig. 5. The cumulative release rate profiles of everolimus obtained on different days by different operators. Data represent mean and S.D. for $n = 12$.

ranged from 74 to 86) (Fig. 5). Moreover, as indicated in Fig. 6, the method remained unaffected by small but deliberate variations in the procedural parameters such as buffer and surfactant concentrations (f2 = 73). These findings ensure that the validity of the method is maintained whenever it is used.

While with the developed method over 90% of everolimus was released within 24 h, with the long-term release method 85% of the everolimus release occurred at 30 days. The correlation between the short- and long-term releases was established for several studies by plotting different levels of release in days *vs*. hours, as shown in Fig. 7. The correlation coefficients (R^2) obtained were 0.9774, 0.9822 and 0.9966, indicating that the developed method correlates

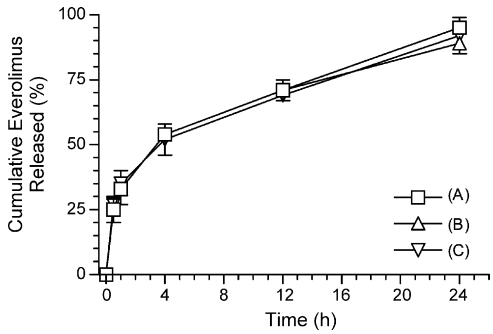

Fig. 6. The cumulative release rate profiles of everolimus in media of deliberate variations in buffer and surfactant concentrations. (A) Control medium composed of 7% (v/v) ACN at 0.5, 1, 4, and 12 h and 10% at 24 h in 0.4% Tween20 and 10 mM sodium acetate (pH 5.0); (B) Medium composed of 7% (v/v) ACN at 0.5, 1, 4, and 12 h and 10% at 24 h in 0.3% Tween20 and 5 mM sodium acetate (pH 5.0); (C) Medium composed of 7% (v/v) ACN at 0.5, 1, 4, and 12 h and 10% at 24 h in 0.5% Tween20 and 15 mM sodium acetate (pH 5.0). Data represent mean and S.D. for $n = 12$.

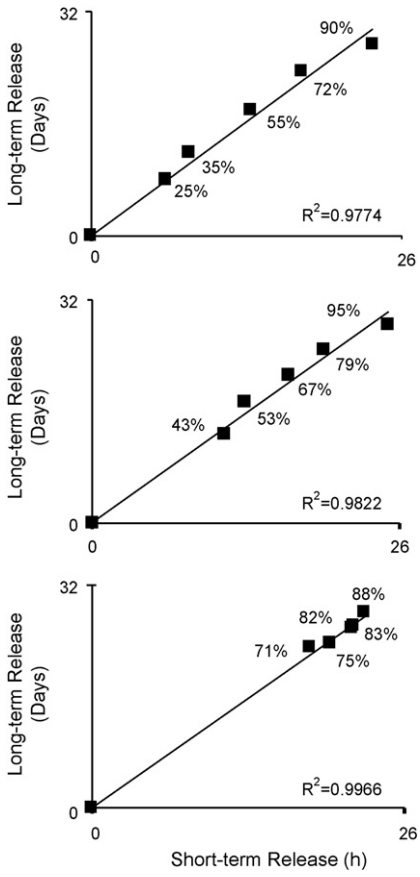

Fig. 7. Short- *vs*. long-term correlation of everolimus release from everolimus/PLGA 75/25 stents. (A) Stents manufactured/sterilized under nominal conditions (spray coater atomization pressure, 15 psi; stent-to-nozzle distance, 2.5 mm; and irradiation, 25 kGy); (B) Stents manufactured under modified conditions (spray coater atomization pressure, 6.5 psi; stent-to-nozzle distance, 9.5 mm) and sterilized with 25 kGy); (C) Stents manufactured under nominal conditions (spray coater atomization pressure, 15 psi; stent-to-nozzle distance, 2.5 mm) and sterilized with 60 kGy. Data represent mean and S.D. for $n = 6$.

well with the real-time release at 37 °C and allows for a prediction of the long-term release from the accelerated release profile (Burgess et al., 2002).

In summary, the incorporation of ACN in the release medium resulted in an increase in the drug release rate due to an increment in the total porosity of the matrices. The developed short-term accelerated release method reflected and discriminated between different sources of variations in the manufacturing process and correlated with the real-time release at 37 °C. The method can be employed as a rapid quality control test during development or commercial manufacturing. Through optimization of the experimental variables (surfactant concentration, buffer components, and percentages of the organic solvent), the current approach may be applied to evaluate drug release from a biodegradable matrix. Based on the obtained knowledge, the selection of an appropriate release medium for in vitro tests of the drug delivery systems can be facilitated, and an accelerated in vitro release method can be developed allowing for a rapid feedback on the release characteristics of a specific polymeric formulation.

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