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Rapid Development of an Accelerated In Vitro Release Method for a Novel Antibiotic-Eluting Biologic Envelope

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ABSTRACT

Introduction: A novel antibiotic-eluting biologic envelope has been developed to secure implantable devices, such as cardiac implantable electronic devices (CIEDs), while minimizing infection risk through the extended release of rifampin and minocycline. This envelope leverages the regenerative properties of an intact extracellular matrix to support tissue integration and healing. To advance clinical applications, product development, and manufacturing processes, a rapid and reliable method for assessing in vitro elution of antibiotics from the biologic envelope is essential. **Methods:** A rabbit subcutaneous dorsal implant model was used to evaluate in vivo drug elution. Initial in vitro studies identified optimal parameters for a final accelerated in vitro elution method. Tested conditions included dissolution media volume, pH, temperature, agitation speed, and surfactant additions. An accelerated elution method was optimized based on the tested parameters. **Results:** In vivo studies demonstrated rapid, immediate elution followed by gradual elution over 14 days, reaching at least 85% of total antibiotic content. Based on exploratory studies testing various parameters, an accelerated in vitro elution method was developed. This accelerated method produced 90% elution of both minocycline and rifampin by the final timepoints (6 and 30 hours, respectively), with minimal variability (relative standard deviation < 10%). Model fitting suggested that the in vitro method mimics the in vivo elution kinetics of the biologic envelope, with a strong linear correlation between dissolution methods for rifampin and minocycline. **Conclusion:** This study demonstrated the feasibility of a rapid process to develop an accelerated in vitro elution method. The accelerated in vitro method was validated and demonstrated a strong correlation with the in vivo elution kinetics of both antibiotics.

KEYWORDS: Antibiotic biologic envelope, accelerated in vitro elution, antibiotic elution, dissolution

INTRODUCTION

Innovations in surgical materials have fostered the development of specialized biologic envelopes to secure and isolate implantable medical devices, such as cardiac implantable electronic devices (CIED) and neurostimulators. These envelopes also offer an opportunity to reduce infection risk, which is a major adverse outcome of implantable devices (*1–4*). Approaches to mitigating the risk of device-related infection include the local delivery of antibiotics via the device envelope (*5*).

A next generation device has been developed that combines the powerful antibiotic drugs, rifampin and minocycline, with the regenerative capabilities of extracellular matrix (ECM) biomaterials to create an antibiotic-eluting biologic envelope. To avoid any physiochemical alterations to the biologic envelope that may be associated with a conventional drug coating or impregnation method, a drug-eluting disc composed of poly(lactide-co-glycolide) (PLGA) is integrated into the envelope. This approach ensures that key ECM properties, such as surface characteristics and porosity, remain unaltered, thereby supporting cell infiltration, angiogenesis, and tissue integration following implantation (*6–8*).

Assessing the release of drugs from the antibiotic-eluting biologic envelope in vitro is essential to evaluate the performance of these devices and ensure that they will

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deliver clinically meaningful antibiotic levels to the surgical pocket for an extended period following implantation. A reliable in vitro method for assessing drug release from the envelope is also needed to support manufacturing and quality assurance and to ensure consistent quality of the medical device between manufactured batches.

Developing a reliable dissolution method for the evaluation of extended drug release from an antibiotic-eluting biologic envelope is challenging. First, assessing the elution kinetics of a two-drug combination requires a dissolution environment suitable to both drugs. Rifampin and minocycline, for example, have different solubilities that could affect the elution characteristics of each drug. An ideal in vitro method would determine the elution of both drugs simultaneously in one experimental setup, with the goal of demonstrating at least 85% drug elution from the envelope by the final time point. Second, the method must provide results in a short time frame that reflect the real-time in vivo elution dynamics following implantation. Previous in vivo studies have demonstrated a biphasic pattern of drug release from an antibiotic-eluting biologic envelope, with an initial rapid elution followed by more gradual release, achieving 80–90% elution by 14 days post-implantation (*9*, *10*). Extended-release PLGA devices often require longer periods of time to demonstrate complete in vitro elution (IVE), which could significantly affect the timeline for lot release of products and negatively impact product shelf-life (*11*, *12*). As such, an accelerated IVE method is needed that can mimic the in vivo elution kinetics of the antibiotic-eluting biologic envelope. Third, a reliable IVE method must account for a range of variables that can affect drug release from biodegradable polymers. Factors demonstrated to affect polymer degradation and/or drug diffusion within the polymer include temperature, pH, and the addition of surfactants, among others (*13*, *14*).

Developing reliable methods for measuring drug elution from an antibiotic-eluting biologic envelope can be time-consuming and resource-intensive. This study aimed to develop an accelerated IVE method for assessing release of antibiotics from the biologic envelope and establish an in vivo-in vitro correlation (IVIVC).

METHODS

This study was conducted in compliance with Good Laboratory Practice (GLP) regulations and ISO-10993-6 guidelines. New Zealand White rabbits were sourced from an accredited and reputable supplier based in the United States that complies with international animal welfare standards. All animal procedures were conducted in accordance with institutional guidelines and approved by the Institutional Animal Care and Use Committee (IACUC). The study adhered to the principles outlined in the Guide for the Care and Use of Laboratory Animals.

Antibiotic-Eluting Biologic Envelope

The device under study is an antibiotic-eluting biologic envelope designed to support and stabilize CIED and other implantable devices post-surgery. The device is constructed from perforated sheets of decellularized, non-crosslinked, lyophilized ECM derived from porcine intestinal submucosa, combined with drug-eluting discs (EluPro, Elutia Inc., USA). The drug-eluting discs are made of PLGA infused with rifampin and minocycline and engineered to provide extended drug release. Rifampin and minocycline used in the formulation were pharmaceutical-grade materials that conformed to United States Pharmacopeia (USP) standards with purities of at least 99% and 91%, respectively, as determined by high-performance liquid chromatography (HPLC). All materials were procured from validated and Food and Drug Administration (FDA)-certified sources to ensure consistency and quality. PLGA is a well-described biodegradable polymer technology for controlled release of drugs in vivo (*15*, *16*). The antibiotic-eluting biologic envelope is engineered to contain 9.3 mg of minocycline and 10.5 mg of rifampin within the complete device (label claim).

In Vivo Elution Test Procedures

The New Zealand White Rabbit subcutaneous dorsal implant model was utilized to demonstrate in vivo drug elution of the antibiotic-eluting biologic envelope. This model enables thorough evaluation of the ability of the antibiotic-eluting biologic envelope to isolate and stabilize CIED and other subcutaneous devices. The anatomical similarity of the rabbit's subcutaneous dorsal pocket to the human chest wall enhances the relevance of this model for assessing drug release kinetics. Each animal underwent anesthesia using a standard protocol, and a small incision was made in the dorsal surface. An antibiotic-eluting biologic envelope containing a dummy CIED was inserted into the subcutaneous pocket, then the incision was closed.

To monitor drug elution, antibiotic-eluting biologic envelope samples for pharmacokinetic analysis were collected at 2 hours and 1, 3, 5, 7, and 14 days post-implantation. There were four animals for each time point. Animals were euthanized at predetermined intervals, and the antibiotic-eluting biologic envelopes were explanted and stored at –80 °C until analysis. Residual rifampin and minocycline in the explanted antibiotic-eluting biologic envelopes were quantified using a validated HPLC with

ultraviolet (UV) detection (HPLC-UV) method. The amount of accumulated drug released was determined by subtracting the residual antibiotic measured from the label claim of each drug within the device.

High-Performance Liquid Chromatography (HPLC) Analysis

Sample analysis was performed using a Waters ARC-HPLC system (205002445) equipped with an auto-sampler, column temperature controller, and UV detector. The column used was a Luna C18(2), 250 × 4.6 mm, with a 5-µm particle size. Mobile phase A consisted of 5-mM ethylenediaminetetraacetic acid (EDTA) in water, pH 7.2, and mobile phase B consisted of 20% 3-mM EDTA in water and 80% methanol, pH 7.2. The flow rate was 1.5 mL/min, and an injection volume of 20 µL was analyzed, with detection at a wavelength of 270 nm.

Calibration curves for rifampin and minocycline were constructed over a concentration range of 2–160 µg/mL, achieving an R^2 value of at least 0.99. The limits of quantitation (LOQ), based on a signal-to-noise ratio of 10:1, were 0.154 and 0.079 µg/mL for minocycline and rifampin, respectively, in 0.05% sodium citrate in phosphate-buffered saline (PBS) media. The LOQ of rifampin in 2% Triton X-100 in PBS with 0.05% sodium citrate was 0.159 µg/mL. The method was validated for accuracy, precision, and reproducibility in accordance with International Council of Harmonisation (ICH) guidance Q2(R1) and the USP.

Baseline In Vitro Elution (IVE) Test Procedures

Initial studies were designed to identify optimal parameters for a final accelerated elution method. The size and shape of the antibiotic-eluting biologic envelope precluded its testing in a compendial USP apparatus; instead, a custom-designed dissolution apparatus was employed to ensure complete immersion and physiological relevance. With approval from the FDA, dissolution testing was performed in an incubating shaker that securely held up to 12 wide-mouthed amber glass jars (250 mL capacity) and allowed for complete submersion of individual devices.

For each test condition, the antibiotic-eluting biologic envelope was submerged in a 250-mL amber glass jar with 60 mL of PBS, with 0.05% sodium citrate as the dissolution medium.

Sodium citrate was included in the formulation as a buffering agent to stabilize rifampin, which is sensitive to pH fluctuations (*17*). Citric acid and its derivatives are widely utilized in pharmaceutical applications for their buffering properties and ability to prevent degradation of sensitive compounds (*18, 19*). The inclusion of buffering agents in dissolution media has also been reported for assessing the release of rifampin from sustained-release formulations (*20*). As both rifampin and minocycline are sensitive to oxidation, previous studies investigating various antioxidants demonstrated that sodium citrate prevented degradation of both drugs effectively (data not shown).

The jar was agitated on an orbital shaker at 100 rpm and 37 °C. At specific time points throughout each experiment, the dissolution media was manually sampled (2 mL per time point), filtered using a 0.45-µm PTFE syringe filter, and replaced with an equal volume of fresh media. Levels of rifampin and minocycline were quantified using HPLC-UV. The accumulated drug released was represented as a percentage from the label claim of each drug within the device.

All baseline exploratory studies were performed with a sample size of 1.

Elution Test Parameters

Factors affecting drug elution were evaluated, including temperature, pH, agitation speed, dissolution media volume, and the addition of surfactants, as follows.

pH

Drug elution from PLGA polymers is sensitive to pH. In acidic environments, hydrolysis of ester bonds in PLGA is accelerated, which can lead to faster degradation of the PLGA matrix and thereby enhance drug release from the polymer. To test whether an acidic environment enhanced elution of rifampin and minocycline from the envelope, dissolution media at pH 4.5, 6.5, and 7.4 were evaluated following the baseline elution test method (i.e., the envelope was submerged in 60 mL of PBS with 0.05% sodium citrate and adjusted with hydrochloric acid [HCl] to pH 4.5, 6.5, and 7.4). Basic pH values were not tested.

Temperature

Elevated temperatures can improve drug elution by accelerating polymer degradation and enhancing drug diffusion within the polymer. As temperatures approach the glass transition temperature (Tg) of polymers, the polymer transitions from a glassy state to a rubbery state. In the rubbery state, polymer chains become more flexible, allowing for better drug diffusion. To test whether increased temperatures can improve elution of both drugs, elution behavior was investigated at 50 °C (slightly higher than the PLGA Tg of 47 °C) and at the

physiologic temperature of 37 °C by maintaining these temperatures within the incubating orbital shaker.

Agitation and Volume

Agitation methods and solution volume are critical in evaluating in vitro drug elution. It was hypothesized that greater agitation speed and greater volume could improve drug elution by the increased shear force generated from increased agitation, thereby promoting polymer degradation and improving sink conditions with greater volume. Drug elution from the antibiotic-eluting biologic envelope was evaluated at an agitation speed of 100 rpm and volume of 60 mL of PBS at pH 7.4 versus 150 rpm and 100 mL of PBS at pH 7.4.

Surfactant

Surfactants are often used in dissolution methods to improve the elution of poorly soluble drugs. Three surfactants were evaluated to improve rifampin release from the device: sodium dodecyl sulfate (SDS), Triton X-100, and Tween 20. Bound rifampin and minocycline in the remaining antibiotic-eluting biologic envelope were also quantified using the HPLC-UV method and presented as a percentage from the label claim of each drug within the device.

Accelerated IVE Method

The accelerated IVE method was optimized based on the above-mentioned parameters to construct a final accelerated dissolution method. Briefly, dissolution testing was carried out in a custom apparatus, as described above. Individual antibiotic-eluting biologic envelopes were submerged in 100 mL of dissolution media within a 250 mL amber jar. The dissolution medium consisted of PBS (pH 7.4) with 0.05% sodium citrate. The temperature of the assay was maintained at 37 °C in an incubating shaker, with agitation provided by orbital shaking at 150 rpm. Sampling intervals (2-mL aliquots) were at 0.5, 2, 6, 24, and 30 hours. After the 6-hour timepoint, Triton X-100 was added to a final concentration of 2% for the remainder of the assay. Samples were filtered through a 0.45-µm PTFE filter and frozen at –80°C until the completion of the assay. All samples were analyzed to determine rifampin and minocycline concentration using a validated HPLC-UV method. To demonstrate effectiveness of the accelerated IVE method, 12 samples from a representative lot of antibiotic-eluting biologic envelopes were tested in accordance with USP general chapter <711> Dissolution guidelines.

Data Analysis

Data were presented as the percentage of cumulative drug release (mean or median) with relative standard deviation (%RSD). Elution profiles were modeled using DDSolver software (add-in to Microsoft Excel) and fit to first-order, Higuchi, Weibull, and Korsmeyer–Peppas kinetic release models. The linear correlations between the accelerated IVE and in vivo elution profiles were determined by plotting the data in a manner similar to a Levy plot, with a best-fit line used to establish the correlation between the in vivo elution profile and the accelerated IVE profile.

RESULTS

In Vivo Elution Profile

Pharmacokinetic analysis using a subcutaneous dorsal implant rabbit model demonstrated continued elution of rifampin and minocycline throughout the 14-day period post-implantation (Fig. 1). As in previous studies, the drug release demonstrated a biphasic profile, with rapid immediate release of the drugs followed by a plateau of continued release for the remainder of the study. Median drug release was achieved by day 2 for both rifampin and minocycline. The cumulative release at day 14 was similar for both antibiotics, reaching 86% of total rifampin and 88% of total minocycline.

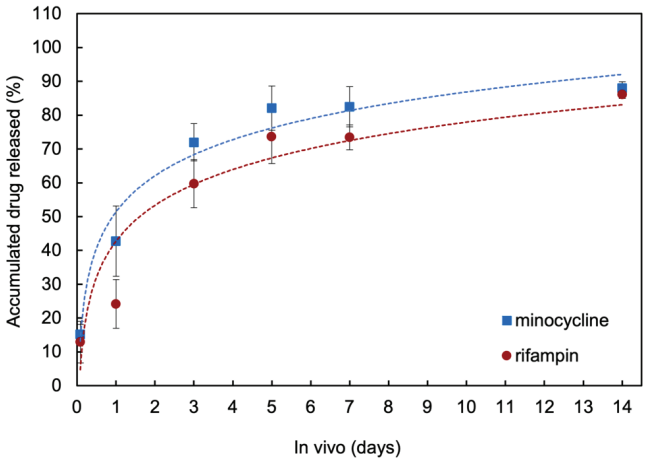

Figure 1. In vivo elution kinetics of minocycline and rifampin from antibiotic-eluting biologic envelope in a rabbit subcutaneous dorsal implant model (n = 4). More than 85% elution of both drugs was demonstrated by 14 days post-implantation.

Assessment of IVE Parameters

Effect of pH

Neutral conditions of pH 7.4 and 6.5 behaved similarly for both drugs, whereas the acidic condition of pH 4.5 resulted in significant loss of drug elution (Fig. 2a). This loss may be the result of drug degradation, as both rifampin and minocycline are unstable at low pH (17). These results justified selecting the physiologic pH of 7.4 for the accelerated IVE method.

Temperature

Although elution at 50 °C resulted in accelerated initial elution of both minocycline and rifampin, minocycline elution decreased after 4 hours (Fig. 2b), presumably due to degradation of minocycline at higher temperatures. Thus, it was concluded that the physiologic temperature of 37 °C was ideal for the IVE method.

Agitation and Volume

The higher agitation speed (150 rpm) and larger volume (100 mL) of dissolution media resulted in greater drug release at 30 minutes compared to lower speed (100 rpm) and volume (60 mL) (Fig. 2c). These findings suggest that increased agitation and volume improve drug release for both drugs, even within 30 minutes.

Surfactants

As observed in the studies evaluating temperature, pH, agitation speed, and volume, minocycline drug release was consistently greater than rifampin. The slower release of rifampin may be due to its poor solubility in aqueous solutions (*21*). Among the surfactants tested, Triton X-100 emerged as the most promising candidate, demonstrating the highest level of drug release (Table 1). Triton X-100 not only promoted drug release but also led to a reduction in the binding of drugs to the envelope, thus potentially improving the overall efficiency of the IVE method.

Although increased rifampin elution was observed with the addition of 2% Triton X-100 to the dissolution media,

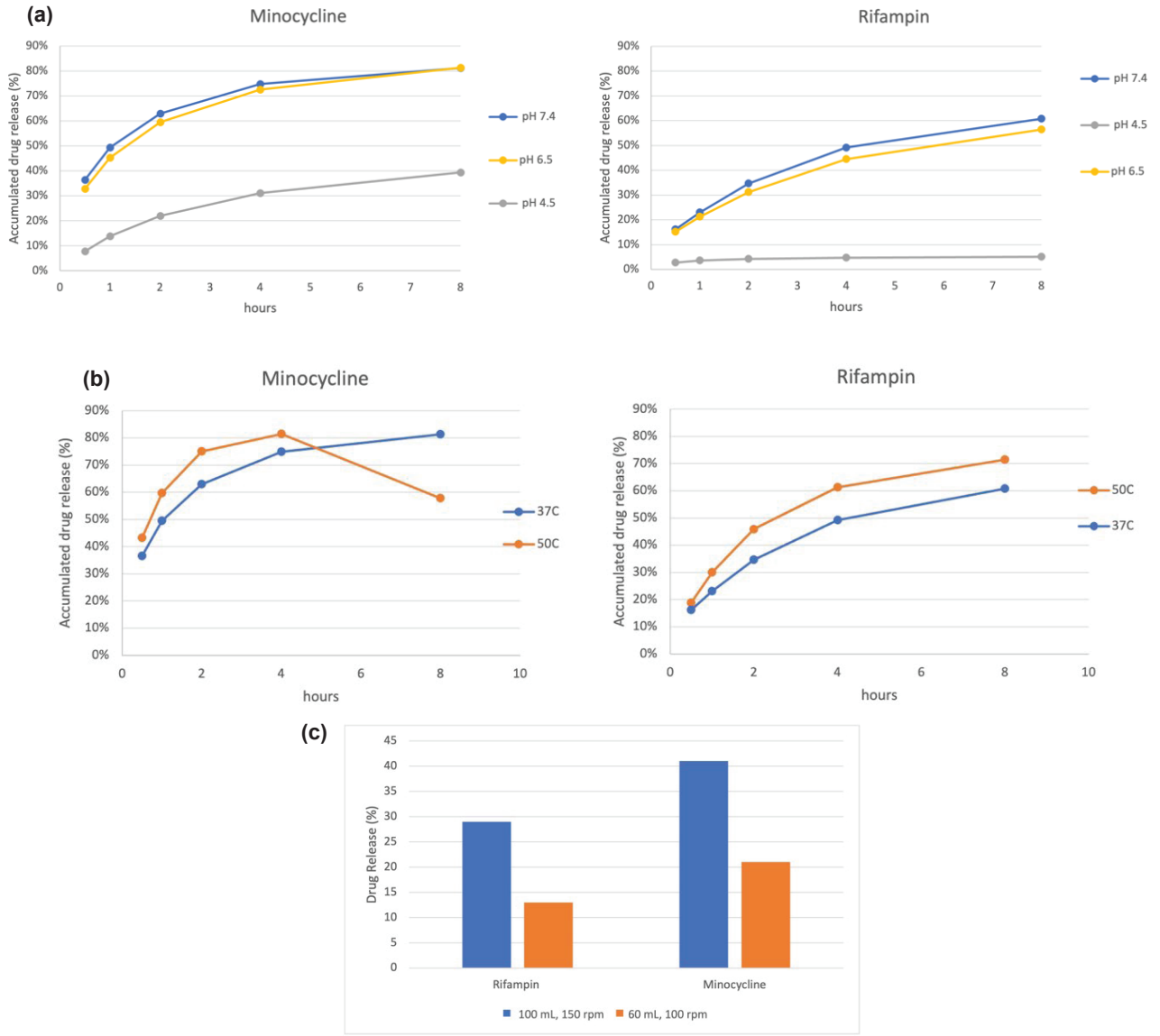

*Figure 2. Elution parameters investigated from the antibiotic-eluting biologic envelope. (**a**) Elution profile of minocycline and rifampin at pH 4.5, 6.5, and 7.4. (**b**) Elution profile of minocycline and rifampin at 37 °C and 50 °C. (**c**) Elution of minocycline and rifampin at 30 minute using different agitation speeds and dissolution media volumes.*

it also resulted in significant degradation of minocycline. This effect was observed when known concentrations of reference standards of minocycline and rifampin were prepared in dissolution media at pH 7.4 with 2% Triton X-100 and incubated at 37 °C for 24 hours. Percent recovery of minocycline at 24 hours was significantly decreased (45.6%) compared to rifampin (92.1%), which was exacerbated at 48 hours. Due to the negative effect of Triton X-100 on minocycline elution, the surfactant was added after minocycline elution was almost complete (6 hours) for the accelerated IVE method. Therefore, to preserve the complete elution of minocycline and maximize rifampin elution, the final IVE method includes adding Triton X-100 to a final concentration of 2% after the 6-hour time point.

Table 1. Effect of Surfactants on Rifampin Elution and Binding to the Biologic Envelope

	Rifampin Eluted	Rifampin Remaining in Biologic Envelope	Rifampin Remaining in PLGA Disc
Control	59%	6%	35%
1% SDS	63%	5%	28%
2% Triton X-100	78%	0.1%	22%
5% Tween 20	71%	0.4%	29%

Note: Rifampin was measured at 8-hour timepoint and presented as percent of expected drug content (Label Claim). PLGA: poly(lactide-co-glycolide); SDS: sodium dodecyl sulfate.

Accelerated IVE Method

Based on results of the exploratory studies assessing parameters affecting drug elution, an accelerated IVE method was developed.

Figure 3 shows the results of the newly optimized and accelerated IVE method using a representative lot of antibiotic-eluting biologic envelopes, demonstrating more than 90% elution of both minocycline and rifampin by the final timepoints (6 and 30 hours, respectively), with minimal variability (< 10% RSD at each time point).

Model Fitting of In Vivo and In Vitro Elution

The in vivo and accelerated IVE profiles were analyzed to determine the best fit models for both methods. The Weibull model provided the best fit for the in vivo and in vitro elution profiles for both minocycline and rifampin, as indicated by R^2 values (Table 2). Figure 4 shows the visual fit of the elution profiles within the Weibull model. This finding indicates that the accelerated IVE method indeed mimics the in vivo elution kinetics of the device. The correlation between dissolution profiles obtained in vivo and in vitro are also depicted in Figure 4. A strong linear correlation between the dissolution profiles was observed for both rifampin (R^2 = 0.9979) and minocycline (R^2 = 0.9990).

Table 2. Model Fitting (R^2 Values) for the In Vivo and Accelerated In Vitro Elution Profiles

		First Order Model	Higuchi Model	Korsmeyer-Peppas Model	Weibull Model
Minocycline	In vivo	0.8728	0.6549	0.9206	0.9706
	In vitro	0.7528	0.6408	0.9970	0.9972
Rifampin	In vivo	0.9141	0.8627	0.9093	0.9669
	In vitro	0.9611	0.6161	0.8562	0.9868

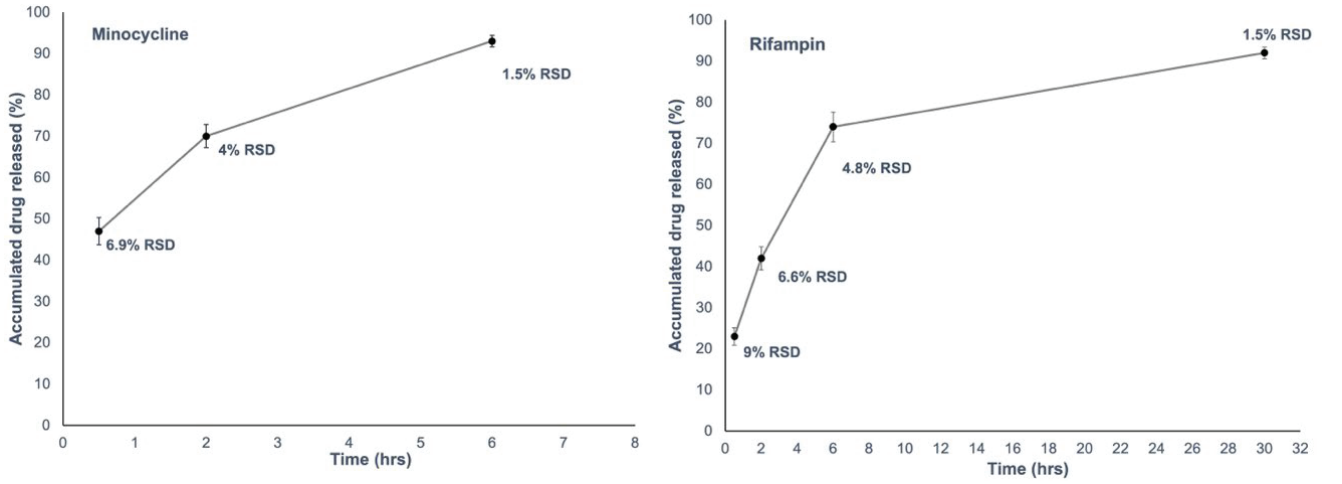

Figure 3. Accelerated IVE method results for minocycline and rifampin elution from antibiotic-eluting biologic envelopes for a representative lot. The mean of 12 replicates (± SD) and %RSD at each time point are plotted for minocycline and rifampin.
IVE: in vitro elution; RSD: relative standard deviation.

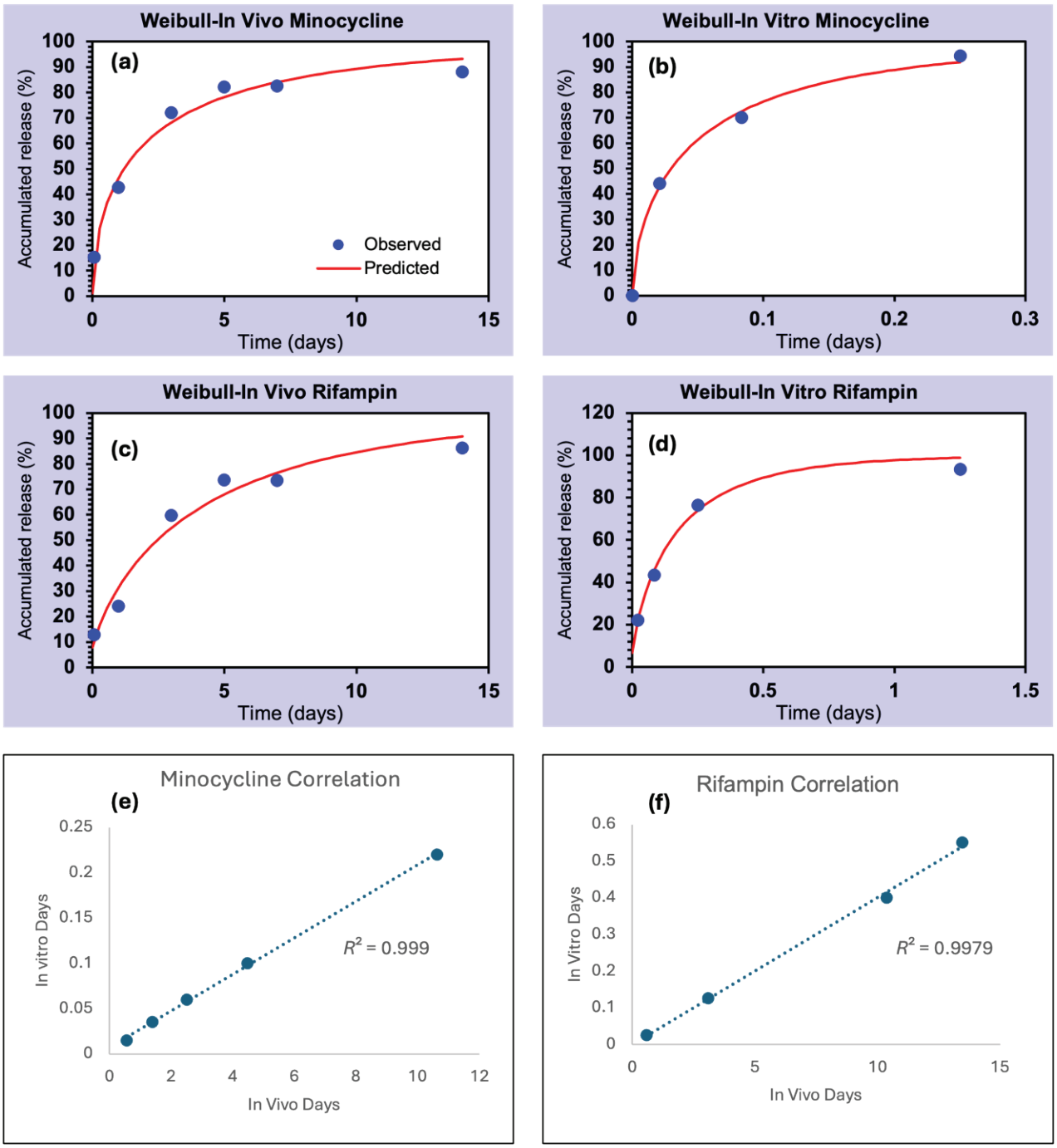

*Figure 4. Weibull model fitting of in vivo and accelerated in vitro elution profiles for minocycline (**a** and **b**) rifampin (**c** and **d**) and in vivo-in vitro correlation (**e** and **f**).*

DISCUSSION

This study demonstrated that an exploratory approach to identify key variables for an accelerated IVE method is feasible and effective. By comparing different parameters for variables such as temperature, agitation speed, pH of the dissolution media, and the addition of surfactants, this process identified a set of optimal conditions for a reproducible, accelerated IVE method to quantify the release of rifampin and minocycline from the antibiotic-eluting biologic envelope in a suitable time frame and with minimal variation.

Previous in vivo studies of antibiotic-eluting biologic envelopes have demonstrated a similar biphasic pattern of drug release as in this study, with an initial rapid elution followed by gradual release over 2 weeks, by which time 80–90% of total drug content was eluted from the envelopes (*9*, *10*). However, other studies have demonstrated slower drug release from PLGA-based

formulations in vitro compared with in vivo, perhaps due to local removal of the drug by blood flow, immunologic effects, or other factors (*14*, *22*, *23*). The accelerated IVE method developed in this study achieved more than 90% elution of both minocycline (within 6 hours) and rifampin (within 30 hours), thereby overcoming slow drug elution from PLGA in vitro. This accelerated method was validated using multiple replicates and demonstrated low variability (1.5–7.4% RSD) at every time point throughout the experiments.

An accelerated IVE method is essential for an assay that is intended for quality assurance, preclinical experimentation, and evaluation of modifications to the product. An accelerated IVE method also supports development of IVIVC studies that allow for comparison of elution kinetics of the antibiotic-eluting biologic envelope between in vitro experiments and physiologic conditions following implantation. Indeed, a strong linear correlation was established for both drugs in this study. The best fit model of kinetic release for both rifampin and minocycline was the Weibull model, suggesting that the accelerated IVE method closely matches the in vivo elution kinetics of the antibiotic-eluting biologic envelope.

Several of the identified parameters mimic physiologic conditions. The physiologic pH of 7.4 outperformed acidic conditions, as did the body temperature of 37 °C when compared to 50 °C. A higher dissolution media volume outperformed lower volumes, perhaps by preventing saturation of the media, thereby ensuring sink conditions and possibly emulating the effects of blood circulation.

Because rifampin is highly insoluble in aqueous media, additional conditions were tested to improve elution of this drug, including the addition of Triton X-100. Although Triton X-100 demonstrated the best elution of rifampin under the test conditions, it also caused degradation of minocycline. To compensate for this effect, the surfactant was added after 6 hours, when at least 90% of minocycline was eluted. Similar two-stage approaches to elution have been widely used in dissolution chemistry and brought the final elution for both drugs to more than 90%, although it required an extra step and additional time.

Limitations

The limitations of this study include the use of single-replicate tests in the exploratory phase to develop the final IVE method. This approach could miss inherent variability in the test conditions or materials and does not allow for a rigorous statistical analysis. Further, this exploratory approach may not be appropriate for the development of an IVE method for other materials, drugs, or test conditions.

CONCLUSIONS

A reliable, accelerated IVE method is essential to support quality assurance, preclinical experimentation, and the evaluation of modifications to drug-eluting biologic envelopes. This study demonstrated the feasibility of a rapid process for the evaluation of test conditions in the development of an accelerated IVE method for the assessment of drug release from biologic envelopes. The final accelerated IVE method was validated and demonstrated a strong correlation with the in vivo elution kinetics for both rifampin and minocycline from the biologic envelope following implantation in a rabbit model.

DISCLOSURES

Dana Yoo, Dan Deegan, Devon Strozyk, and Michelle LeRoux Williams are employees of Elutia Inc., and the manuscript has been written as part of their employment. No other financial support or conflicting interests have been declared by the authors.

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