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TUNABLE DUAL-PHASE DUAL-DRUG DELIVERY SYSTEM USING A PLGA MICROPARTICLE/PVA HYDROGEL COMPOSITE

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by

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A Thesis

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Dedications

I would like to dedicate this to my mom and my dad, without their support I would not be able to be where I am today, as well as my friends and family who helped me during all the stages of my life. I appreciate each and every one of you.

Acknowledgments

I would like to thank Dr. Erik Brewer, for his teaching, wisdom, guidance, and encouragement throughout my entire process. It was a privilege to work with and learn from him. I would like to thank my committee members, Dr. Vince Beachley and Dr. Sebastián Vega, for their continual support throughout my path to completing this thesis. I would like to thank the Rowan School of Engineering, both faculty and students, who helped me along the way whether they knew it or not. In particular, I would like to thank Ryan Bach and Lucinda Lau – without their contributions to our research, this thesis certainly would not be possible. I did not get here alone. I appreciate everyone who helped me achieve this goal.

Abstract

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Current drug-eluting coatings have demonstrated controlled long-term, sustained release but have only tried to mitigate burst release as a negative side effect. For applications like wound healing, there is a need for a drug-eluting coating which is adjustable in both short- and long-term release, independent of each other. We present a tunable dual-phase dual-drug delivery coating composed of drug-loaded polymer microparticles and drug-loaded hydrogel which can control short term and long-term release individually in this study. This coating was created using lidocaine and dexamethasone encapsulated in poly(D,L-lactide-co-glycolide) particles combined with lidocaine- and dexamethasone-loaded poly(vinyl alcohol) hydrogel. Hydrogel drug concentration and microparticle mass fraction were investigated for their impact on short-term and long-term release, respectively. A two week- long drug release study was performed with formulations varying only hydrogel drug concentration and only microparticle mass fraction. The results of this study show that PVA hydrogel drug concentration can control short-term release independently and drug-loaded PLGA particle mass fraction may control long-term release. This drug-eluting composite could extend the wear time of insulin infusion sets.

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Chapter 1

Introduction & Background

1.1 Diabetes

In the United States, 11.3% of people suffer from diabetes [1]. The United States spends over 327 billion dollars related to diabetes each year [2]. When a person with diabetes opts against using insulin injections, an insulin pump is the best option for treatment [3]. Patch pumps and inhalers also offer a sophisticated treatment option for diabetes patients. Some people do opt for these solutions, but they have their limitations. Patch pumps are expensive, have few available brands and most need to be changed after 3 days, which means replacing the whole device [4]. Insulin inhalers cause damage to lungs, coughing, can have compromised bioavailability and are still in need of long-term adverse effects data [5]. Insulin pumps offer many benefits over other treatment options and are a component of the artificial pancreas, the ultimate aspiration of diabetes treatment. However, there are critical weaknesses of the insulin pump that are preventing it from becoming more popular. Primarily, these weaknesses lie with the insulin infusion sets [6].

Insulin infusion sets, or IISs, provide a pathway for insulin to flow from the pump into the user's body. They consist of thin plastic tubing attached on one end to a cannula with a needle inside. The needle is used to insert the cannula into the skin where it will remain until it is removed. The insertion of the needle immediately triggers the foreign body response (FBR). The resulting inflammatory and fibrotic sequences of the FBR lead to critical failures of the IIS. These failures result in the need to change most IISs every

2-3 days due to increased variability of insulin absorption [7], [8]. One insulin infusion set, the Medtronic Extended infusion set, was able to achieve 7 days of wear time before the need to change it [9]. The resulting frequency of IIS change leads to a buildup of scar tissue at injection sites, which limits the amount and effectiveness of injection sites as time goes on. Moreover, even the seven-day wear time of the Medtronic Extended infusion, which is only available with the Medtronic MiniMed insulin pump, trails the wear time of a crucial component of an artificial pancreas, the continuous glucose monitor (CGM). Wear time for CGMs like the Eversense XL CGM System can reach up to 180 days [10].

1.2 Anti-Inflammatory Drugs

Pharmaceutical therapeutics, collectively called anti-inflammatories, have been developed to suppress the foreign body response (FBR) systemically. Dexamethasone and lidocaine are appealing choices for use in suppression of FBR. Dexamethasone is a corticosteroid commonly used as an anti-inflammatory [11]–[13]. Research groups have used dexamethasone on many occasions to suppress the foreign body response surrounding implantable devices [14]–[21]. Lidocaine, used typically as an anesthetic, is also promising as an anti-inflammatory [22]. It has been used to treat inflammatory conditions such as burn wounds, herpes simplex, ulcerative proctitis, and arthritis [23] and has been compared to steroids and NSAIDs in its anti-inflammatory action [24]. When these drugs are used in combination, there is a synergistic effect which improves the anti-inflammatory actions of either drug used individually [25]. Additionally, the dose of dexamethasone required to achieve local suppression of FBR is lower than that which

elicits a negative systemic response [26], [27]. These two drugs are promising candidates to combat local inflammation surrounding the IIS, but they come with a number of side effects. Corticosteroids, e.g. dexamethasone, can lead to adverse effects like increased blood pressure, gastritis, and decreased bone density [28]. These side-effects also include osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, Cushing's syndrome, psychiatric disturbances, and immunosuppression [29]. Lidocaine will also have serious negative side effects when accumulated in large doses in the blood plasma. These effects include dizziness, numbness, twitching, seizures, loss of consciousness, and comas [30]. Limiting the dosage of anesthetics, like lidocaine, can help prevent local anesthetic systemic toxicity (LAST), a life-threatening adverse effect of local anesthetic injection [31]. For these reasons, it is imperative to deliver these therapeutics to the target site as efficiently as possible. Local delivery of these drugs can prevent the unsafe effects of excess accumulation in the blood.

1.3 Drug Eluting Coatings

Drug eluting coatings are a proven method for dispatching drugs to the site of desired absorption. Coatings of this nature have long been used on implantable devices, like stents and glucose sensors [17], [18], [32], [33]. In the case of glucose sensors, polyvinyl alcohol (PVA) has had great success as a matrix for other drug containing vehicles. PVA demonstrates desirable material properties for inclusion in implantable coatings. It can be cross linked using the freeze-thaw cycle process, removing the need to use cross-linking agents. It also has a modulus similar to that of human skin which can be adjusted using the freeze thaw cycle [19]. However, drug eluting coatings typically

require a method for longer term drug release than a polymer matrix affords. For this purpose, polymer microspheres serve as a tunable vector for drug payloads that can increase the length of release.

1.4 Microspheres

Microspheres have been utilized for targeted drug delivery as early as 1974 [34]. More specifically, microspheres made from poly(lactic-co-glycolic acid) have been used clinically since 1986 as a system for controlled drug release [35]. Today, PLGA is one of the most common polymers used in drug delivery carrier systems [36]–[38]. It can be configured to control the release rate of its payload [19], [40]. It has desirable biocompatibility and biodegradability [41], [42]. PLGA's safety has been recognized by the US FDA and the European Medicines Agency, with the FDA considering it a pharmaceutical excipient [43]–[45]. As of 2021, at least twenty PLGA-based biodegradable microsphere systems have been approved for use in the market [46]. PLGA microspheres are an ideal candidate to incorporate into a drug-eluting coating for an implantable device for their pharmacokinetic and biocompatible properties.

Achieving zero-order release, or those that follow "near zero-order", is an ideal that many drug delivery systems hope to attain [47]. Benefits of zero-order, or sustained, release profiles include maintaining constant therapeutic blood levels of a drug for desired periods [48], eliminating toxic peak and inadequate valley drug concentrations stemming from multiple bolus deliveries [49], increasing the bioavailability of therapeutics [50], improving therapeutics cost-benefits [51], and improving patient-compliance to prescribed dosages [52]. Multiple strategies have been employed to

achieve this release profile, including biphasic polymer hydrogels [53], three-layer asymmetric floatable systems [54], double-layered porous films [55], and hydrogels with entrapped PLGA microspheres [56]. Despite extensive advances in novel delivery methods, these predictable release patterns are often difficult to achieve in practice [57].

One frequent phenomenon and problem that has hindered those targeting controlled release methods are short-term or "burst" releases, characterized by an initial large bolus of drug that is eluted before the release rate reaches stable profile upon placement in the surrounding medium [58]. Burst release is typically regarded as a negative consequence of creating drug delivery devices, often leading to local or system toxicity, shorter half-life of drugs, therapeutically inefficient systems, and more frequent dosing [58]. Numerous attempts at mitigating burst release have been made when creating a drug delivery system (DDS) with limited success [54], [56], [59]–[63]. Other attempts aimed to explain and model the release patterns to make them more predictable [64]–[66]. Even with these efforts, controlling burst release profiles remains a challenge.

In contrast, some researchers have used this phenomenon to their advantage. Huang *et al.* described favorable burst release conditions, including wound treatment applications, encapsulation of flavors, triggered burst released in targeted systems, and pulsatile release systems [58]; Lischer *et al.* utilized anti-bacterial-containing plasma polymer coatings with burst releases for preventing the onset of bacterial colonization [67]. Similarly, Setterstrom *et al.* developed burst releasing antibiotic coatings for topical administration to wounds [68]. While these groups acknowledge the favorable results of rapid release caused by this effect, little research exists on drug delivery systems that

actively incorporate this effect, let alone optimize it. There is a lack of investigation the deliberate incorporation and manipulation of burst release in a drug delivery system which can be used as a drug-eluting device coating.

Certain applications of drug delivery have demonstrated that using two different rates of release can be most beneficial for administering a drug [69]. A study by Kastellorizios, Papadimitrakopoulos, and Burgess has shown, for instance, that to better combat the foreign body response against implantable devices, a large burst release of anti-inflammatory dexamethasone (100 µg) immediately after subcutaneous implant insertion followed by smaller, continuous doses each day (10 µg) provide optimal results [14]. This investigation suggests that there is a valuable use for drug eluting coatings for implantable devices which can integrate a burst release phase and zero-order release phase, both of which can be controlled independently [14].

1.5 Coating

Polymer, drug-loaded microspheres can achieve the desired drug release profile for sustained anti-inflammatory action. To be applied to an insulin infusion set, they must be constructed into a coating in a way that protects them until they are implanted. A hydrogel matrix is a demonstrated method of providing a vessel for microparticles. Polyvinyl alcohol, a hydrogel, has been used effectively with drug-loaded PLGA particles in the application of drug-releasing coatings for implantable devices, like glucose sensors [18], [19], [33]. PVA is also itself a drug delivery system for dexamethasone and lidocaine which exhibits burst release of both drugs [70], [71]. A

combination of drug-loaded PLGA microparticles and PVA hydrogel would supply all the desired elements of a drug-eluting coating for insulin infusion sets.

1.6 Mathematical Modeling

Drug release studies of these systems provide data on the release rate of the total system. However, there are properties about the individual components which cannot be determined from that type of study. Other valuable parameters can be estimated by creating mathematical models from the release study data. Having an accurate model of the system allows future iterations of the systems to be tailored to different drug release profiles.

1.7 Proposal

We propose that lidocaine and dexamethasone can be simultaneously encapsulated within and released from PLGA microparticles over the course of at least 14 days. Furthermore, by combining these drug-loaded PLGA microparticles into a PVA hydrogel matrix with raw, crystalline undissolved lidocaine and dexamethasone in concentrations above hydrogel saturation concentration, we can create a composite material which can be coated onto an insulin infusion set, allowing the payload to be delivered directly to the site of inflammation in a short-then-long term biphasic manner.

In this study, we investigated how altering the ratio of hydrogel matrix-encapsulated drug to particle-encapsulated drug determines the drug released during the short-term release period and long-term sustained period. Mathematical modeling was then used to estimate the pharmacokinetic properties of the individual components of the

delivery system. We also investigated how different coating parameters affected the coating's dimensions and ability to survive implantation.

1.8 Research Goals

As of 2017, 9.4% of the US population, or 30.3 million people, have been diagnosed with diabetes, who incur a cost of $245 billion collectively due to diabetes [7]. Of these people, about 1.5 million are diagnosed with Type 1 diabetes, which requires supplemental insulin, and often delivered via an insulin infusion pump [7]. When the cannula of an insulin pump catheter is inserted through the skin, the body immediately begins the inflammatory response against it. The local products of the inflammatory response disturb the absorption of insulin into the bloodstream. To prevent this, diabetes patients must change their cannula infusion site daily. This, however, quickly depletes the sites on the body which a person can use due to subcutaneous inflammatory tissue.

The objective of this work is to create a novel drug delivery system using established technologies that diminishes the foreign body response and can be coated onto insulin infusion catheters. Implantable medical devices have frequently been coated in polyvinyl alcohol hydrogels containing anti-inflammatory drugs to reduce the FBR caused by implantation; PLGA microparticles have been shown as an effective method for controlling drug release in such scenarios as well. Our team intends to use poly(lactide-co-glycolide) (PLGA) microparticles loaded with anti-inflammatory drugs in a polyvinyl alcohol coating loaded with the same drugs to create a dual phase release of lidocaine and dexamethasone. The controlled short-then-long term release of anti-

inflammatory drugs from this system will reduce the onset of FBR, thus improving device function and reliability of coated insulin infusion sets.

The goals of this research are:

Chapter 2: Demonstrate controlled release of anti-inflammatory drugs, with initial short term release followed by consistent sustained release

Chapter 3: Create a computational model which estimates parameters of system

Chapter 4: Coat an insulin pump catheter (insulin infusion set) with drug eluting composite which survives implantation into and extraction from tissue

Chapter 2

Controlled Drug Release

2.1 Introduction

Similar to insulin infusion sets, glucose sensors suffer from issues related to local inflammation and fibrosis. Groups attempting to mitigate this issue have looked to drug-loaded polymer particles and coatings as an answer [18]–[20], [72]–[75]. These efforts have focused on consistent, long-term delivery of therapeutics to extend the functional life of these sensors, which are largely successful. Several of these studies which performed in-vitro drug release noted that their therapeutic was released from their system at a relatively higher rate for a relatively short period of time, commonly called "burst" release. Burst release is often looked upon as a negative, but certain applications could benefit from integrating burst-style, short-term, rapid release into the total delivery profile, like wound healing [14], [58]. The purpose of this research is to develop a drug delivery system which can deliver a therapeutic aimed at combating inflammation associated with implanted devices. This system aims to deliver in two distinct phases, a short-term, rapid release phase followed by a zero-order phase, both of which can be tuned independently of each other. Two mechanisms of drug delivery with demonstrated pharmacokinetic qualities will be combined – PLGA particles, which can provide slower, consistent release, and PVA hydrogel, which can be loaded directly with undissolved, crystalline drug whose speedy dissolution provides rapid short-term release as well be a matrix for the particles. Analogous to the coating used on glucose sensors, this PLGA

particle-PVA hydrogel composite will have properties suitable for coating on insulin infusion sets.

2.2 Materials/Methods

2.2.1 Creating PVA Polymer

Polyvinyl alcohol pellets were mixed with distilled water to create a 20% w/w PVA/water solution. The solution was heated in an autoclave until completely melted. Once heating was completed, the solution was mixed to homogeneity then allowed to cool.

2.2.2 Creating Drug Loaded PLGA Particles

Drug-loaded particles were created using an oil-in-water emulsion method. 1125 mg of lidocaine, 36 mg of dexamethasone and 3375 mg of PLGA were dissolved in 45 mL of dichloromethane then homogenized with an overhead mixer at 1515 RPM for 120 seconds. Previous studies on therapeutic levels of lidocaine [76]–[78] and dexamethasone [14] informed the concentration of lidocaine and dexamethasone used in the microparticles. The resulting solution was added slowly to 225 mL of 2% w/w solution of PVA/water and stirred overnight to allow the solvent to evaporate. The remaining solution was rinsed with DI water, centrifuged and the supernatant was discarded. This was repeated 3 times. After the third time, DI water was added to the solution and the particles were agitated to homogeneously disperse them in the water. The particles in water were allowed to freeze at least 24 hours. Once the solution was frozen completely, it was lyophilized until all water was removed. Loading was determined by dissolving 5

mg particles in triplicate in 1 mL of acetonitrile and the dissolved sample was analyzed using the HPLC method described below.

2.2.3 Size & Morphology

Images of the microparticles were taken on a scanning electron microscope (SEM). ImageJ was used to estimate the radius of a sampling of particles within a given area of the SEM image. Items which did not fit the anticipated spherical shape of the particles were noted and not included in the calculation.

2.2.4 Creating PVA-PLGA Particle Composite

Four formulations of PVA-PLGA particle composite were manufactured into cylindrical pellets for this study according to Table 1.

Table 1

Formulation Names and Descriptions

Formulation Name	Undissolved Drug Mass	Particle Encapsulated Drug Mass	Notes
0:1	0	1	No undissolved drug added
1:1	1	1	Equal drug loading of both sources
5:1	5	1	Much more undissolved drug than particle encapsulated drug
1:2	1	0.5	Half the mass of particles as 1:1

0:1 contains a 0:1 mass ratio of hydrogel-encapsulated drug to microparticle-encapsulated drug. 1:1 contains a 1:1 mass ratio of hydrogel-encapsulated drug to microparticle-encapsulated drug. 5:1 contains a 5:1 mass ratio of hydrogel-encapsulated

drug to microparticle-encapsulated drug. 1:2 contains a 1:0.5 mass ratio of hydrogel-encapsulated drug to microparticle-encapsulated drug. Each pellet of composite totaled 1 g of total mass. 200 mg of particles were used in all formulations except 1:2, which used 100 mg. Powdered lidocaine and dexamethasone were added equal to the prescribed ratios for each formulation. The PVA solution was heated in the autoclave until melted. Once liquid, the PVA solution was added into a disposable syringe with drug-loaded particles and powdered dexamethasone and lidocaine. The PVA, particles and powdered drug, if needed, were added in a layered fashion with the first and last layer being PVA, then mixed within the syringe. While the mixture was fluid, it was expelled from the syringe into a disposable, cylindrical plastic vessel. The vessel was placed in the freezer for at least 24 hours. Once completely solidified, the plastic vessel was cut away to access the cylindrical PVA-PLGA particle composite molded pellet. The pellet was then allowed to thaw before use, completing one cycle of freeze-thaw. Each pellet received one freeze-thaw cycle.

2.2.5 Drug Release Study

Pellets of each formulation were divided into 3 equal parts and placed into release media for 12 days in an incubator set to 37°C. Samples of release media were taken over the course of 13 days with decreasing frequency. The timepoints for samples were 1 hour, 5 hours, 24 hours then one each day after that for 12 additional days. Samples were refrigerated until they could be analyzed via HPLC.

2.2.6 Chromatographic Analyses

The HPLC system employed was a Waters e2695 liquid chromatography with a 2998 photodiode array detector reading at 210 nm. Separation was performed on a 250mm x 4mm (5 µm) C_{18} reversed-phase column C_{18} pre-column 4 x 4 mm (5 mm). A 15 minute gradient mobile phase consisting of acetonitrile and water (both with 0.1% trifluoroacetic acid) was employed: the method starts at ratio of 90/10 water:acetonitrile for 5 minutes, then moves to 65/35 over the course of the next 3 minutes. The ratio holds there for 2 minutes then returns to 90/10 over the next 1 minute where is stays for another 4 minutes to conclude the method.

2.3 Results

2.3.1 Particle Characterization

2.3.1.1. Size & Morphology. Particle quantity and diameters were assessed using ImageJ, and the size distribution plotted in the histogram in Figure 2. Table 2 provides statistics on the particles sample used for characterization.

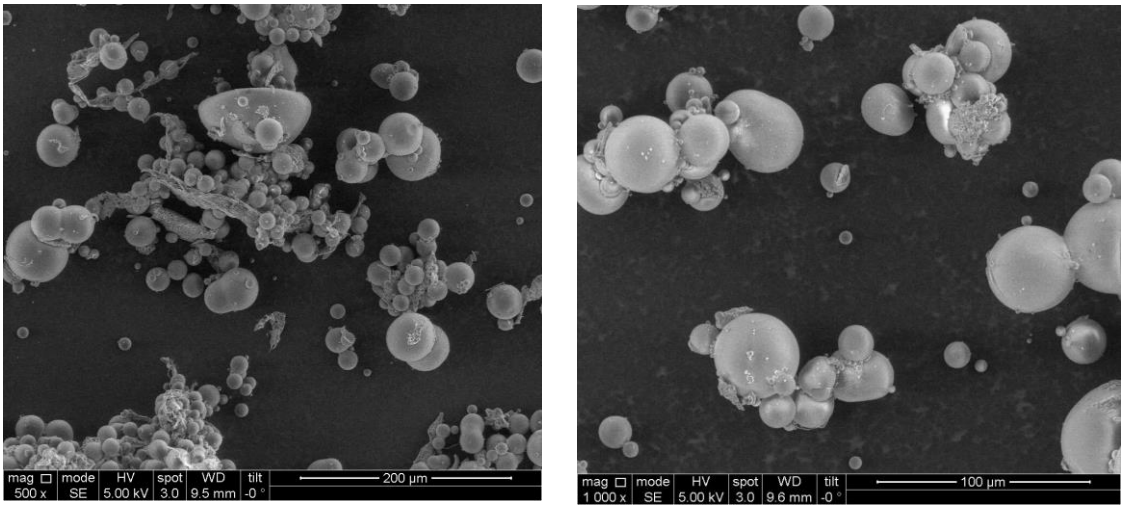


Figure 1. SEM Images of Particles Containing Lidocaine and Dexamethasone.

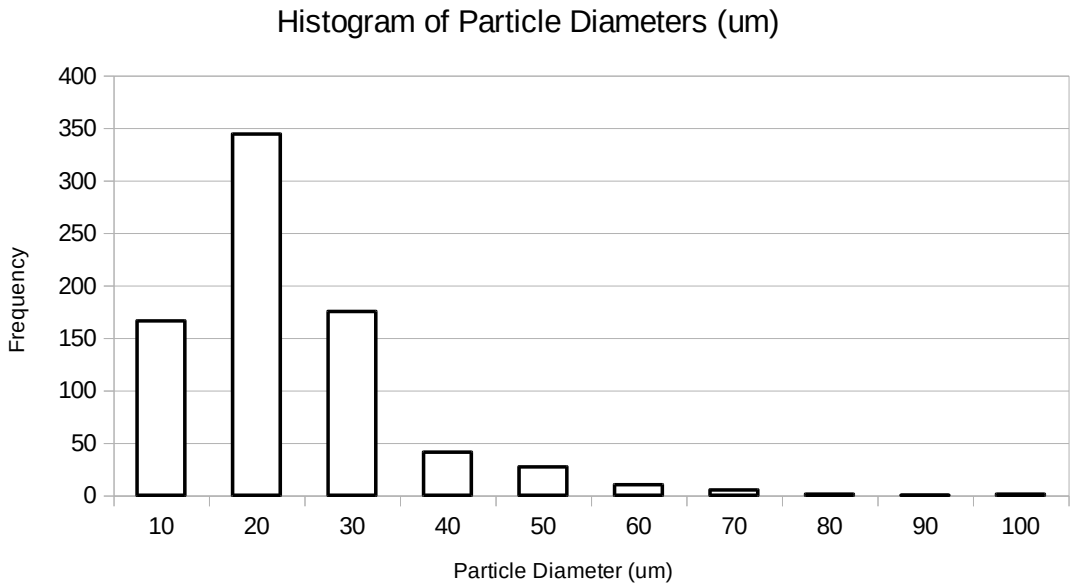


Figure 2. Histogram of Particle Diameters (µm)

Table 2

Statistics of Particle Diameters (µm)

Median	16.4
Mean	18.6
Std. Dev.	11.2
n	770.0
Range	2.9 94.0

The average diameter of particles was estimated to be 18.6 +/- 11.2 µm. This value is used to calculate the total surface area of particles in the computational model later in the study.

2.3.1.2. Drug Loading. After dissolving the aliquots of particles in acetonitrile and testing samples via HPLC, the loading of lidocaine in the particles was found to be 11.2 +/- 1.18 % w/w and the loading of dexamethasone was found to be 0.4 +/- 0.01 % w/w.

2.3.1.3. Comparison of Short-Term Release. Figure 3 shows the cumulative release of all 3 formulations contrasting short-term release across the duration of the release study.

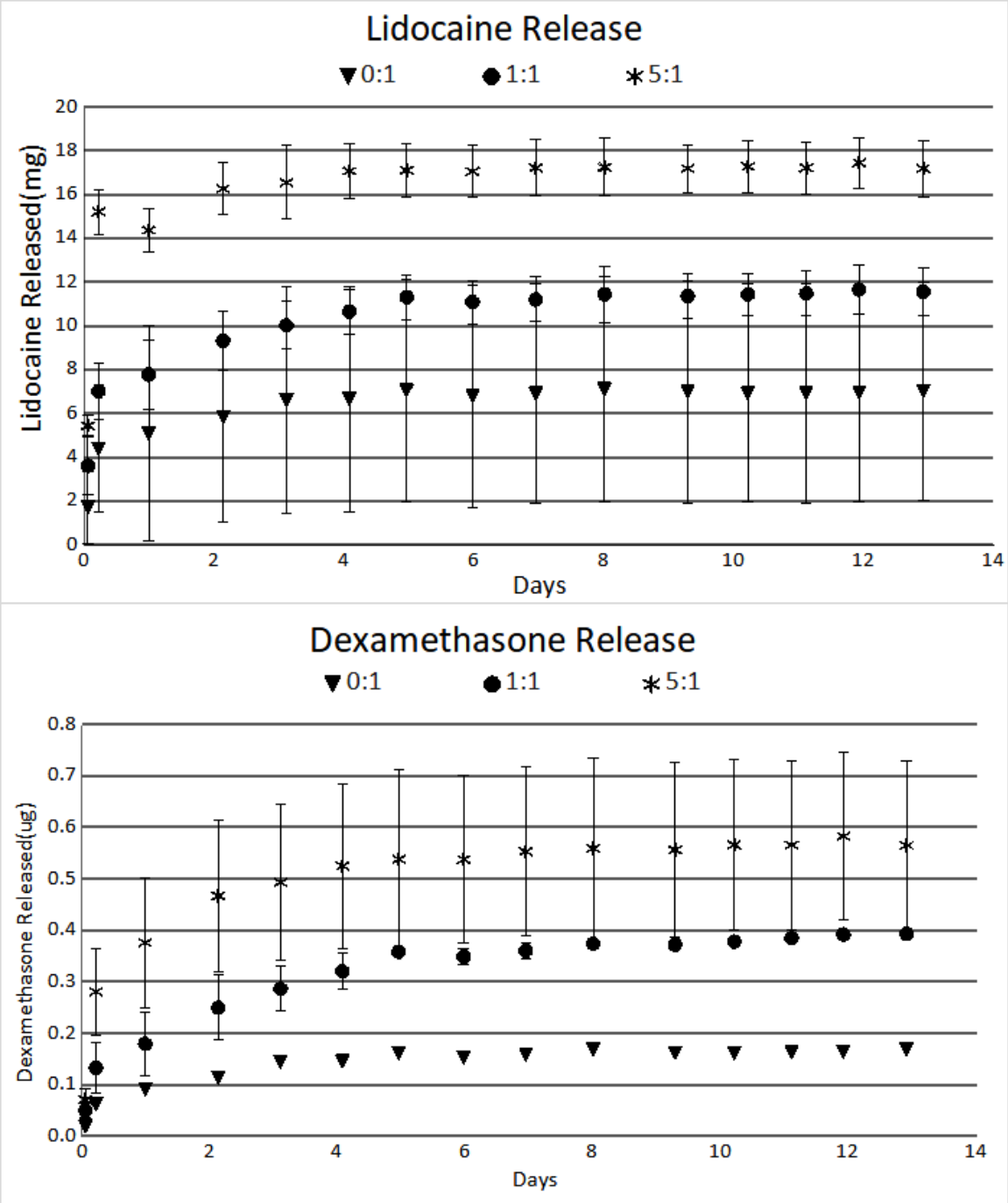


Figure 3. Cumulative Drug-Release Curve Comparing 0:1, 1:1, and 5:1 Formulations. Lidocaine is displayed on top, dexamethasone on bottom.

Figure 4 below show the mass of lidocaine and dexamethasone released in mg during each phase for 0:1, 1:1, and 5:1. An asterisk represents significant difference of the data ($p<0.05$).

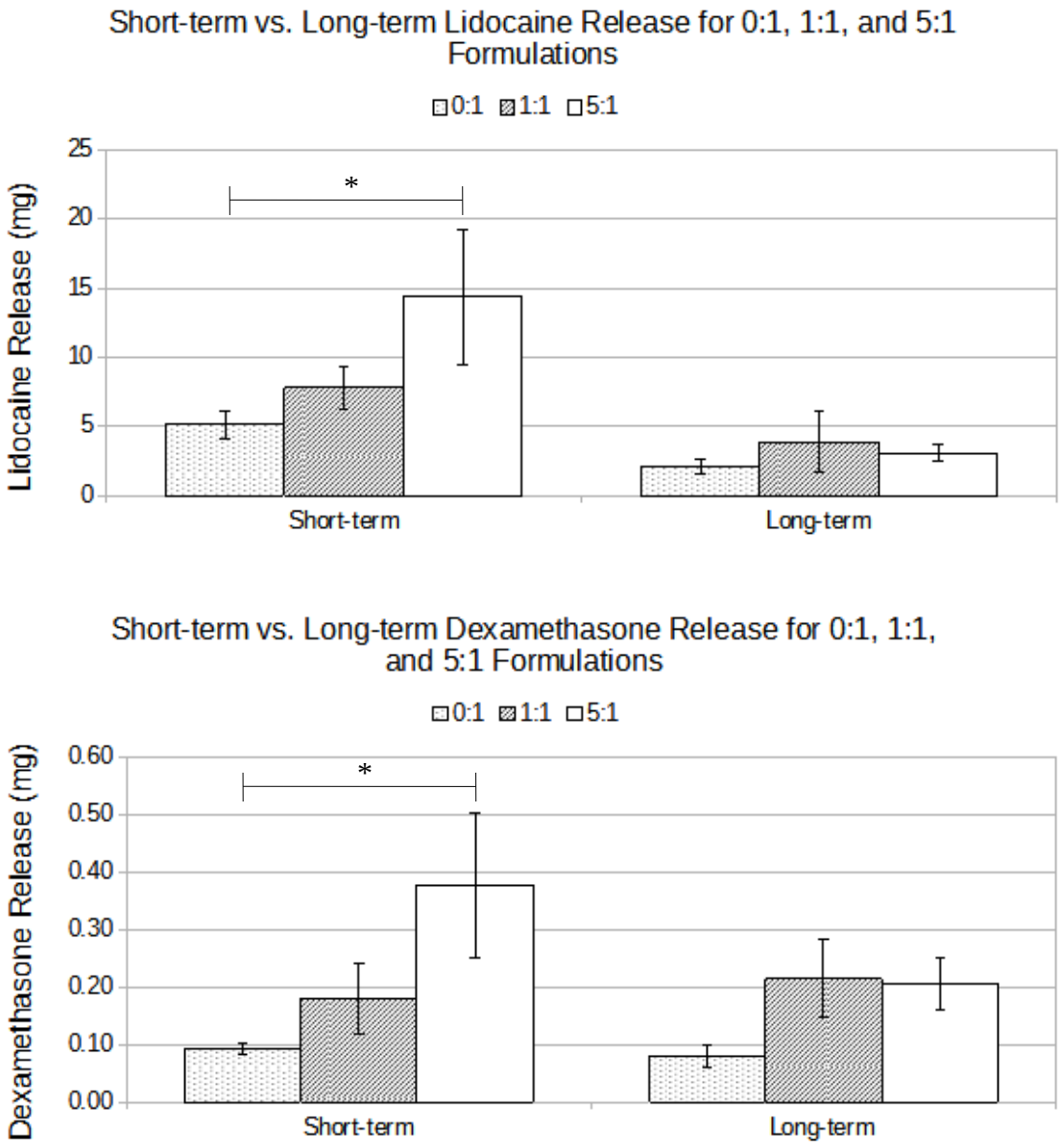
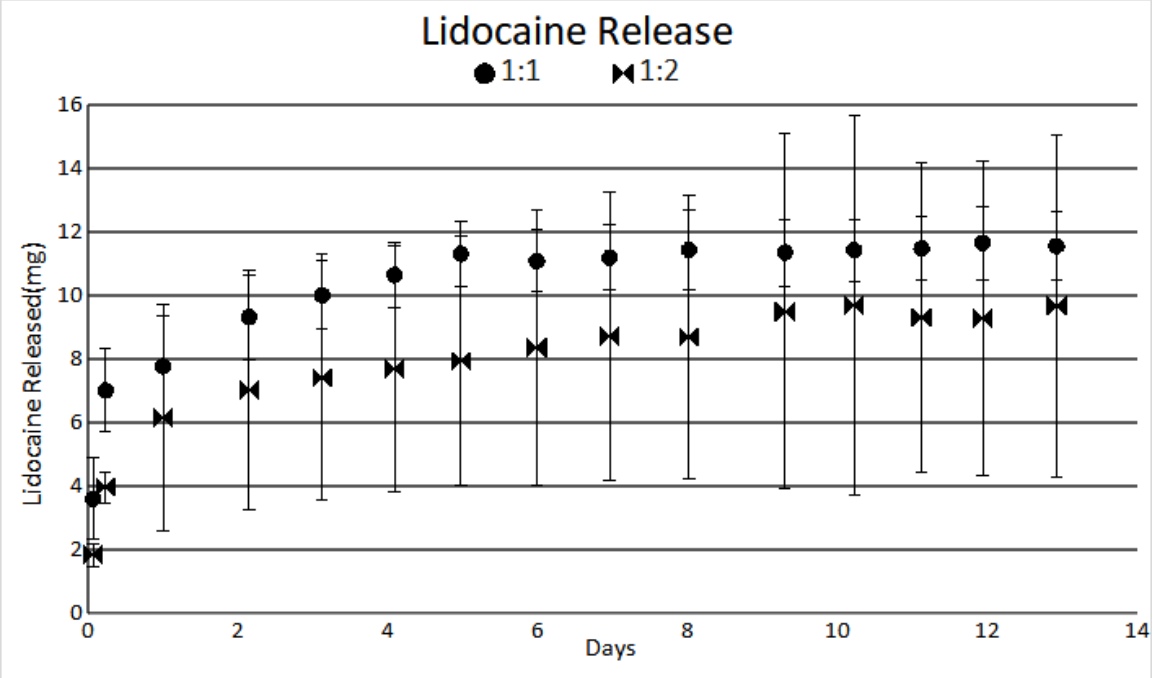


Figure 4. Short-Term Release and Long-Term Release of 0:1, 1:1 and 5:1 Formulations for Lidocaine (Top) and Dexamethasone (Bottom)

A two-way ANOVA showed that there is a significant difference between formulation-release phase pairs of **lidocaine** demonstrated by a p-value of less than 0.05. The Sidak comparison test showed that these short-term release formulation pairs had significantly different short-term releases of lidocaine: 5:1 vs. 0:1 (p=0.006). While the 1:1 short-term release was not significantly different from the 5:1 short-term release, the data was only slightly outside the range of significance (p=0.071). The Sidak comparison test showed that no formulation pairs had significantly different sustained release of lidocaine.

Similarly, a two-way ANOVA showed that there is a significant difference between formulation-release phase pairs of **dexamethasone** demonstrated by a p-value of less than 0.05. The Sidak comparison test showed that these short-term release formulation pairs had significantly different short-term releases of dexamethasone: 5:1 vs. 0:1 (p=0.003). While the 1:1 short-term release was not significantly different from the 5:1 short-term release, the data was only slightly outside the range of significance (p=0.054). The Sidak comparison test showed that no formulation pairs had significantly different sustained release of dexamethasone.

2.3.1.4. Comparison of Sustained Release. Figure 5 below show the mass of lidocaine and dexamethasone released in mg during each phase for 1:1, and 1:2.



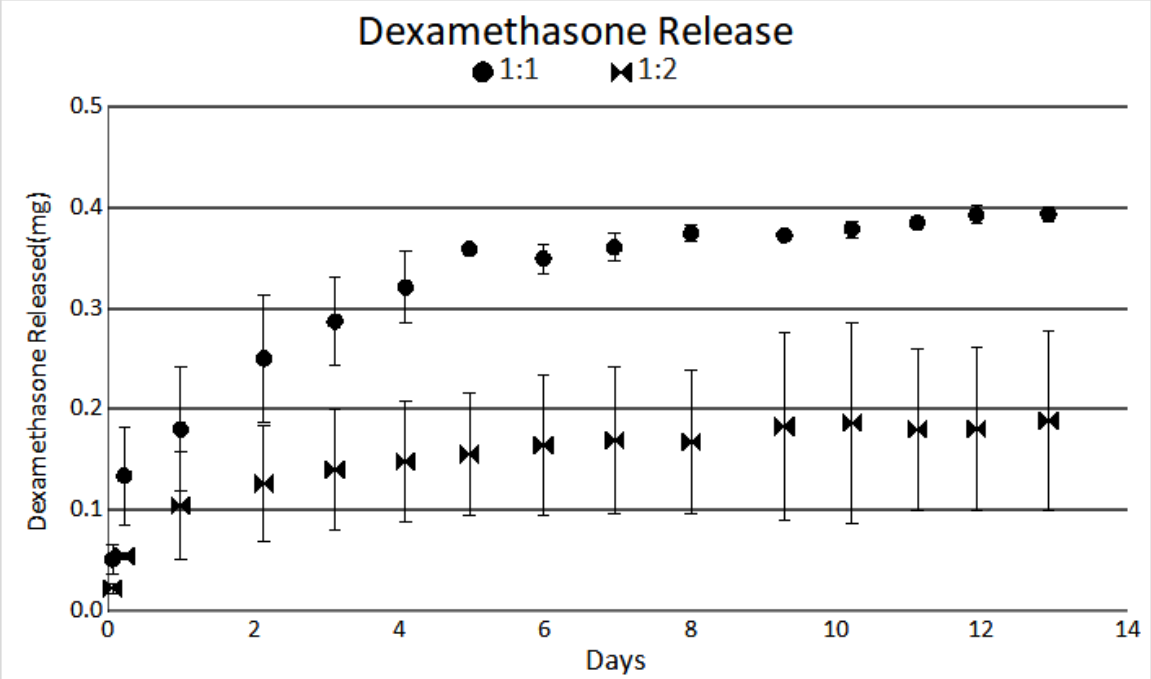


Figure 5. Cumulative Drug-Release Curve Comparing 1:1 and 1:2. Lidocaine is displayed on top, dexamethasone on bottom.

Figure 6 below show the mass of lidocaine and dexamethasone released in mg during each phase for 1:1 and 1:2.

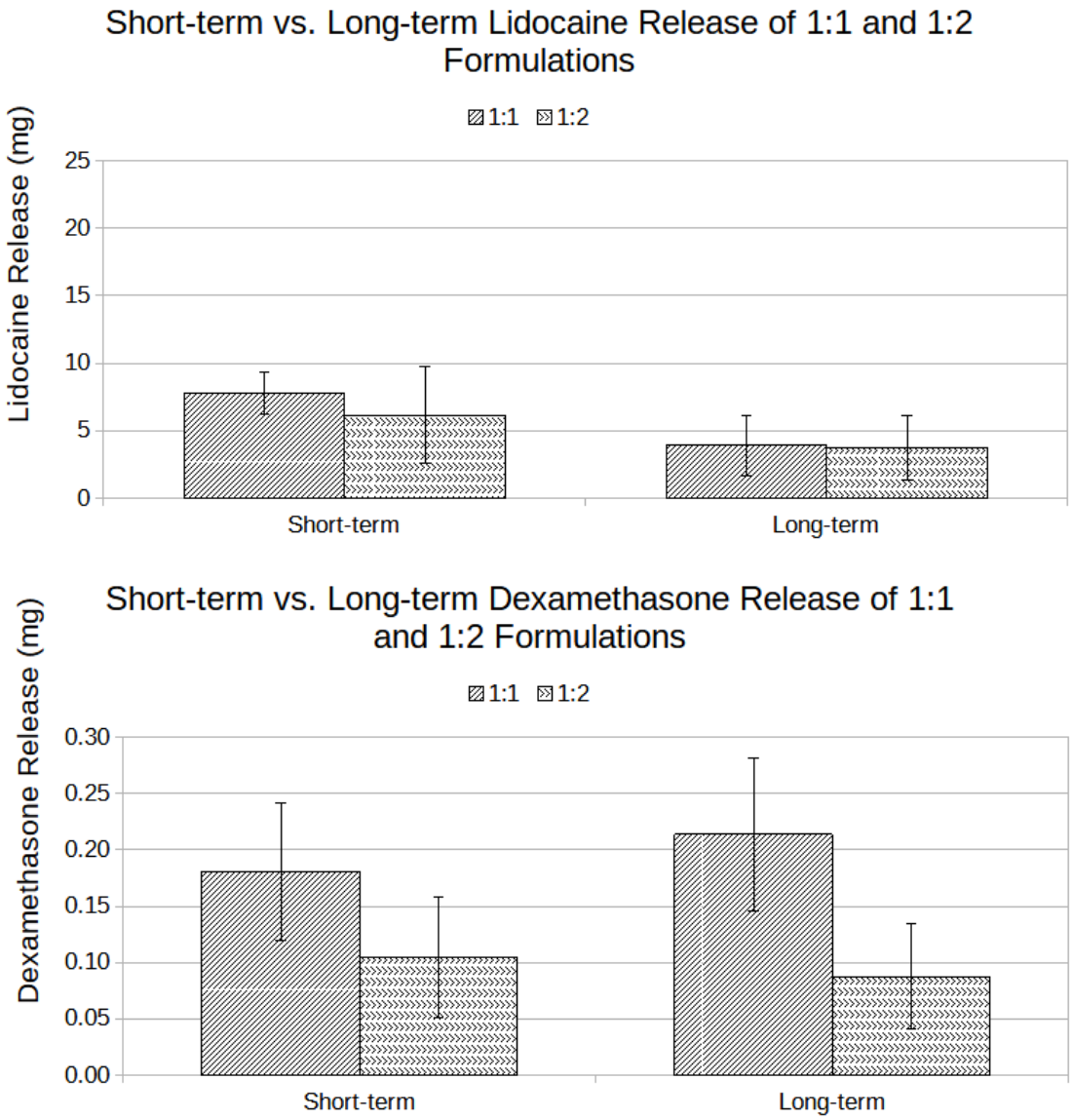


Figure 6. Short-Term and Long-Term Release of 1:1 and 1:2 Formulations for Lidocaine (Top) and Dexamethasone (Bottom)

A two-way ANOVA showed that there is not a significant difference between formulation-release phase pairs of either **lidocaine or dexamethasone**.

2.4 Discussion

2.4.1 Particle Characterization

2.4.1.1. Size & Morphology. The size of the particles is in the same magnitude as other researchers who have created particles with a similar process. Wang et al. obtained dexamethasone loaded PLGA particles with an average diameter of 7.64 ± 6.64 μm and saw active drug release over the course of at least 30 days of PLGA particles alone and PLGA particle/PVA hydrogel composite [18]. With a smaller surface area/volume ratio, we would expect our particles to have active release over a longer period, but we did not observe that. A major difference between these particles is the dexamethasone loading. The Wang et al. particles had a dexamethasone loading of 7.6 ± 0.24% compared to our 0.4 ± 0.0001%. Several others have obtained a noticeably higher loading of dexamethasone particles than we did [33], [79]. We expect that in the future, the particle loading could be improved which would provide more mass of drug for longer duration of delivery. Investigating the effect of multiple drugs being encapsulated simultaneously would also be prudent. We were not able to find any studies which highlighted this.

2.4.2 Creating PVA-PLGA Particle Composite

Manufacturing of the hydrogel-particle composite pellets proved to be a challenge which we believe affected the consistency of the composite's homogeneity. We chose a 20% PVA hydrogel solution to increase the viscosity of the hydrogel. We believed a

higher viscosity of hydrogel would improve the ability of the composite to be coated onto a catheter, as opposed to glucose sensors, which used a lower PVA% hydrogel [14]. Glucose sensors in the Kastellorizios, Papadimitrakopoulos and Burgess study were coated using a different method than the catheters coated later in this study. Particles were assumed to have evenly mixed into the large pellets which were divided into three even sections. However, we observed a higher-than-expected variance among pellet samples within a formulation. The assumption that all particles were evenly mixed may not be true. The difficulty of combining all the ingredients evenly along the length and radius of the pellet was noted as we performed that step. This could also lead to differing release rates within samples of a formulation as some pellets would have a higher density of particles distant from the surface than others. The use of a lower concentration of PVA in the hydrogel would improve variability of both lidocaine and dexamethasone release.

2.4.2.1. Drug Loading. The drug loading of the particles used in this study was noticeably different than what was observed in similar PLGA-based particles. Dexamethasone was discussed earlier. We saw much higher drug loading of lidocaine than other similarly created PLGA particles, which saw a maximum of 2.86% loading when using 50 mg of lidocaine in 10 mL of solvent [80]. This study establishes that the amount of drug dissolved in the organic phase while particles are created influences drug loading of particles. This makes sense as we used 1125 mg of lidocaine in 45 mL of solvent. There are other factors, like the type of PLGA used, which also influence drug loading. The duration of drug release from our particles would stand to increase from improved drug loading. Delivering therapeutic doses of anti-inflammatory drugs would

require less particles so smaller volumes of hydrogel could be used leading to a more beneficial, thinner catheter coating profile.

2.4.2.2. Comparison of Short-Term Release. These 3 formulations – 0:1, 1:1, and 5:1 - were devised to see how short-term release of the system could be manipulated without affecting the sustained release. One pairing of short-term release of the formulations had a significant difference in both lidocaine and dexamethasone: 0:1 vs. 5:1, while the 1:1 and 0:1 formulations were nearly significant in this regard. This is a promising result which shows that even though one formulation, 5:1, has 6 times as much drug mass loaded into the total system, the sustained release phase of each formulation is statistically indistinguishable. This also demonstrates that the drug incorporated into the hydrogel matrix does noticeably change the amount of drug released from the whole system during the short-term release phase.

As the amount of crystalline drug in the matrix increases, there is a corresponding increase in release of lidocaine and dexamethasone in the first 24 hours. However, the increase in drug release during short-term release phase is not exactly proportional to the ratio of crystalline drug in the matrix. We suspect this is due to the short-term release of encapsulated drug from the particles. Burst release from PLGA particles is a known phenomenon that occurs when there is drug accessible at the surface of the particle. 0:1 formulation demonstrates that even with no crystalline drug in the matrix and only drug encapsulated in particles, 72% of available lidocaine and 54% of available dexamethasone was released within 24 hours. This contribution to short-term release from the particles is likely happening in the formulation with crystalline drug in the

matrix as well. We are trying to manipulate short-term release in this system, but not via the particles so reducing burst release in the particles would aid in designing a more accurate system [81].

While these particles did not allow us to control their burst release, the other source of short-term release did show evidence that it can be manipulated by the content of crystalline drug in the hydrogel matrix of the system. Long *et al.* and Li *et al.* established that PVA alone can be used as a vehicle for dexamethasone and lidocaine, respectively, and can be altered to change the release rate of the drug [70], [82]. For instance, Galeska et. al demonstrated how increasing the number of freeze-thaw cycles that the PVA undergoes will slow down the release rate from the hydrogel [81]. When the PVA hydrogel undergoes freezing, the solvent crystallizes which concentrates the polymer chains in the regions surrounding the crystallized solvent. This encourages zones of physical cross-linking which last after the hydrogel is thawed. Beyond the number of cycles, other conditions of the freeze-thaw cycle, like time to freeze, freezing temperature, and time to thaw, can be used to alter the resulting polymer [83]. Our study shows that PVA can function as a tunable source of rapid drug release in a composite with drug-loaded PLGA particles.

2.4.2.3. Comparison of Sustained Release. These 2 formulations – 1:1 and 1:2 - were devised to see how sustained release of the system could be manipulated without affecting the short-term release. Neither pairing of short-term release nor sustained release of the formulations were significantly different. On one hand, this is a favorable result because the short-term release of the two formulations, which had

equivalent mass of drug loaded into the hydrogel, was indistinguishable. However, the 50% reduction of particle mass in 1:2 compared to 1:1 did not lead to a noticeable reduction in sustained release. Several challenges could have led to this result. Manufacturing the pellets becomes increasingly difficult with smaller masses of particles and PVA that are used due to the viscosity of the hydrogel. The 1:2 formulation used the smallest mass of particles of any formulation which led to increased variance in particle mass in the pellet as well as increased difficulty to mix the pellet homogeneously. Despite these challenges, there was a pattern emerging in the dexamethasone sustained release showing that 1:1 was releasing more drug than 1:2. Increasing sample sizes could show this pattern to be significant.

Combining drug-loaded hydrogel with drug-loaded PLGA particles has created two sources of drug delivery within one system, both of which have proven tunable attributes. This system has shown that there is promise of a tunable drug eluting coating which can deliver two drugs simultaneously in a short-then-long term release pattern. To optimize the coating's drug release profile, it would help to understand the impacts of each individual source of release over time. This was not possible to measure during the release study that was performed. A computational model would provide a prediction of such impacts.

Chapter 3

Drug Release Modeling

3.1 Introduction

The drug release experiment completed in goal 1 provided data on the drug release kinetics of the entire delivery system of the coating. We wished to explore further the input of each source of drug release to the overall result and how the combination of all these components affects the dissolution of drug. While this isn't possible with the data provided in the drug release experiment, a computational model can provide an estimation of the pharmacokinetic constants of the different components of the system – the PLGA particles, the undissolved crystalline drug, and the PVA hydrogel. The goal of this research section is to estimate the drug release kinetics of the individual system components as well as the saturation concentration of the composite for each drug that was incorporated.

3.2 Materials/Methods

Four groups of equations based on Fickian diffusion governed the mass flux of drug [84]. Concentration gradients with respect to distance within each system (i.e. microparticles, hydrogel, and release media) are negligible, so that all mass transfer equations are dictated by the concentration gradients between the boundaries of the individual systems These are the elements of the model and the corresponding equation which defines flux:

<u>Flux out of particles:</u>

There are three equations used in the model for flux out of the particles. The equation used changes depending on the instantaneous concentration of the drug in the particles and in the hydrogel. The three equations for flux of drug out of particles are defined as the following:

If $C_{particles} > C_S$ and $C_{hydrogel} < C_S$:

$$N_{particles} = -k_{particles}(C_S - C_{hydrogel}) \quad (1)$$

If $C_{particles} < C_S$ and $C_{hydrogel} < C_S$:

$$N_{particles} = -k_{particles}(C_{particle} - C_{hydrogel}) \quad (2)$$

If $C_{hydrogel} > C_S$:

$$N_{particles} = 0 \quad (3)$$

Where C is concentration, N is flux, and k is pharmacokinetic constant.

Flux out of crystalline drug:

There are two equations used in the model for flux out of the crystalline drug i.e. the dissolution of crystalline drug into the hydrogel matrix. The equation used changes depending on the instantaneous concentration of the drug in the hydrogel and the presence of undissolved crystalline drug. The two equations for flux of drug out of crystalline drug are defined as the following:

If $C_{hydrogel} < C_S$:

$$N_{crystalline\ drug} = -k_{cyrstalline\ drug}(C_s - C_{hydrogel}) \quad (4)$$

If $mass_{crystalline\ drug} < 0$:

$$N_{crystalline\ drug} = 0 \quad (5)$$

Flux out of hydrogel:

$$N_{A,Hydrogel} = -k_{hydrogel}\left(C_{hydrogel} - C_{releasemedia}\right) \quad (6)$$

Flux into hydrogel:

$$N_{Hydrogel} = N_{particles} + N_{crystalline\ drug} \quad (7)$$

Flux into release media:

$$N_{Media} = -N_{hydrogel} \quad (8)$$

Non-linear regression analysis was performed manually to determine the best-fit of these parameters for each drug: C_S (saturation concentration), $k_{particles}$, $k_{hydrogel}$, $K_{crystalline\ drug}$. The non-linear regression analysis was performed manually. Parameters were fit one at a time until the sum of squared residuals decreased by 5% or less. This process was repeated 3 times for each parameter. A "recovery factor" was incorporated into each element of the release model to account for the difference between the assumed loaded drug and the amount detected by the end of the release study. It was assumed at the start of the study that the hydrogel was saturated with drug due to the time needed to manufacture the pellets where drug-loaded particles were in contact with the hydrogel. Consequently, drug was released from particles and dissolved from crystalline drug into the hydrogel before the freezing of the pellets.

3.3 Results

The following tables display the formulations' saturation concentration (C_S) and kinetic coefficients of each component of the system for each drug. 0:1 formulations do not have a $K_{crystalline\ drug}$ term because there was no crystalline drug in the system. 1:1 does not have a $K_{crystalline\ drug}$ term because the computational model showed that there was no undissolved crystalline drug at the start of the release period.

Table 3

Computational Parameters of Composite Formulations for Lidocaine

Formulation	C_S, Lido (mg/μm^3)	$K_{Particles}$ (μm/hr)	$K_{Hydrogel}$ (μm/hr)	$K_{crystalline\ drug}$ (μm/hr)
0:1	7.19E-10	9.70E-04	7.20E+01	N/A
1:1	8.97E-10	2.41E-03	1.48E+02	1.38E+07
5:1	1.56E-09	7.30E-02	1.40E+02	1.76E+07
1:2	6.40E-10	5.40E-03	8.60E+01	2.20E+07
Mean	**9.54E-10**	**2.04E-02**	**1.12E+02**	**1.78E+07**
St Dev	**4.18E-10**	**3.51E-02**	**3.81E+01**	**4.10E+06**
% CV	**43.8%**	**171.6%**	**34.2%**	**23.1%**

Table 4

Computational Parameters of Composite Formulations for Dexamethasone

Formulation	C_S, Dex (mg/μm^3)	$K_{Particles}$ (μm/hr)	$K_{Hydrogel}$ (μm/hr)	$K_{crystalline\ drug}$ (μm/hr)
0:1	8.80E-12	6.90E-03	7.70E+01	N/A
1:1	4.70E-11	1.00E-04	6.20E+00	N/A
5:1	1.00E-11	7.00E-04	2.00E+02	7.70E+09
1:2	6.75E-12	6.40E-03	4.40E+01	1.05E+10
Mean	**1.81E-11**	**3.53E-03**	**8.18E+01**	**9.10E+09**
St Dev	**1.93E-11**	**3.62E-03**	**8.39E+01**	**1.98E+09**
% CV	**106.3%**	**102.8%**	**102.6%**	**21.8%**

Figure ***7*** shows the simulated total release and experimental release for each drug over the release period used in the total drug release study.

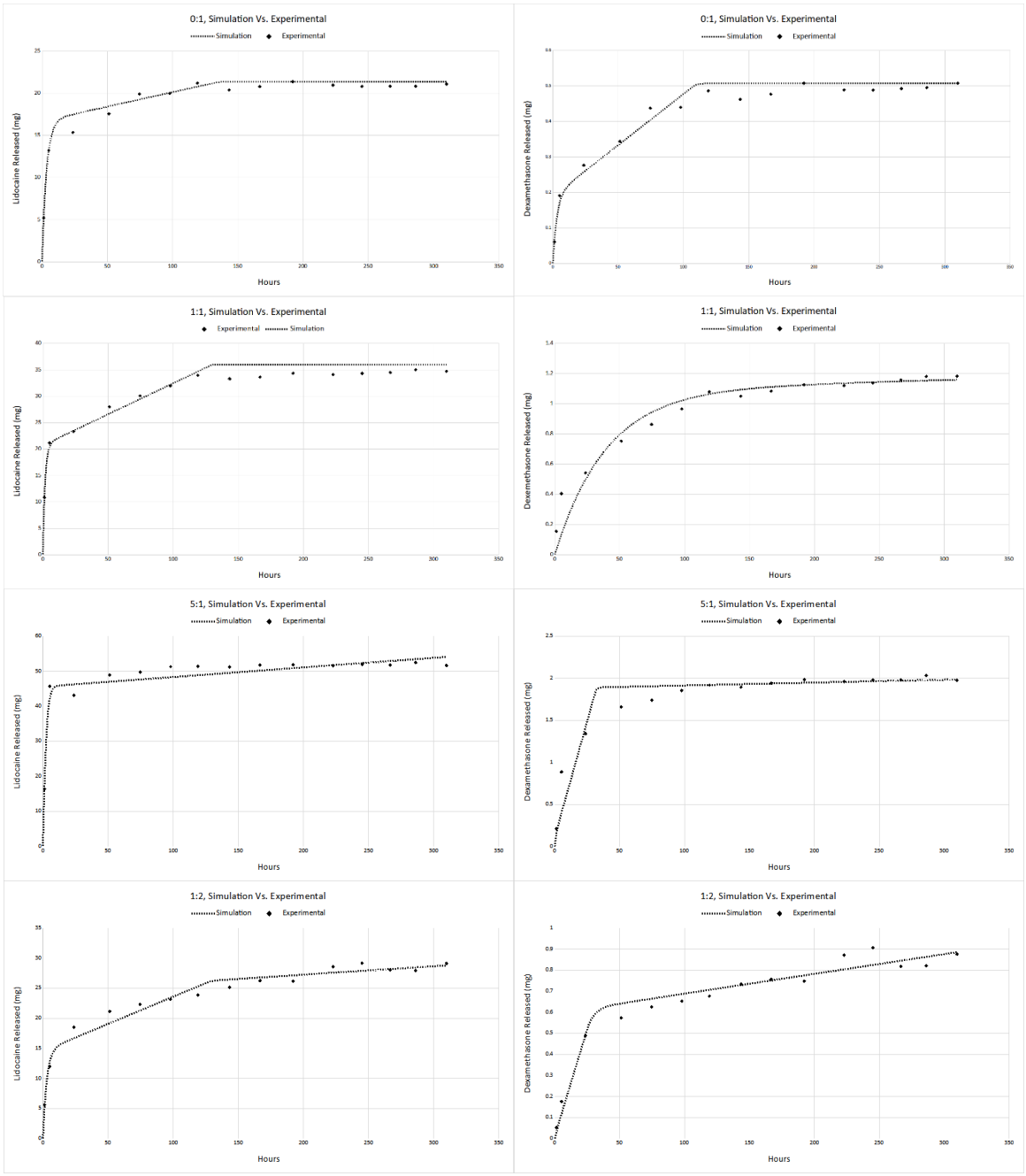


Figure 7. Simulated Release and Experimental Release of Lidocaine (Left) and Dexamethasone (Right) Over Period of Release Study.

3.4 Discussion

A central hypothesis of this bi-phasic formulation containing both crystalline drug and microparticles was that crystalline drug would provide tunable, early release, due to the high dissolution rate of crystalline drug compared to microparticles, while microparticles would release over a longer period. The results of the model fitting and the comparison between $k_{particles}$ and $k_{crystalline\ drug}$ back up this hypothesis. The results show that $k_{crystalline\ drug}$ is up to 10 orders of magnitude higher than $k_{particles}$ in lidocaine release and up to 13 for dexamethasone release. Even considering the %CV of $k_{particles}$ and $k_{crystalline\ drug}$ for each drug, we can see that the two sources of drug provide noticeably different release rates and that drug from crystalline drug release much faster than drug from particles. This is in accordance with previous research demonstrating the release rates of one of the drugs, dexamethasone, from hydrogel and from particles.

The parameters for each formulation were fit independent of one another and the % CV values demonstrate that they are close in value to one another. This indicates that the particles and hydrogel matrix maintain their pharmacokinetic properties across a wide range of initial concentration conditions. In the future, when creating systems of a similar design, the short-term release component can be selected independent of the sustained phase and vice versa. This will make application of this system to different sizes and severity of wound healing a simpler decision than if the drug release parameters were dependent on each other.

To improve the accuracy of this model, smaller time steps could be utilized. This was not a practical option as it requires more processing power than was available. Being

able to fit parameters to all 4 formulations simultaneously would also improve the accuracy of the model.

This model is a useful tool which informs future iterations of the drug delivery system. However, it needed some adjustments to account for abnormalities in the release study. The computational model incorporated a term which represented the difference between the amount of drug loaded into the system and the amount of drug that was released from the system. This was deemed the “recovery factor”. For lidocaine, it ranged from 40-95%. For dexamethasone, it ranged from 37-85%. Without this term, it would be possible for the model to predict a total mass of drug release greater than what was experimentally measured, invalidating the model.

Chapter 4

Catheter Coating

4.1 Introduction

The coating on the insulin infusion set must be able to both be loaded with enough particles and crystalline drug to achieve a therapeutic dose as well as maintain its integrity throughout the lifetime of the catheter. Other groups have studied coated catheters, forces associated with implanting catheters and the strength of attachment of coated materials onto catheters. Insulin infusion catheter coatings present a unique situation considering the methods with which they are implanted and the issues that insulin infusion sets face. In this research goal, we attempted to investigate optimal parameters for applying the composite to catheters of a similar diameter to insulin infusion sets and to determine what level of force these coated catheters could experience during their implantation through the skin.

4.2 Materials/Methods

4.2.1 Creating Coating Formulations

Four different formulations of coating were created that would be used for dip coating with two parameters, PVA concentration and $BaSO_4$ mass fraction, that would be tested at a high and low condition. $BaSO_4$ was used in this part of the study as a substitute for PLGA particles. The high condition of PVA concentration is 12.9% and the low condition is 7.7%. The high condition of $BaSO_4$ mass fraction is 20%. and the low condition is 5%. These were predicted to be practical ranges of these parameters for drug

delivery and coating purposes. The formulations were created according to the following table:

Table 5

Dip Coating Formulation Parameters

Coating Formulation	PVA %	BaSO4 %
1	12.9	20
2	12.9	5
3	7.7	20
4	7.7	5

4.2.2 Dip Coating

Once formulations were determined, PVA hydrogel was melted and combined with the determined mass fraction of $BaSO_4$ powder. The melted mixture was kept in a heated water bath set to the high temperature condition, 40°C, or the low temperature condition, 25°C. Ten centimeters of 0.5 mm diameter polyurethane tubing was cut to length and placed over a metal rod to maintain the straightness of the tubing while being dip coated. The catheter with metal rod inserted were dipped into the coating mixture at 200 mm/sec and left to dwell in the mixture for 3 seconds. The catheters were then withdrawn from the mixture at either 30 mm/sec, the high condition, or 20 mm/sec, the low condition. Catheters were hung in a freezer immediately after withdrawal until the coating was completely solidified.

4.2.3 Coating Thickness Measurement

Once the catheters were ready to be imaged, they were removed from the freezer and any catheters tip where excess coating had accumulated were removed with a razor blade. A thin slice, about 0.5mm thick, was removed from each catheter and imaged on a microscope slide. ImageJ software was used to calculate the thickness of the coating using manual measurements.

4.2.4 Insertion/Extraction

Catheters were slid over a 23 Ga needle long enough to have 1 cm of needle tip exposed. A silicone pad was clamped between 2 pieces of metal with holes on both sides, leaving one circular area of the silicone pad exposed. An entry hole was created in the silicone with a needle larger than 23 Ga. The 23 Ga needle with catheter was inserted through the entry hole until 1 mm of catheter was exposed on the other side of the hole. The silicone and catheter were secured on the bottom mount of a tensile tester and the needle was clamped into the specimen jaw. Catheters were inserted through the silicone at 500 mm/min until a defined distance from the bottom of the tester. Once fully inserted, the needle unclamped from the tester and pulled out of the catheter. The specimen jaws were clamped onto about 0.5 cm length of the end of the catheter closest to the jaws. The catheter was fully extracted out of the silicone at 500 mm/min. Images were taken of each catheter after extraction to determine if the coating had survived.

4.3 Results

4.3.1 Coating Thickness Design of Experiments

The high condition (H) of PVA is 12.9%. The low condition (L) of PVA is 7.7%. The high condition of BaSO4 is 20%. The low condition of BaSO4 is 5%. The high condition of temperature is 40ºC. The low condition of temperature is 25ºC. The high condition of dip speed is 30 mm/sec. The low condition of dip speed is 20 mm/sec.

Table 6

Results of Dip Coating Design of Experiments

Catheter	PVA	BaSO4	Temp	Speed	Calculated Thickness (µm)	Max Insertion Force (N)	Max Extraction Force (N)
1	**H**	**H**	**L**	**L**	127	**1.666**	**0.587**
2	**H**	**H**	**L**	**L**	154	**2.127**	**0.611**
3	**H**	**H**	**L**	**H**	152	**2.412**	**0.611**
4	**H**	**H**	**L**	**H**	80	**1.153**	**0.561**
5	H	L	L	L	0	0	0
6	H	L	L	L	0	0	0
7	H	L	L	H	0	0	0
8	H	L	L	H	0	0	0
9	L	H	L	L	0	0	0
10	L	H	L	L	0	0	0
11	L	H	L	H	0	0	0
12	**L**	**H**	**L**	**H**	50	**0.662**	**0.620**
13	L	L	L	L	0	0	0
14	L	L	L	L	0	0	0
15	L	L	L	H	0	0	0
16	L	L	L	H	0	0	0
17	H	H	H	L	0	0	0
18	**H**	**H**	**H**	**L**	147	**1.211**	**0.608**
19	**H**	**H**	**H**	**H**	186	**1.370**	**0.564**
20	**H**	**H**	**H**	**H**	161	**1.615**	**0.513**
21	H	L	H	L	0	0	0
22	H	L	H	L	0	0	0

Catheter	PVA	BaSO4	Temp	Speed	Calculated Thickness (µm)	Max Insertion Force (N)	Max Extraction Force (N)
23	**H**	**L**	**H**	**H**	127	**0.509**	**0.564**
24	**H**	**L**	**H**	**H**	106	**0.635**	**0.583**
25	**L**	**H**	**H**	**L**	26	**0.526**	**0.620**
26	**L**	**H**	**H**	**L**	33	**0.587**	**0.576**
27	**L**	**H**	**H**	**H**	32	**0.510**	**0.415**
28	**L**	**H**	**H**	**H**	29	**0.383**	**0.506**
29	L	L	H	L	0	0	0
30	L	L	H	L	0	0	0
31	L	L	H	H	0	0	0
32	L	L	H	H	0	0	0

Fourteen of the 32 catheters received coatings that survived the freeze-thaw process and measurement. The remaining 18 catheters had coatings which were not adherent enough to the survive freeze-thaw process and/or measurement.

Table 7 describes the number of successful coatings per each condition.

Table 7

Number of Successful Catheter Coatings

	PVA	**BaSO4**	**Temp**	**Speed**
High	9/16	12/16	9/16	9/16
Low	5/16	2/16	5/16	5/16

The effect of PVA content change on coating thickness is 62.4 µm. The effect of BaSO4 content change on coating thickness is 58.9 µm. The effect of temperature change on coating thickness is 17.8 µm. The effect of dip coating speed on coating thickness is

27.3 µm. The catheters which did not register a measurable coating were included in the effect analysis as a value of 0.

Analysis of the design of experiments shows that the mass % of PVA in the hydrogel and the mass % of BaSO4, which represents the PLGA particles, have a similarly greater effect on the coating thickness than the temperature of the hydrogel or the extraction speed of the catheter. Of important note, more than half of the catheters that were coated in the hydrogel-BaSO4 composite did not result in a coating that was measurable and that maintained attachment after the freezing process and handling.

4.3.2 Insertion

Figure 8 shows the maximum forces recorded during insertion of the catheter through silicone. The maximum force recorded for any catheter was 2.412 N.

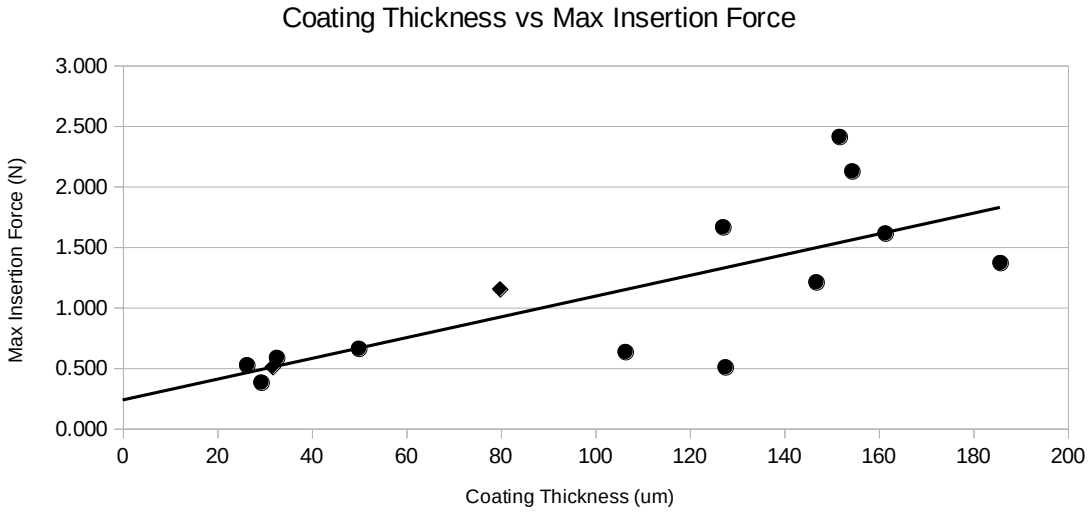


Figure 8. Maximum Insertion Force Versus Coating Thickness

Table 8 provides statistics on the insertion forces of the catheter samples which were successfully coated.

Table 8

Descriptive Statistics of Insertion Forces (N)

Insertion	
Mean	1.097
Standard Error	0.176
Variance	0.436
Standard Deviation	0.660
Range	2.030
Minimum	0.383
Maximum	2.412

4.3.3 Extraction

Figure 9 shows the maximum forces recorded during extraction of the catheter through silicone. The maximum force recorded for any catheter was 0.620 N. Table 9 provides statistics on the extraction forces of the catheter samples which were successfully coated.

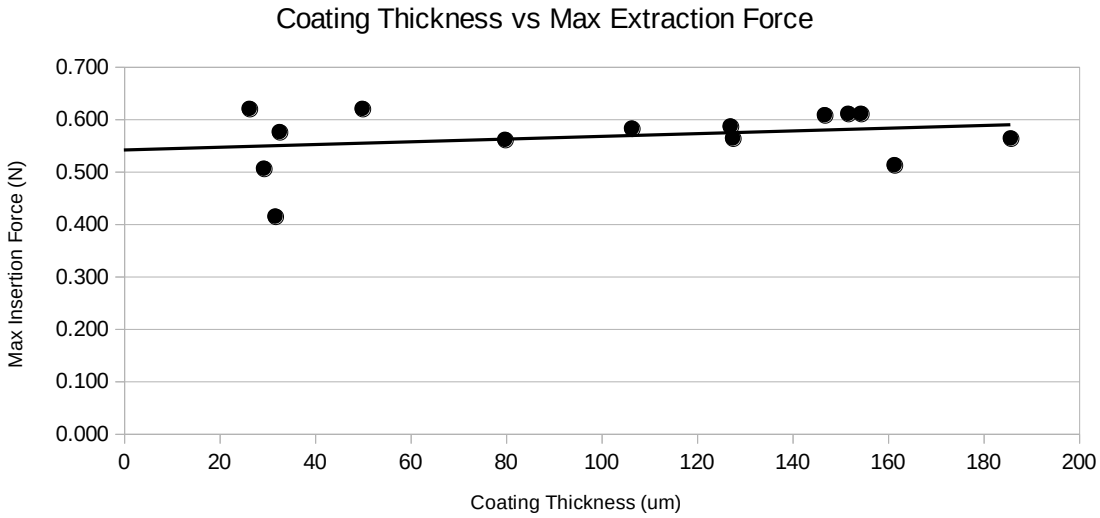


Figure 9. Maximum Extraction Force Versus Coating Thickness

Table 9

Descriptive Statistics of Extraction Forces (N)

Extraction	
Mean	0.567
Standard Error	0.015
Variance	0.003
Standard Deviation	0.057
Range	0.205
Minimum	0.415
Maximum	0.620

4.4 Discussion

4.4.1 Design of Experiments

The previous release studies and release modeling both help define the desired release kinetics for a catheter coating. However, to achieve a therapeutic effect, the

magnitude of the release rate would need to be tailored against clinically accepted therapeutic values. Furthermore, the safety profile of a coated catheter is dependent on the stability of a coating Therefore, this experiment was devised to investigate the effects of dip coating parameters on the thickness of the coating and the ability of the coating to survive insertion and extraction through the skin. Before discussing the nature of the coating, it is important to consider the coatings which did not manifest. Of the 32 catheters which were coated, 18 of them resulted in coating which did not survive the freezing and handling process prior to being imaged. One assumption of a design of experiments is that all parameters lead to a measurable outcome, an assumption that was false in this instance. We considered these results to be a value of 0 in the effect analysis to keep the responses even for each factor. Ideally in this situation, the design of experiment would be repeated using the information from the failed responses to define a range of factors that would be more suitable. However, due to limited resources, repeating it was not an option. Additionally, if factor ranges could not be adjusted, a D- or I-optimal design could be applied to the DOE to consider the constraints of the factors. Despite not meeting the assumptions required for a DOE, these results do provide a direction to improve future iterations of this experiment; within each parameter, the high condition always resulted in more successful coatings. Shifting the range of PVA content, $BaSO_4$ content, temperature and speed higher would yield more successful coatings until a usable range could be determined for all factors.

We wanted to determine if the coating thickness of the catheters could feasibly contain a therapeutic dose of anti-inflammatory. For dexamethasone, this dose profile is

known. The dose required to combat the foreign body reaction is 100 µg in the first day and 10 µg each day thereafter while the catheter is implanted [14]. This would result in at least 130 µg which must be loaded into the particles to achieve this goal over the release period of this study. Additionally, the minimum an insulin infusion catheter can be inserted into the skin is 4.5mm [6]. Using these constraints and a particle mass fraction of 20%, the high condition of the DOE, the coating thickness must be at least 2769 µm to contain enough dexamethasone in the particles to maintain a therapeutic dose over 14 days, which was not achieved and would be impractical for a catheter of this radius. The maximum coating thickness achieved in this experiment was 186 µm. Improvements to the efficiency of this coating are required to meet the goal of a therapeutic release profile. There is an opportunity to improve the drug loading of the PLGA particles; one such group reported a dexamethasone loading as high as 5.91 % w/w [18]. It is important to keep in mind that 186 µm is also larger than other known coatings that have been used on catheters. The thickness of other hydrogel coatings on catheters have been measured as thin as 10 µm and on the scale of nanometers for catheter coatings in general [85]. We saw in our results that an increase in coating thickness is correlated with an increase in force experienced during insertion. This could lead to delamination of the coating before entering the tissue, nullifying any benefit.

While there is not much in the way of information on anti-inflammatory releasing catheter coatings, other groups have been successfully using hydrogels to coat different types of catheters for adjacent purposes. Many of these coatings are focused on preventing catheter-related bacterial infections [86]–[88]. Interestingly, one group even

examined how coating a catheter in polymer-based coating affects inflammation of the intravascular endothelium [89]. There are also several studies investigating different methods of improving attachment strength of coatings to substrates [90]. However, none of these studies focus on insulin infusion sets, particle-hydrogel composites and the forces experienced during insertion through skin. The study presented here is one of the first known to our group that examines the ability to coat such a composite on a catheter resembling an insulin infusion set and explores how that coating responds to simulated use.

4.4.2 Insertion

All catheters with coatings that were inserted through a skin analog remained intact and visibly unaffected by insertion. There is not an established upper limit for force required to insert an insulin infusion catheter, but recommendations have been made for urethral catheters, which can be used as a reference for this study. The maximum force experienced by the coatings during insertion, 2.41 N, is 52% less than that maximum force recommended to insert a urethral catheter, 5 N [91]. These results support a safe and efficacious insertion of these coated catheters. However, the method of insertion in this study had a noticeable difference from the insertion method of an insulin infusion set. An insulin infusion set typically uses a spring-loaded mechanism to pass a needle through the skin along with the catheter into the subcutaneous tissue. We did not have access to this equipment, so an entry hole was required in the skin analog before insertion. We suspect this reduced the friction and resulting insertion force experienced by the coating. Insulin infusion sets can also be inserted at different angles and in different tissues. The

requisite fixturing and tissue analogs were not available during this experiment to investigate these factors. Future work should explore these conditions during insertion.

4.4.3 Extraction

There are not any examinations known to our group on extraction forces experienced by insulin infusion sets. However, this study provides some reference of what scale of force can cause delamination of catheter coatings. A study of urinary catheter coatings found that urinary catheters typically experience around 0.3 N at most when being extracted after hydration. The PVP-coated catheters in this paper delaminated and their coating was removed upon extraction [92]. The coatings in our study demonstrated that they could survive upwards of twice this amount of force. The catheters in this experiment were tested in a dehydrated state. We can expect our coating to hydrate after implantation into tissue which would likely reduce the amount of force the coating could withstand. Coating delamination has proven to be a problematic pattern for certain catheters in recent years [93], [94]. In the circumstance of an insulin infusion catheter, it could become a benefit during extraction. If the coating under the skin were to delaminate and remain in place after the catheter were removed, the beneficial effects of the anti-inflammatory drugs could persist while the insertion wound recovers. Controlled delamination could extend the release period of the coating and improve wound healing of the insertion site, a meaningful advantage for insulin pump users.

Chapter 5

Future Work

We have identified several areas of improvement and directions which would develop the work presented here. Improving the loading of lidocaine and dexamethasone in the PLGA particles would reduce the mass of particles needed to achieve therapeutic doses, leading to thinner coatings. In particular, we would like to see an increased loading of dexamethasone, which we know can reach as high as 61.9% seen in other studies [79]. Reducing the burst release of the particles would make the difference in short-term release of formulations clearer. We were not able to differentiate where the short-term release came from in our release study - whether it was from particles or directly from hydrogel; with zero-order release particles or close to that, we could be confident short-term release would strictly come from drug loaded into the hydrogel. We believe this is achievable based on other PLGA particle-based systems that have done this using dexamethasone and other drug payloads [17], [56], [95]. A lengthened release period could then be expected after loading increase and burst release decrease [95]. Composite manufacturing methods were sufficient, but left aspects to be desired. We would hope to see changes made which improved mixing, minimized material waste, and increased yield of composite end-product.

With a lengthened release period, we would hope to see release studies in the future extend beyond two weeks. It is possible to deliver drugs actively for more than two weeks, up to multiple months, as other similar systems have demonstrated [18], [21], [33]. Insertion and extraction studies in the future should attempt to mimic real-world use

more than those presented in this paper. This includes the catheter tubing, the needle used to pierce the skin, the skin or skin analog and the method used to insert the catheter. Looking towards the long-term future and potential commercialization, coated insulin infusion sets would need to be compared to other options currently available by using them in animal studies and evaluating inflammation at the end of the given period. Other investigations have laid groundwork for methods to evaluate drug-eluting coatings [14], [18], [21], [33] and insulin infusion sets [96], [97] using animal models.

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