LOCALIZING CHEMOTHERAPEUTIC DRUG RELEASE THROUGH THE USE OF POLYMER-BASED SURGICAL SEALANTS TO TREAT STAGE III COLORECTAL CANCER

Abstract

Current cancer treatments, such as systemic chemotherapy, induce several complications that affect the entire body; localizing chemotherapy to the tumor site has the potential to minimize harmful side effects. Solution blow spinning (SBS) offers the possibility of incorporating chemotherapy drugs into a polymer solution through the use of a compressed airbrush. This would allow for direct deposit of a polymer mat after surgically removing the tumor. Sutures, in combination with polymer sealants, could be used to prevent complications after surgery. This study focuses on stage IIIA colorectal cancer because cancer cells have not spread distantly yet, and treatment typically involves surgery followed by chemotherapy. Three key aims were addressed in this study to assess polymer-drug combinations' compatibility with SBS, observe drug release patterns, and evaluate the effect of drug incorporation on polymer adhesion to intestinal tissue. Our results suggested that the polymer-drug combination of poly(L-lactide-co-ε-caprolactone) (PLCL) and capecitabine shows promise as an adhesive surgical sealant with a drug release pattern that is complementary to a typical resection healing timeline.

Localizing Chemotherapeutic Drug Release Through the Use of Polymer-Based Surgical Sealants to Treat Stage III Colorectal Cancer

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Chapter One: Introduction

Research Problem

Current common cancer treatments such as systemic chemotherapy, which targets the whole body, cause adverse side effects including pain, fatigue, and vomiting. Recurrence is also common, resulting in patients having to endure these side effects several times [1]–[3]. Optimizing a targeted chemotherapy delivery system to reduce recurrence and side effects has been a major scientific goal. Localized drug delivery devices have a promising potential for cancer therapy, distinguishing themselves from traditional treatments due to their ability to provide local anticancer activity with minimal systemic side effects.

Team TUMOR aimed to incorporate chemotherapeutic agents into polymer-based surgical sealants sprayed directly onto tumor resection sites using a polymer fiber deposition technique called solution blow spinning (SBS). Team TUMOR focused their research efforts on colorectal cancer as it is presently being treated with both chemotherapy and resection upon reaching stage III. Currently, blow-spun sealants are used to close wounds from intestinal anastomosis, a common procedure following colorectal cancer resection. Factors such as metastasis and recurrence rate make colorectal cancer an ideal candidate for developing the chemotherapeutic polymeric sealant. Team TUMOR hypothesized that the combination of the blow-spun polymer sealant, which would reduce anastomotic leakage and thereby reduce recurrence [1], along with the chemotherapeutic drug incorporation to treat residual cancer cells would work on two fronts to reduce recurrence rates. Out of the colorectal cancer stages, stage III is the most applicable to use in researching a chemotherapeutic surgical sealant

because metastasis is typically not present in stage III. The absence of metastasis is beneficial because metastasis would increase the chances of recurrence and compromise other organs in the body, making the sealant a relatively ineffective form of treatment [2].

Relevance

In any given year, over 140,000 people (roughly 8.1% of all new cancer cases in the U.S.) are diagnosed with colorectal cancer, making it the fourth most common new cancer diagnosis [3]. That gives a rate of more than approximately 400 new colorectal cancer diagnoses each day. In addition, colorectal cancer accounts for about 50,600 deaths annually, roughly 8.3% of all cancer deaths [3]. This statistic gives a rate of over 100 deaths per day due to colorectal cancer. Taking these figures into consideration and acknowledging the widespread nature of this particular type of cancer justifies researching ways to improve existing treatments.

A patient's colorectal cancer stage can be divided into three subcategories: localized, regional, and distant. Localized cases are confined to the primary site and account for 39% of cases [3]. Regional cases constitute another 35% of all cases and occur when cancer has spread to the regional lymph nodes, small glands surrounding organs [3]. With such high levels of localized and regional diagnoses, improving localized drug delivery to tumor sites could greatly reduce the prevalence of colorectal cancer recurrence.

Current Treatments

There is a wide variety of current cancer treatment methods, the most prominent being surgery, radiation therapy, chemotherapy, or combinations of the three [4]. Systemic chemotherapy, such as the use of fluorouracil-based adjuvants, or drugs often used in conjunction with fluorouracil, and others like oxaliplatin and irinotecan, typically come with many side effects [5]. A study on self-reported side effects in cancer patients not in clinical trials reported that 86% of patients felt at least one side effect after receiving chemotherapy, with 67% feeling six or more side effects. Around one-third of patients (35%) experienced a moderate (grade III out of IV) side effect at least once in the study, while 27% experienced severe (grade IV) side effects at some point [5].

Surgical tumor resection is another standard cancer treatment, but often surgery alone cannot remove the entire tumor. In stage III colorectal cancer, cancer is still found on the lymph nodes after surgery in 45% of patients, 33% of patients will have a recurring disease, and there is a 70% chance of mortality in 5 years following surgery [6]. Although surgery is a viable option for treatment, surgery alone may not be adequate.

Radiation therapy is not as successful as surgery; however, preoperative radiotherapy is more successful than postoperative radiotherapy and reduces failure by 50–70% [7]. Similar to chemotherapy, the effects of radiation therapy are not localized. Therefore its widespread toxic effects justify a search for cancer treatments that are less harmful to the body as a whole.

Other treatments include some combination of the treatments previously described, also known as combined modality therapy. There are three main types. The first is adjuvant chemotherapy, the use of chemotherapy after the tumor is removed by

surgery or radiotherapy, reducing the need for further surgery. In stage III colorectal cancer, fluorouracil and levamisole given after surgery reduce recurrence rate by 40% and death rate by 33% [4]. However, the recurrence rate in stage III colorectal cancer is still 30% for this treatment; if adjuvant chemotherapy is somewhat successful, then providing localized therapy after surgery, instead of chemotherapy, could lower the recurrence rate further [8]. Chemotherapy before radiation or surgery, also known as induction chemotherapy, aims to reduce the tumor so that surgery becomes less or no longer necessary; however, it creates an unpredictable response that may make surgery a nonviable option altogether and reduce chances of success [4]. Unlike induction surgery, in which surgery follows chemotherapy, the therapy being researched is used in conjunction with surgery and therefore mitigates the chance of an unpredictable result. The third form of combined modality therapy, concomitant therapy, is most similar to the treatment being researched because two treatments are used simultaneously [4]. Such a treatment plan may cause unpredictable side effects due to how the different treatments interact. For example, the localized effect of treatment on a body still recovering from surgery could present a potential challenge in the research. Stage III colorectal cancer is most likely to be treated with a combination of surgical intervention and systemic chemotherapy, however, still justifying the research being proposed [9].

Main Research Question

The principal research question is: What is the most effective way to incorporate a chemotherapeutic agent into a surgical sealant to deliver therapeutics over a certain time and maintain adhesion in an effort to prevent tumor recurrence for those individuals

diagnosed with stage III colorectal cancer? The following subsidiary research questions pertain to each aim of this research:

Aim 1: What polymer and drug combination is suitable for this application of solution blow spinning?

In aim 1, experiments focused on testing physical properties, such as solubility and biodegradability. These results helped determine the ideal drug and polymer combination for blow spinning.

Aim 2: How does the polymer-drug combination affect drug release?

In aim 2, studies focused on observing the release time of drugs integrated into a polymer. The goal was to identify the polymer-drug combination that best mimicked the ideal release pattern for chemotherapy.

Aim 3: How does the incorporation of chemotherapy drugs affect the mechanical properties of the polymer?

In aim 3, the mechanical properties of the polymer and drug combination were tested. The answer to this question was determined by conducting *ex vivo* experiments assessing the sealant's success in a typical physiological environment.

Chapter Two: Literature Review

Introduction

Previous innovations in oncological research have produced colorectal cancer treatments with adverse side effects, such as nausea, vomiting, and extreme pain [5]. When using these conventional methods, the patient may experience several side effects due to incompatibility between different treatments [4]. These treatments, such as systemic chemotherapy and surgery, are stressful on the body, hindering healing and making recurrence more likely [10]. While the methods explored by this project involve the surgical process, the chemotherapy is localized to the resection site, potentially reducing systemic side effects. Anastomosis in the existing combined therapy requires resection of the tumor and subsequent suturing of the colon to allow post-operative healing. However, patients treated this way often experience anastomotic leakage, which requires additional procedures involving repair [1]. The fibers' morphology in this proposed experimental design has proven capable of adhering to tissue, and may not cause the same complications as sutures [11]. Additionally, incorporation of chemotherapeutic agents could further aid in reducing recurrence through not only reducing anastomotic leakage, but also by eradicating remaining cancer cells. Therefore, we will begin a comprehensive literature review covering colorectal cancer and its surgical process, chemotherapeutic agents, polymers, and conclude with related mathematical models of drug release.

Colorectal Cancer

Cancer is characterized by uncontrolled, abnormal cell division, which can metastasize by traveling through the blood and/or lymphatic system. Colorectal cancer is one of the three most common types of cancer, impacting both men and women at a rate of 10% [12]. It also is the second leading cause of death in cancer patients [13]. Colorectal cancer cells form in clumps along the colon's lining [12]. These cells reproduce in such large numbers that they produce a tumor, abnormal tissue composed of cancer cells. The cells resist apoptosis through the utilization of Interleukin-4, or IL-4 [14].

20% of patients with colorectal cancer have tumors that have metastasized already at the time of diagnosis [2]. Therefore, there will be a more significant focus on stage IIIA colorectal cancer, where cancer has spread through the colon wall's mucosa to the submucosa. Due to the absence of metastasis, which would increase the chances of recurrence and compromise other body organs, this stage of colorectal cancer is the most applicable in developing a chemotherapeutic surgical sealant as a relatively effective form of treatment [2]. Stage IIIA colon cancer varies in the number of lymph nodes that are positive for regional metastasis, with either 1 to 3 positive lymph nodes and tumor growth in the submucosa and muscle of the colon, or 4 to 6 positive lymph nodes and tumor growth in only the submucosa [15]. Approximately 1 in 3 stage III colorectal cancer patients experience recurrence [16]. The use of targeted chemotherapeutic drugs aims to prevent recurrence and metastasis.

Tumor resection is the preferred method to treat colorectal cancer tumors and is generally the first step in a combined treatment plan; the resection may be laparoscopic or

open [13]. Stage IIIA colorectal cancer treatments generally include surgical intervention that may be followed by chemotherapy, making this stage ideal for treatment via solution blow spinning. Since stage IIIA colorectal cancer's recurrence rate is relatively high, a surgical sealant that concentrates chemotherapy at the resection site can be useful and potentially preferable to systemic chemotherapy following a resection. The rapid growth and durability of the $CD133^+$ cells that cause colorectal cancer are largely responsible for the difficulty in treatment [17].

Surgical Process

The surgical procedure used for the treatment of stage IIIA colorectal cancer is a partial colectomy, which involves removing a portion of the colon. In a 2013 study, 38 patients were examined after a partial colectomy. Recurrence-free survival was 97%, 80%, and 67% at 1, 5, and 10 years, respectively, demonstrating the effectiveness of this procedure [18].

After the colectomy is performed, the colon segments are reconnected to each other, forming an anastomosis. Various intraoperative complications such as bleeding, bladder and bowel injury, and ureteral lesions, as well as postoperative complications such as wound infection and anastomotic leakage, are relatively common in patients receiving colectomies. The patient's anatomical characteristics and the surgeon's experience are among many factors that affect surgical outcomes [19]. In order to reduce complications, many surgeons opt to perform the resection laparoscopically, aided by a camera inserted into small incisions. Laparoscopic-assisted colectomies (LAC) often have a lower morbidity and blood loss rate than open colectomies (OC), making LACs

the preferred choice of many surgeons [13]. In a study by Krarup et al. [1], a nationwide cohort examination of 9,333 patients registered in a colorectal cancer group, distant recurrence of colorectal cancer developed in 14.9% of patients and more frequently after anastomotic leakage was observed. Anastomotic leakage was significantly associated with increased rates of distant recurrence, and mortality was higher in those patients with leakage than those without.

For colorectal anastomoses, polymer-based sealants showed the most positive results for adhesion and mechanical properties [20]. This indicates that along with their potential applications in localized cancer drug delivery, surgical sealants also display significant mechanical action, which can be combined to make an effective surgical tool. Sealants applied around a colon may help prevent anastomotic leakage by adding tensile strength to the mechanical strength provided by the sutures at the surgical site and allowing healing. Additionally, an effective sealant can prevent bacteria in the intestinal contents from leaking into the peritoneal space.

Effective use of surgical sealants after colon cancer resection is noted in a 1993 study. After a partial colectomy and anastomosis were performed on a group of rats, they were divided into three groups. A circumferential ring of tissue sealant was placed around the entirety of the anastomotic sites in group A, 50% of the site in group B, and no sealant was applied in group C. The incidence of anastomotic penetration by tumor cells and subsequent tumor growth was significantly lower in group A. This shows that the fibrin sealant formed an effective barrier in preventing intraluminal tumor cells from penetrating the anastomosis and causing anastomotic leakage [21]. Through this mechanism, the physical barrier of the polymer can reduce the risk of recurrence by

limiting the spread of tumor cells, while incorporating chemotherapeutic agents can offer another route to eliminate those remaining cancer cells.

Chemotherapeutic Agents

Although many chemotherapeutic agents are used to treat colorectal cancer, some are more common, more accessible, and less expensive than others. Among the most common agents are oxaliplatin, 5-fluorouracil (5-FU), and capecitabine. The method generally used for administering these medications is an oral pill.

5-FU is one of the most commonly prescribed chemotherapeutic drugs for colorectal cancer. Its primary purpose is to prevent RNA synthesis in metastasizing colon cancer cells, to halt tumor growth [22]. Capecitabine is a prodrug of 5-FU, meaning it produces the same effects and is very chemically similar, according to a review by Walko and Lindley [23]. After ingestion, the body metabolizes capecitabine, and the product of the biochemical reaction is 5-FU [23]. Oxaliplatin forms bonds between DNA strands that should not be bound for replication, preventing cells from replicating [24]. While these chemotherapeutic agents act in different ways, they work to prevent cancer cell replication and metastasis.

Polymers

Certain properties of polyesters make them useful in biomedical settings, such as wound sealants and delivery systems for chemotherapeutics. Adhesive properties of polyesters facilitate increased local drug delivery to cancer cells, indicating a unique ability to limit apoptosis of healthy cells, unlike systemic chemotherapy. This adhesion

ultimately allows the delivery of drugs to localized sites. In a 2017 study by Tavakoli et al. [25], a drug delivery system consisting of polycaprolactone (PCL) and Temozolomide showed a greater ability to induce apoptosis of U87- glioma cells than Temozolomide itself due to its ability to adhere to the glioma cells. This is a prime example of polymers being used as localized drug delivery devices, which led to an increase in cancer cell apoptosis. Tissue adherence can be adjusted using different polymers, as demonstrated in a 2018 study by Xu et al. [26]. There are many properties of polymers that can be studied and utilized in order to create sealants for specific purposes, in this case, prolonged local drug release.

The chemistry and morphology of a polymer, such as its molecular weight or tacticity, affect how it reacts to various drugs and their release. These properties and the chemical interactions between drugs and polymers in a drug-incorporated polymer system could correlate to different release patterns or delayed drug release [27]. By increasing drug entrapment, drug toxicity is minimized due to a stronger association between drug and polymer, leading to a slower release rate [27]. This indicates that differing polymer entrapment efficiencies allow for the manipulation of drug release patterns [28].

Molecular Weight

The chosen polymer's molecular weight is the most prominent trait in changing the drug's release profile. According to Ihre et al. [27], a "high" molecular weight is considered to be greater than 20,000 Da, while a "low" molecular weight is 1000 Da or less when using specific polymers. At 1000 Da, polymers are considered below the

entanglement molecular weight because they can only form non-interacting single chains. They exhibit poor mechanical strength and degrade at a faster rate. At higher molecular weights, 20,000 Da and greater, the polymers overlap and interact with one another, allowing them to exhibit increased mechanical strength and elasticity [29]. When decreasing the molecular weight of the polymer, the drug releases more rapidly [30]. Inversely, increasing the polymer's molecular weight may slow down the rate of erosion front movement, which dictates drug release. Therefore, as the rate of erosion slows, the drug release slows as well, indicating the negative correlation between polymer molecular weight and drug release rate [31]. In addition to changing the release rate, an increased molecular weight also has higher efficacy in cancer treatment [27]. This results from the molecular weight and the number of ester bonds in the polymer, which are positively correlated. Increasing molecular weight slows the release rate of drugs because more ester bonds react with the drug [32].

Cross Linkages/Polymer Tacticity/Porosity

The relationship between drug release and drug entrapment is influenced by crosslinking within polymer systems. As the number of cross-linkages in an interpenetrating polymer system (IPN) increases, entrapment also increases [33]. Since entrapment is more significant in polymers with greater linkages, drug release is slower in such polymers. A negative correlation was noted between the number of cross-linkages in an IPN and the percent of drug released [33].

Furthermore, the tacticity of the polymer affects its physical properties. A polymer's tacticity refers to the stereochemistry and arrangement of the polymer [34].

Isotactic polymers, in which all asymmetric carbons in the polymer have the same configuration, may have a longer drug release pattern since they tend to be crystalline. Drug release from polylactic acid (PLA) matrices is primarily dependent on the polymer's tacticity and occurs in a highly controlled pattern [32].

The drug release rate can be altered by increasing the polymer porosity as soluble drugs are dependent on porous matrices to diffuse [35]. Increased porosity is correlated with faster drug release [35]. Additionally, with the introduction of a surfactant to the drug-polymer complex, pore depth is decreased, reducing initial burst release [34]. It is important to note that drug loading reduces surface porosity and will decrease the burst release effect as it will take longer for the exterior to degrade [36], [37].

Effects of Polymer Processing

Variations in polymer system release profiles depend on the loading process, fiber diameter size, and hydrophobicity of the polyester matrix. Blow spinning or electrospinning may be used to form fibers and create fiber mats from polymers. Therefore, the physical features of fiber mats can also be altered by using different combinations of polymers. The incorporation of other polymers changes the size, elasticity, and tensile strength, altering the drug's release pattern. Del Valle et al. [38] demonstrated that incorporating PLA micro/nanofibers led to a significant increase in the elastic modulus and tensile strength. The release pattern was an initial burst, then slow and sustained with PLA's addition [38]. PLCL may be added to reduce the tensile strength of a polymer system [39]. PCL and PLCL are very compatible for low levels of PLCL. However, as the PLCL percentage increases, PLCL tends to form its own domain

and form its own distinct morphology. The release rate can also be increased by mechanical stretching of fibers, which decreases the diameter [40].

Drug and Polymer Interactions

A polymer-drug system's relative hydrophobicity or hydrophilicity plays a critical role in determining polymer-drug interactions and release profiles. It has generally been noted that hydrophobic polymers and drugs typically portray slower release than their hydrophilic counterparts. A study conducted by Yuan et al. [41] found that the hydrophobic drug doxorubicin hydrochloride (Dox-HCl), when interacting with the hydrophobic polymer PLA, buried itself within the polymer rather than interacting with the polymer at its surface. This interaction between Dox-HCl and PLA contributed to a slow release of the drug from the core of the polymer-drug complex. Similar studies have concluded that this interaction between a hydrophobic drug and the hydrophobic region of its respective polymer results in drug entrapment, leading to the slower drug release due to tight binding interactions between the drug and polymer [42]–[44]. A common polymer used to increase hydrophilicity is PEG, which separates from PCL in its solid-state [43], [45], [46]. Vassiliou et al. [47] found that hydrophilic drugs release faster than hydrophobic drugs, which generally portray a burst release followed by a sustained, slow release. Geiger et al. [48] additionally found that hydrophobic substances can be used to partition drugs into regions of polymer with different levels of hydrophobicity and hydrophilicity, allowing for more sustained release. In another study conducted by Chou et al. [40], it was found that most sustained release systems to date have been limited to the delivery of biologics or small hydrophobic molecules. For hydrophilic

small molecule drugs, the high aqueous solubility, poor partitioning, and incompatibility with insoluble polymers pose a challenge to long-term release. Some studies have found that entrapment of hydrophilic drugs in a hydrophobic core can prolong the duration of release [49]. Additionally, it has been found that the polymer hyperbranched polyether amine (HPE-A) can create hydrophobic cavities for drug entrapment [43], [45], [46].

Another focus of research has been the prevalence of electrostatic interactions, including hydrogen bonding and ionic interactions, in a drug-polymer combination. In a study conducted by Huang et al. [50], it was found that hydrophobic drugs illustrate the potential for controlled release, given that they can be stabilized within polymer systems through hydrogen bonding. Ionic interactions are another key factor in determining release patterns. Negatively charged polymers are more suitable for loading positively charged drugs, leading to increased entrapment and delayed-release [51]. Electrochemical interactions between functional groups on polymers and drugs can also change drug delivery systems' release profiles. The most common example of this type of interaction involves terminal groups on polymers. Hydrophilic drugs bond with carbonyl groups for more uniform distribution [40] and acidic functional groups can control release in many polyester systems [52]. In PLGA, there is a 0.9 correlation between the addition of terminal acidic functional groups and the percentage of drug release, with the effect being carried out by altered polymer erosion patterns [52], [53]. Another factor in release profiles is the lactic: glycolic acid ratios of the polymer. Chou et al. [40] found that Young's modulus undergoes dramatic changes based on the lactic: glycolic ratio used. Kasperczyk et al. [54] used infrared (IR) spectroscopy to characterize covalent bonds between Doxorubicin and the lactide sections of polymers, altering release timeframes.

These findings demonstrate the potential for lower toxicity and targeted release, with the drug bonding to the polymer's side chains.

Many modifications can be made to polymers to change their interactions with the drug through physical and chemical mechanisms. One such modification is the addition of a polymer coating to increase stability and prolong release. Adding a polymeric coating adds another physical barrier between the polymer system and its surrounding environment to slow the drug's diffusion rate. Nuclear Magnetic Resonance (NMR) spectra show no chemical interaction between the coating and the drug [55]. This mechanism can also be used to produce pulsatile release depending on the polymer and coating combinations. In most cases, the initial burst of drug release is decreased, as demonstrated by Manna [56] using a PLGA/PGA coating. Hydrolysis of the coating provided a steady, prolonged release. Both Su et al. [57] and Mylonaki et al. [58] have shown that incorporating drugs into either the shell of a core-shell system or the coating itself can decrease the initial release time of the drug while still allowing for extended release. Similar to adding a polymer coating, layering polymers is another method for altering release patterns. This method stems from alternating layers of polymer with drug and layers without drug, according to Kim et al. [59].

Layering polymers can also result in more even drug distribution and more predictable release patterns [40]. Branching of polyesters results in a faster breakdown, and this property can be utilized to expedite drug release. There are two specific types of branching patterns that have been studied for their effects on release rate: comb-branching and star-shaped branching patterns. A polymer exhibits a comb-branching pattern when the polymer's central backbone includes several side

chains or arms [60]. On the other hand, star-shaped branching patterns include several linear polymer chains, each connected at a common point [61]. Polymers with comb-branching patterns exhibit faster degradation rates and a porous structure that allows for drug delivery in 2 to 3 weeks. Star-shaped branching patterns exhibit longer retention due to interactions between PLA and PEG blocks, leading to accelerated degradation after about three weeks [62]. The hydrophobicity of the backbone or branches adds another component that alters release. Zhang et al. [46] found that an inner hydrophobic element to a branched polymer system allows for better entrapment of hydrophobic drugs with greater stiffness and lowered porosity. This system initially underwent quick degradation, followed by an extended drug release. Additionally, using a hierarchical structure of microfibers and nanofibers allows for greater drug retention by reducing porosity [63]. Other alterations are still being studied, such as an increase in the number of ester bonds in a polymer that increases the length of drug release [32].

Drug loading efficiency is higher for hydrophobic polymer and hydrophobic drug systems due to favorable hydrogen and electrochemical interactions between the drug and polymer [42]–[44]. In a hydrophilic environment, hydrophobic drugs will more likely be found in the hydrophobic region of a polymer, increasing entropically favorable interactions and drug entrapment [47]. Some polymers, including hyperbranched polyether amine (HPE-A), have been able to create hydrophobic cavities as a result of their chemical structure, such that the release of hydrophobic drugs is delayed due to increased entrapment [43], [45], [46].

Solution Blow Spinning

To administer the surgical sealant over the colon, a technique called solution blow spinning (SBS) is utilized. In SBS, a polymer is dissolved in a solvent and sprayed through an airbrush [11]. Once deposited, the solvent quickly evaporates before contacting the tissue, and the polymer forms adhesive fibers [11]. Compared to the more common method of electrospinning, SBS is advantageous due to its lower cost [11]. Unlike electrospinning, blow spinning does not require an electric current and instead utilizes an airbrush and pressurized gas to propel the fibers, making use of accessible and portable equipment [11]. Blow spinning typically uses acetone as a solvent, while electrospinning often uses more toxic solvents, such as chloroform, making blow spinning suitable for applications within the body [11]. Kern et al. [64] found success when using solution blow spinning to repair bowel anastomosis, demonstrating this method's clinical applicability.

Mathematical Models of Drug Release

Drug release can be modeled using two major methods: bulk erosion and surface erosion. Bulk erosion occurs when there is a lag period without significant polymer mass loss followed by the rapid mass loss [65]. This overall pattern of degradation has been described as sigmoidal [66], and many have found the period of mass loss to be first-order [67]. First-order release kinetics are dependent on the concentration of the drug. In other words, the rate of release is proportional to the drug concentration. It is represented by the equation:

$$ln\,(1 - F) = -K_1 t$$

where “F” is the fraction of drug released, “t” is time, and “K_1” is the first order release constant [68]. Another common form of the equation represents the release as a log cumulative percent of drug retained versus time. This is represented by the equation:

$$logQ_t = logQ_o - K_1 t/2.303$$

where “Q_t” is the amount of drug dissolved at time “t,” “Q_o” is the initial amount of drug in the solution, and “K_1” is the first order release constant [69].

When a drug is incorporated into the polymer, bulk erosion has the potential to provide a pulsatile release [65], in which there is a rapid release of drug from the polymer following a period of dormancy. Pulsatile systems can be divided into two categories: time-controlled systems and stimuli-induced systems. A thermoresponsive (stimuli-induced) pulsatile release was described mathematically for the first time by Yang et al. [70]. The fraction of drug release from a thermoresponsive polymer by time t is represented by the equation:

$$\frac{M(t)}{M(\infty)} = \begin{cases} 1 - \sum_{n=1}^{\infty} \frac{2}{\lambda_n} \exp\left(-\lambda_n \frac{D_c t}{H_c^2}\right), & 0 \le t < t_1, \\ 1 - \sum_{n=1}^{\infty} \frac{2}{\lambda_n} \exp\left(-\lambda_n \left(\frac{D_c t_1}{H_c^2} + \frac{D_s(t - t_1)}{H_s^2}\right)\right), & t_1 \le t < t_2, \\ 1 - \sum_{n=1}^{\infty} \frac{2}{\lambda_n} \exp\left(-\lambda_n \left(\frac{D_c t_1}{H_c^2} + \frac{D_s(t_2 - t_1)}{H_s^2} + \frac{D_c(t - t_2)}{H_c^2}\right)\right), \\ t_2 \le t < t_3, \\ \vdots \end{cases}$$

Where Where “M(t)” and “$M(\infty)$” are the amount of drug released at time “t” and time “∞" respectively, “t” is time, “D_c” is the constant diffusivity of the condensed

polymer film, " D_s" is the constant diffusivity of the swollen film, "H_c" is the constant thickness of the condensed film, "H_s" is the constant thickness of the swollen film, and "λ_n" $= ((2n-1)^{2\pi^2})/4$ [70]. Treatments that aim to replenish or support existing processes in the body may benefit from a release that parallels natural mechanisms. Additionally, pulsatile release allows repeated release over a few weeks [71]. This could reduce the amount of times treatment must be administered, allowing multiple doses to be released internally.

Surface erosion occurs when the exterior of the polymer degrades first, causing a delay in the mass loss [66]. This prevents the interior of the polymer from breaking down until the surrounding layers have been degraded. Surface erosion allows for delayed drug release, as the incorporation of drugs prevents rapid hydrolysis of lactone functional groups present in polyesters, as seen in bulk erosion [28], [66]. It has been found that a high surface area to volume ratio increases surface erosion and thus drug release rate [63]. This observation is supported by the Hixson-Crowell mathematical model that recognizes that the dissolution rate depends on the surface area contacting the applied solvent with an increase in the surface area resulting in faster dissolution of the system. It is represented by the equation:

$$W_0^{1/3} - W_t^{1/3} = K_{HC}$$

where "W_0" is the initial amount of drug, "W_t" is the remaining amount of drug at time "t," and "K_{HC}" is the Hixson-Crowell constant describing the proportion between the surface area to volume at time "t" [72]. Furthermore, the Hopfenberg model can be applied to surface eroding polymers where a zero-order surface detachment of the drug is the rate-limiting release step, the slowest part of the drug release. It acts as a kinetic

bottleneck, preventing the overall drug release from proceeding any faster than that slowest step. Moreover, a zero-order release kinetic is one where the rate of release is constant over a period of time [73]. The Hopfenberg model is represented by the equation:

$$M_t / M_\infty = 1 - [1 - k_0 t / C_L a]^n$$

Where "K"$_0$ is the zero-order rate constant describing the surface erosion process, "C_L" is the initial drug loading through the system, "a" is the system's radius, and "n" is the system's geometry. The equation [73] is valid for slabs, cylinders, and spheres with:

n=1 for flat slab

n=2 for cylinder

n=3 for sphere

More comprehensively, the Weibull mathematical model is commonly used in drug dissolution studies and can be applied to all types of dissolution systems. It is given by the equation:

$$m = 1 - exp[- (t - T_i)^b / a]$$

Where "m" is the accumulated fraction of drug release in solution at time "t," "a" is the time scale process, "T_i" is the lag time (generally zero), and b is the shape parameter with

b=1 indicating an exponential curve

b=2 indicating a sigmoid curve

b=3 indicating a parabolic curve.

The Weibull mathematical model is most applicable when determining dissolution curves, especially when determining if a surface eroding polymer's dissolution curve is

linear. Drug release following this model will have a linear trend when a log(m) vs. log(t) plot is constructed [74].

There are many advantages to a delayed-release system. By releasing lower drug concentration over a long period, this treatment could reduce the accumulation of cytotoxic drugs at healthy normal sites and focuses circulation of the drug at the tumor site [50]. Additionally, the sustained release could provide a prolonged treatment over a much more extended period of time than the pulsatile-like release characteristic of bulk erosion [75].

Conclusion

Colorectal cancer is one of the most common cancer types and is the second leading cause of death in cancer patients [12], [13]. Many gaps exist in prior research regarding the SBS technique, especially in its applications to colorectal cancer. Evaluating the efficacy of a local drug delivery method, determining the optimal polymer type for use in SBS, and testing this technique on diseased tissue remain areas for further experimentation. The purpose of a polymer sealant is to reduce anastomotic leakage, a common complication of tumor resection that increases risk of recurrence [1], while incorporating chemotherapeutic agents is likely to reduce risk of recurrence as well. The following chapters focus on creating a tissue-adhesive chemotherapeutic device, aiming to control drug release within a polymer-drug system and provide local treatment at the site of tumor resection.

Chapter 3: Materials and Methodology

Polymers for Use in Surgical Sealants

One biodegradable polymer that can be used to facilitate drug release is poly(lactic-co-glycolic acid) (PLGA). This polymer can be dissolved in acetone and applied by blow spinning with an airbrush to create adhesive fibers for use in the body [11], [76]. PLGA does not actively aid the tissue healing process. Instead, it adds tensile strength to the anastomosis to facilitate natural healing [11], [76]. However, PLGA degrades in only 30 days *in vitro*, which would not suffice for a long-term chemotherapy treatment [76]. This means that PLGA-based drug delivery is not optimal for treating colorectal cancer because it will release drugs too quickly and not allow for a suitably long treatment window.

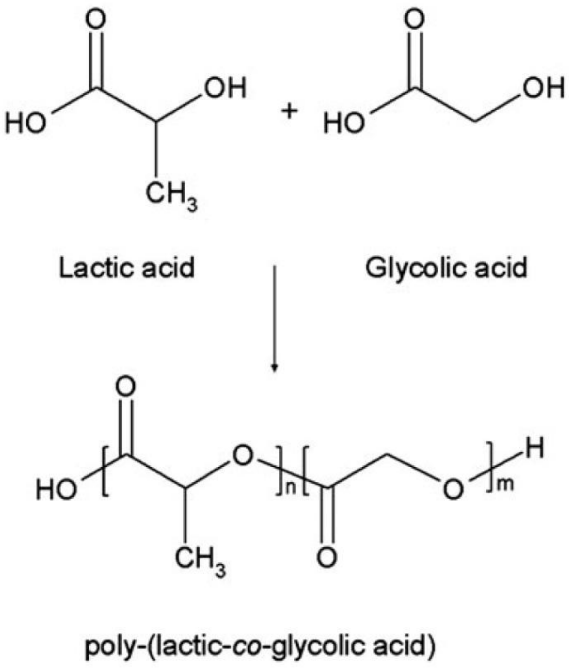

Figure 1*: Structure of lactic acid, glycolic acid, and PLGA.*

A polymer that is more suited for extended-release chemotherapy treatment is PCL or PLCL. These polymers have a much longer degradation time than PLGA, degrading over the course of multiple months and lasting for up to two years [77], [78]. This would allow for a long-term release of chemotherapy drugs to the anastomotic site. However, PCL solutions were comparatively more difficult to use with the airbrush than PLCL and PLGA. The PCL solutions were more viscous and repeatedly blocked the nozzle of the airbrush. Therefore, our methodologies were conducted with only PLCL and PLGA polymer and drug solutions.

Aim I Methodology

The main goal of Aim 1 of our experiments was to determine how the incorporation of chemotherapeutic drugs into polymers affected the properties of the polymer. Three chemotherapeutic drugs were used for this experiment: 5-fluorouracil (5-FU), oxaliplatin, and capecitabine. These drugs are all common for treating colorectal cancer and have IC_{50} concentrations of 24.2 μM, 24.2 μM, and 0.97 μM, respectively. [79], [80]. The IC_{50} concentration is the concentration of drug required to kill 50% of colon cancer cells *in vitro*. Each drug was dissolved at twice its IC_{50} concentration (48.4 μM, 48.4 μM, and 1.94 μM, respectively). Double the concentration was used because it was expected that the evaporating acetone would lead to a decreased amount of drug in the resulting polymer sealant. The high volatility of acetone mitigates its potentially harmful side effects in the body. Acetone will evaporate before it reaches the target area, thereby making it the most viable candidate for the blow spinning procedure instead of more harmful solvents such as chloroform or methanol. After the solutions of each drug

in acetone were made, 20% w/v solutions of PLGA and PLCL were made by dissolving approximately 1 g of polymer in 5 mL of each drug/acetone solution. For each polymer, molecular weights of both 40 kDa and 80 kDa were used. Additionally, four control solutions were made with 1 g of each polymer at each molecular weight dissolved in 5 mL acetone without a drug to make 20% w/v solutions. Each of the experimental solutions used for this methodology is outlined in Table 1.

After the solutions were made, 1 mL of each solution was sprayed via SBS onto a glass slide positioned about 20 cm away from the airbrush. Each PLCL fiber mat was examined immediately under an optical microscope to view the fiber mats before they transitioned into a film. Qualitative observations were made about the consistency and general appearance of the fiber mats and morphology and fiber diameter. The polymer fibers loaded with drug were compared to their corresponding controls (with the same polymer at the same molecular weight) to determine what effects, if any, the incorporation of chemotherapy drugs had on the polymer fiber structure.

Table 1. *Different polymer and drug combinations used in the methodology.*

PLCL	40 kDa	Oxaliplatin
		Capecitabine
		5-fluorouracil (5-FU)
	80 kDa	Oxaliplatin
		Capecitabine
		5-fluorouracil (5-FU)
PLGA	40 kDa	Oxaliplatin
		Capecitabine
		5-fluorouracil (5-FU)
	80 kDa	Oxaliplatin
		Capecitabine
		5-fluorouracil (5-FU)

Aim II Methodology

The main goal of Aim II was to determine which drug and polymer combination was ideal for release at a surgical site. Desirable characteristics include delayed-release, to permit post-operative site healing, and drug release concentration that would be effective for treating Stage IIIA colorectal cancer.

One of the critical features of the ideal drug for incorporation into a surgical sealant was its release profile. During chemotherapy treatment, drugs are administered over multiple treatment sessions to achieve a consistent circulation of drugs in the body without being lethal to the patient. Therefore, the release patterns of capecitabine, 5-FU, and oxaliplatin from 40 and 80 kDa PLCL were studied to compare with the typical treatment timeline of Stage IIIA colorectal cancer. The drug release was measured by using UV-Vis spectrophotometry. The changes in the absorbance of the solution surrounding the drug and polymer showed the drug concentration released in a certain period. In order to initiate this study, the lambda max (λ_{max}) values (the wavelength at which the light absorbance of the drug is maximized) for capecitabine, 5-FU, and oxaliplatin were determined by running a full range UV-Vis scan from 250–700 nm and observing which wavelength showed the highest absorbance. Standard curves were created by measuring the absorbance at various concentrations in a serial dilution starting from the IC_{50} value.

The λ_{max} and standard curve information were used to obtain a release profile of each drug. Drug solutions with a concentration of twice the IC_{50} values were mixed with 20% solutions of 40 and 80 kDa PLCL in phosphate buffer saline (PBS). Twice the IC_{50} value was used to account for any drug lost in the solution blow spinning process.

Blow-spun fiber mats were placed in a Petri dish with 10 mL each of PBS of pH 7.4 and stored at 37^{o} C to mimic internal body conditions. Three Petri dishes for each drug and molecular weight were made, and three measurements were taken for each dish. The Petri dishes were sealed with electrical tape and Parafilm to prevent leakage and evaporation of PBS. Measurements were taken every day for the first week to determine whether the drug was immediately released and then once a week by removing 3000 μL of the PBS solution from each Petri dish, placing it in a cuvette, and measuring the absorbance at the lambda max of the drug it contained. Oxaliplatin in PBS was treated with Iron (III) Chloride in the presence of Phenanthroline (retrieved from Sigma-Aldrich) to shift the lambda max and appear visible with spectrophotometry [81]. Capecitabine showed a delayed stepwise and delayed-release profile which was of interest compared to standard treatment, so it was used for all experiments moving forward. To ensure the accuracy of the capecitabine release pattern, the same procedure was repeated.

The same procedure was repeated with 40 and 80 kDa PLGA. PLGA is more hydrophilic than PLCL, and comparison to PLCL would help explain chemical interactions between the drug and polymer. Measurements were taken until a 20% release was reached to confirm whether the expected release pattern would occur and compare the delay in drug release. For PLGA, the release would be expected to start earlier than capecitabine and then continue steadily until 20% was reached rather than taking several weeks to start and then releasing in a stepwise fashion as PLCL did.

Aim III Methodology

This experiment's main goal was to compare a PLCL polymer's mechanical properties with and without chemotherapeutic drugs at different molecular weights. The first mechanical property to be tested was the degradation of the polymer. Four 1000 μL samples of 20% polymer solution (40 kDa PLCL control, 80 kDa PLCL control, 40 kDa PLCL + 48.4 μM capecitabine, and 80 kDa PLCL + 48.4 μM capecitabine) were solution blow-spun onto a pre-massed glass slide and placed into pre-massed Petri dishes. Twice the IC_{50} concentration of drug was used because it was expected that some drug would evaporate along with the acetone during the spraying process. The combined mass of the pre-massed slide and pre-massed Petri dish were recorded. The slides were submerged in 10 mL of PBS and kept in an oven at 37°C. After one week, the samples were removed from the PBS, blotted dry with a Kimwipe, and placed in a vacuum desiccator for 48 hours. After 48 hours, the samples were massed in the Petri dishes, and the combined mass of the pre-massed Petri dish and the slide was subtracted to determine the mass of the polymer. 10 mL of PBS was then placed back into the Petri dish, and the sample was put back into the oven. In order to observe any differences in the mass of the polymer solution over time, this process was repeated over a span of approximately 112 days with n=3 samples per polymer solution. This time was selected to generally follow the time span of the drug release from Aim 2.

The next mechanical property to be tested was the adhesion of the polymer. The adhesive capabilities of the PLCL fibers with and without capecitabine at different molecular weights were tested via pull-off testing through a Dynamic Mechanical Analysis (DMA) machine. Four 500 μL samples of 20% polymer solution (40 kDa

PLCL control, 80 kDa PLCL control, 40 kDa PLCL + 48.4 μM capecitabine, and 80 kDa PLCL + 48.4 μM capecitabine) were solution blow-spun onto 8 by 8 mm clamps. Twice the IC_{50} concentration of drug was used because it was expected that some drug would evaporate along with the acetone during the spraying process. Porcine intestinal tissue was trimmed to size and super-glued to an 8 mm by 10 mm clamp. The two clamps were compressed together at a force of 1 N for 5 minutes at 37°C, allowing the fiber mats to transition as they would *in vivo* and overall to mimic physiological body temperature [82]. The DMA then performed a "pull off," pulling the two clamps apart at a force that increased by 1 N per minute at a fixed temperature of 37°C until the fiber mat failed to adhere to the tissue. The maximum force was then recorded and divided by the area of the 8 by 8 mm clamp to determine the maximum amount of stress the polymer could take before failing to adhere to the tissue. This procedure was repeated for five trials per polymer solution.

Chapter 4: Results

Morphological Analysis of Blow-Spun Fibers

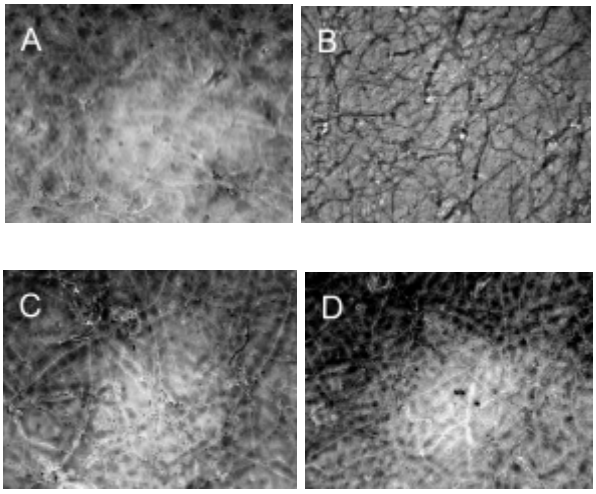

Figure 2. *Micrographs of each polymer-drug condition. A) 40 kDa PLCL without drug, B) 40 kDa PLCL with capecitabine, C) 80 kDa PLCL without drug, D) 80 kDa PLCL with capecitabine. The fiber mats' observable qualities do not significantly change between the control groups and the solutions with capecitabine. Both 80 kDa PLCL samples were denser than the 40 kDa PLCL samples.*

5-Fluorouracil, capecitabine, and oxaliplatin were all able to dissolve at double their IC_{50} concentrations in 20% solutions of both molecular weights of PLCL and PLGA in acetone. Since all of the drugs were soluble in the polymer solutions, surfactants were not used. The glass slide functioned as the surface to which the polymer could adhere and form a fiber mat. Upon analysis of the fiber mats under a microscope, there was no significant difference in the observable morphology of PLCL fibers in the control trials compared to the trials in which chemotherapeutic agents were present. Additionally, there were no significant differences in the fiber density between the control and drug-loaded

fibers or in the adhesion of fiber mats to the glass slide. 80 kDa PLCL fibers were shown to be denser than 40 kDa PLCL fibers for both the control and experimental groups. Typical diameters of blow spun fibers according to literature range from 0.25µm and 2.5µm; though the PLCL fibers shown here were not measured, they are expected to be similar [76], [83]. PLGA images were unable to be obtained due to time constraints imposed by the COVID-19 pandemic. However, PLGA fibers were successfully spun using solution blow spinning and there were no observable differences in the fibers spun with the chemotherapeutic agent and the control.

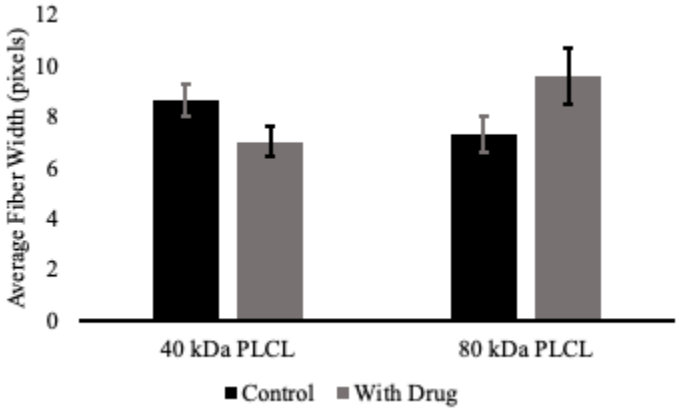

Figure 3. *Comparison of average fiber width between 40kDa and 80kDa samples with and without drug incorporated. The mean fiber width and standard error of n=10 are graphed above. The black bars represent the control samples without drug and the gray bars represent drug-incorporated samples. Measurements were taken using ImageJ analysis software.*

T-test for 2 independent means was used to determine if fiber width was affected by the incorporation of drug. Measurements of the fiber width in PLCL were analyzed with ImageJ software. Both 40 and 80 kDa PLCL samples show no significant difference

in average fiber width between samples with and without drug incorporated ($p>0.05$, n=10 for each sample).

Drug Release Trials

Drug release of three different drugs with varying molecular weights of PLCL show different release profiles. 5-FU shows a periodic release of drug, followed by a burst release that reaches 100% release of the loaded drug within 80 days for 40 kDa and 60 days for 80 kDa (Figure 4).

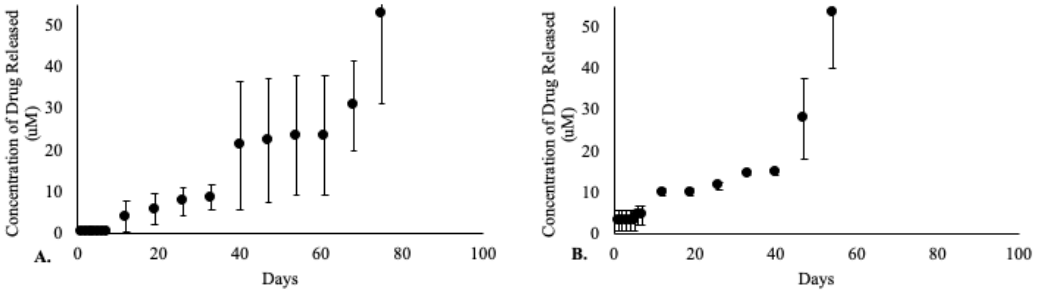

Figure 4. *Drug release of 5-FU dissolved in A. 40 kDa and B. 80 kDa PLCL. The means and standard errors of samples of n=3 are graphed as a percent of original concentration released as a function of time.*

Capecitabine shows different release profiles between the 40 kDa and 80 kDa PLCL samples (Figure 5). Both samples were not 100% released at the conclusion of the study at 96 days. 40 kDa PLCL shows a large burst release at about 40 days. 80 kDa PLCL shows a periodic step release throughout the duration of the study. Both molecular weights show some degree of delay before the drug's initial release, with a longer delay in 80 kDa PLCL trials.

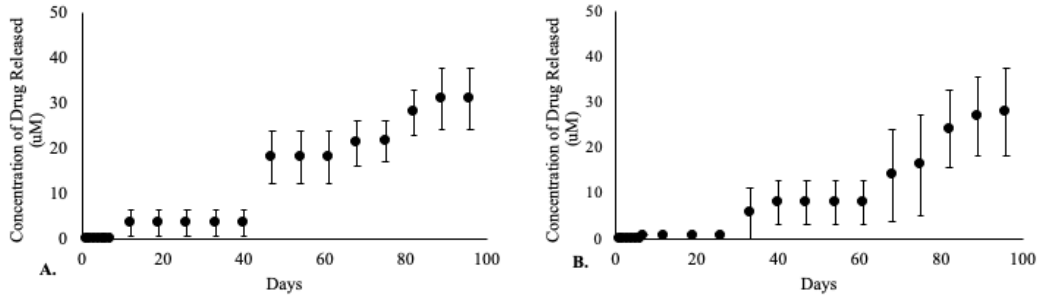

Figure 5. *Drug release of capecitabine dissolved in A. 40 kDa and B. 80 kDa PLCL. The means and standard errors of samples of n=3 are graphed as a function of a percent of original concentration released as a function of time.*

Oxaliplatin exhibited continuous release of drug throughout the duration of the study (Figure 6). 40 kDa reaches 100% release between 50–60 days, whereas 80 kDa reaches 100% release around 70–80 days.

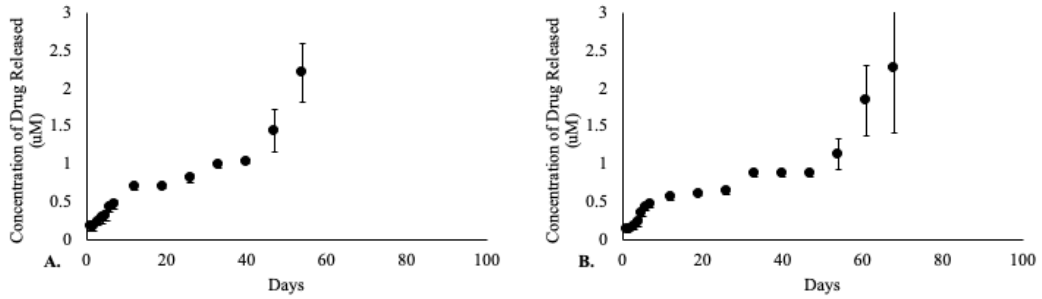

Figure 6. *Drug release of oxaliplatin dissolved in A. 40 kDa and B. 80 kDa PLCL. The means and standard errors of n=3 are graphed as a function of a percent of original concentration released as a function of time.*

For 5-FU and capecitabine, there was a delay in the release of the drug, with 80 kDa capecitabine exhibiting the most prolonged delay before releasing. Oxaliplatin began

releasing almost immediately, according to the data. This was true of both 40 kDa and 80 kDa. In both capecitabine and oxaliplatin, the 80 kDa molecular weight had a slower release rate than the 40 kDa molecular weight.

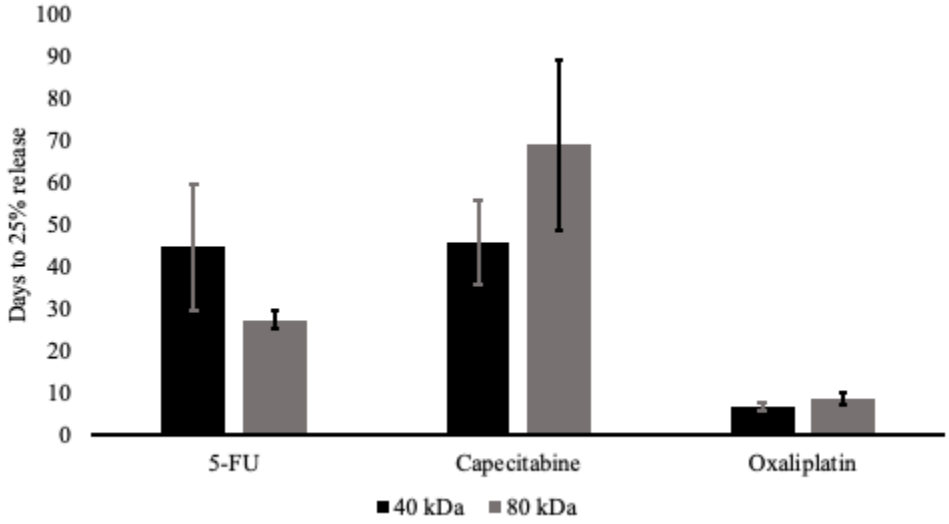

Figure 7. *Average amount of days until 25% release of initial concentration of drug from PLCL. The mean number of days and standard error of n=3 are graphed above. Black bars represent 40 kDa samples and grey bars represent 80 kDa samples.*

Comparison of the delay in release was performed and results are shown in Figure 7. Average amount of days until 25% of release was calculated among the 3 trials for each drug combination with PLCL. 25% release would indicate that half of the IC_{50} value, or 12.1μM, was released, since the initial concentration incorporated was twice the IC_{50} value. Previous studies have indicated 50% of the IC_{50} value as significant release in drug release experiments [84]. Across all molecular weights, capecitabine took the longest to reach a 25% release, on average 45.4 days for 40 kDa samples and 69.1 days

for 80kDa. Oxaliplatin was released almost immediately, reaching 25% release at an average of 6.7 days for 40 kDa samples and 8.1 days for 80 kDa. The release time of 5-FU is intermediate between oxaliplatin and capecitabine, releasing 25% of drug in an average of 44.7 days for 40 kDa and 27.4 for 80 kDa.

Due to its longer delay in release compared to the other drugs, Capecitabine in conjunction with PLCL was retested with specific focus on release until half the IC-50 value. The average number of days to reach 25% release in this second trial were compared to the initial capecitabine trial. 40 kDa and 80 kDa means across both samples were compared using a t-test for 2 independent means. There was no significant difference between the means of both the 40 kDa and 80 kDa samples from these two studies ($p>0.05$, $n=3$ for each sample).

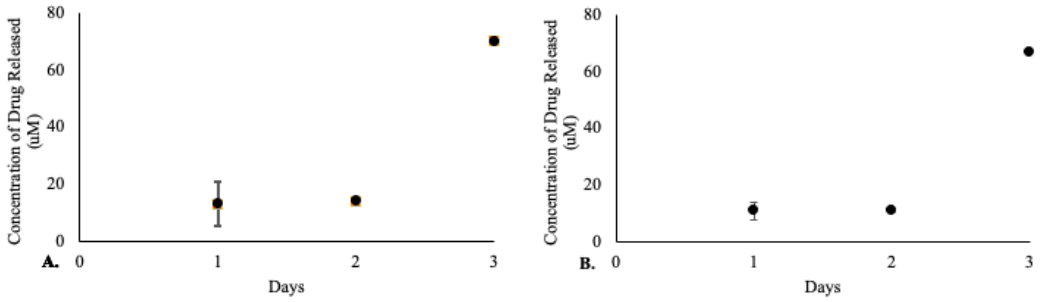

Figure 8. *Drug release of capecitabine dissolved in **A.** 40 kDa PLGA and **B.** 80 kDa PLGA. The means and standard errors of the mass loss of n=3 are graphed as a percent of mass remaining over time.*

To further investigate the delayed-release and the role of capecitabine in this process, the drug release pattern of capecitabine was investigated in a different polymer:

PLGA (Figure 8). Both 40 kDa and 80 kDa PLGA displayed a release within three days, with two days of maintained mass loss followed by complete release to 100%.

Mass Degradation Study

The 40 kDa PLCL with drug had a significant degradation during the first week, then had a negligible increase in mass, and then continued to degrade (Figure 9). The 40 kDa PLCL without the drug (control) had an even more significant degradation during the first week and then had a negligible increase in mass, but appears to have degraded more significantly than the 40 kDa PLCL with the drug after this point. The 80 kDa PLCL with capecitabine had significant degradation over the first three weeks but then appeared to slightly increase in mass. The 80 kDa PLCL control displayed an almost exact trend compared to the 80 kDa with drug (Figure 10).

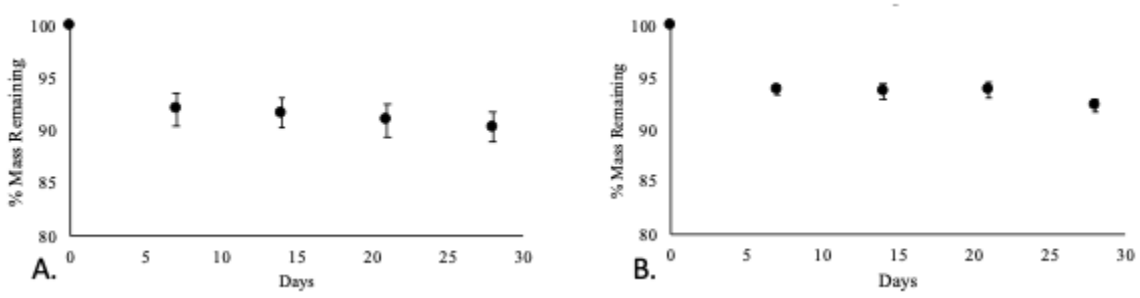

Figure 9. *Degradation of 40 kDa PLCL at **A**. control and **B**. with capecitabine. The means and standard errors of the mass loss of n=3 are graphed as a function of percent of mass remaining over time.*

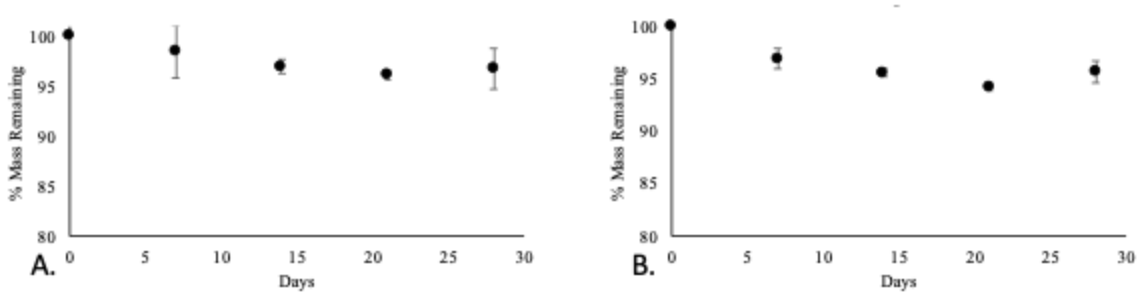

Figure 10. *Degradation of 80 kDa PLCL at **A.** control and **B.** with capecitabine. The means and standard errors of the mass loss of n=3 samples are graphed as a function of percent of mass remaining as a function of time.*

DMA Pull-Off Testing

Preliminary results were obtained comparing the stress, in kPa, required for adhesion failure between drug-loaded and control fiber mats of 40 kDa PLCL and porcine intestine. Five trials were performed for the control and experimental groups. The average stress to induce adhesion failure between the control polymer and the intestine was 11.82 kPa, with a standard error of 2.40 kPa. For the capecitabine-loaded polymer, the average stress to induce adhesion failure was 12.0825 kPa, with a standard error of 1.22 kPa. These results are shown below in Figure 11.

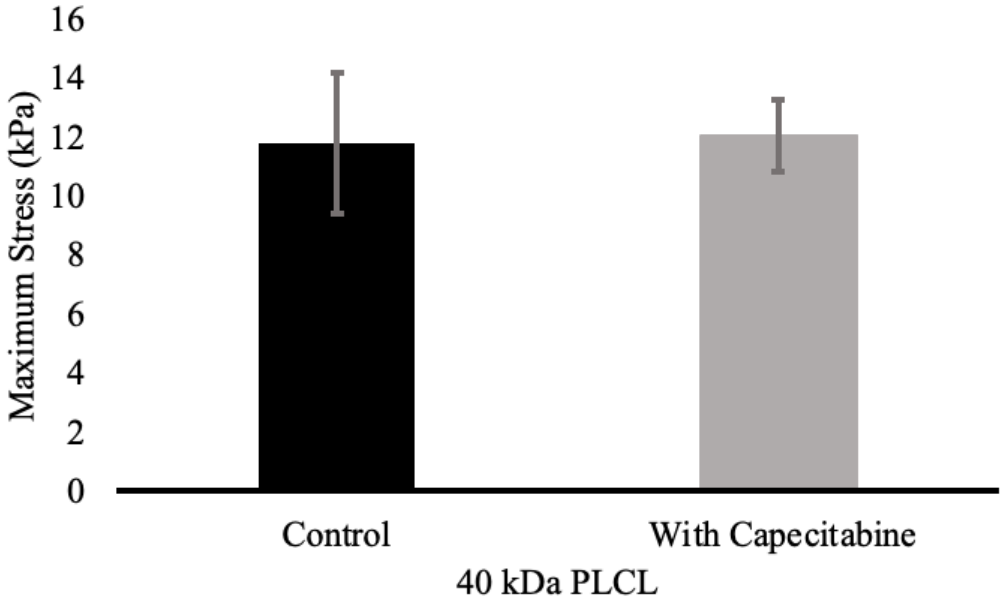

Figure 11. *The average maximum stress (kPa) to induce adhesion failure in control and capecitabine-loaded 40 kDa PLCL. Means and standard error of n=5 samples are graphed above.*

Chapter 5: Discussion

Polymers incorporated with chemotherapeutic drugs have the potential to provide localized treatment. This application can be used in a multitude of medical settings, including, but not limited to, cancer treatment. It has the ability to be administered in conjunction with sutures, the traditional method of sealing an anastomosis after tumor resection. Typical treatment for stage IIIA colorectal cancer involves a combination of both surgery and systemic chemotherapy [1], making this stage suitable for treatment via solution blow spinning. Due to the high recurrence rate and the utilization of surgical resection in the treatment of colorectal cancer, the potential provided by polymer fibers to create a localized, extended drug-delivery system while also functioning as a surgical sealant is of interest [16], [18]. While sutures aid the colon in healing after anastomosis, it can often lead to leakage at the resection site exposing healthy tissue to remains of cancerous tissue and GI contents [1]. The use of a sealant can also help mitigate the adverse effects that may result from only using sutures [20]. The experiments conducted were done with the goal of assessing the structural, mechanical, and chemical properties of various combinations of polymer and chemotherapeutic agents. In addition to releasing at the site of resection, the incorporation of drugs should not hinder the structural or mechanical integrity of the polymer fibers. PLCL exhibits longer degradation time (ranging from a few months to two years) in comparison to previously studied polymers such as PLGA, which makes it a potential candidate for use in long-term treatments [77], [78].

PLCL and PLGA with incorporated drug are compatible with SBS

The solubilities of PLCL and PLGA in acetone were not impacted by the addition of chemotherapeutic drugs, and all polymer solutions at each molecular weight were able to form fibers via solution blow spinning. The morphology of these fibers indicate that there are no manipulations necessary, such as the use of surfactants, to ensure the inclusion of the drug into the fiber mat. The morphology also indicates that the structural properties of the polymer are similar between the fiber mats that contain or lack chemotherapeutic drugs. The results from these studies enabled the continuation of investigating the behavior of drug release *in vitro* and the mechanical properties of the fibers. These properties could be assessed and compared between the two molecular weights, as well as between fibers that contain or lack chemotherapeutic drugs.

Various polymer-drug combinations display different release patterns

The drug release study results suggest there is a difference between the release profiles of 40 kDa and 80 kDa PLCL fiber mats. At higher molecular weights, starting at 20 kDa, the polymers overlap and interact with one another, allowing the fiber mat to exhibit increased properties of mechanical strength and elasticity [29]. Increasing the molecular weight may slow down the rate of erosion front movement, which dictates drug release. Therefore, as the rate of erosion slows, drug release slows as well, again showing the negative correlation between polymer molecular weight and drug release [31]. In addition to changing the rate of release, an increased molecular weight also has higher efficacy in cancer treatment, because of the permeability of cancer cells which allows for larger molecules to be delivered to nearby tissue sites and increases drug

circulation time in the plasma [27]. The 40 kDa fiber mats release chemotherapeutic drugs rapidly in a shorter period of time. In contrast, the 80 kDa fiber mats tend to release chemotherapeutic drugs in smaller quantities over extended intervals of time, with periods of no release in between. This observation holds true for all the combinations tested in our experiments with the exception of 5-FU and PLCL. The result we saw displays 80 kDa releasing near 100% of the incorporated drug before 40 kDa. Although we cannot confirm whether this is accurate, previous literature points to experimental error that may have produced this result.

5-FU and capecitabine exhibited a delayed release at both molecular weights. It was concluded that this delayed release may be ideal because it allows time for the anastomosis to partially heal prior to initial drug release. Patients, on average, wait about 2–6 weeks after surgery before the introduction of systemic chemotherapy [85]. This time span allows patient recovery and anastomotic healing, making the delayed release preferable and in conjunction with normal treatment periods. Through the release study, it was determined that capecitabine was the more favorable chemotherapeutic agent when compared to 5-FU and oxaliplatin. Not only does it show a delayed release within the parameters of 2–6 weeks, but it also exhibited a burst release at 40 kDa and a periodic release at 80 kDa which allows for further comparison of these two profiles using PLCL. Burst release may not be preferable, as it can lead to uneven, and potentially harmful, dosing of the chemotherapeutic agent. A stepwise release appears to be a better pattern to follow post-tumor resection, considering that it results in more tolerable dosing and more than one administration of treatment [86]. In general, PLCL's degradation pattern more resembles surface erosion, in which a layer of the polymer degrades fully before the next

layer begins [66]. This typically leads to a sustained release over time. Previous studies have corroborated the PLCL is a surface eroding polymer [84], attributed to the chirality and electrophilicity of the polymer's functional groups.

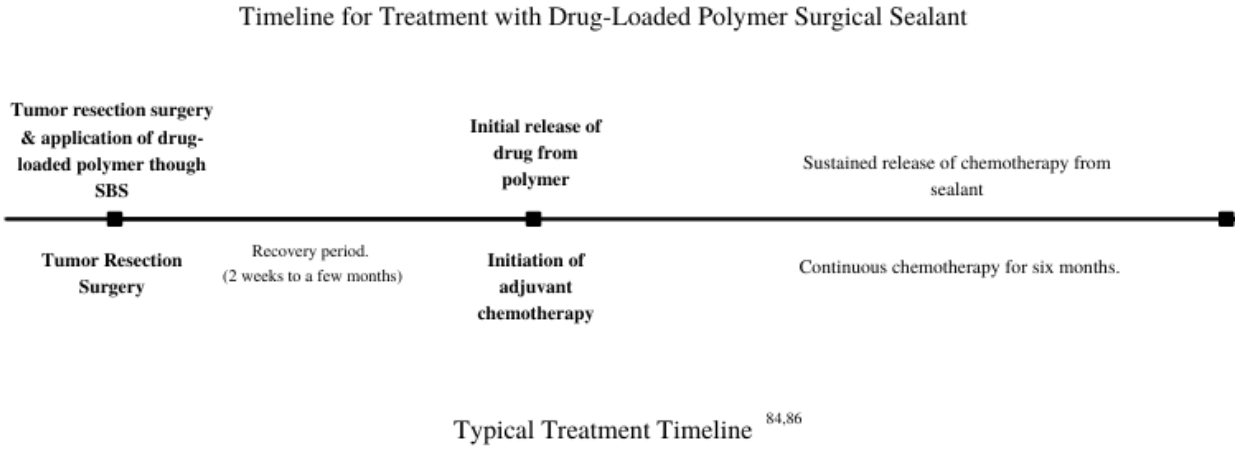

Figure 12. *A comparison of the proposed treatment timeline using PLCL and capecitabine following surgery and the typical treatment timeline.*

Figure 12 demonstrates the potential compatibility of a PLCL-capecitabine system with the traditional colorectal cancer treatment timeline. The lag period exhibited by PLCL in which no drug is released from the polymer coincides with the necessary recovery period patients undergo to allow healing of the surgical site. The release of drugs from PLCL begins around the same time a patient would typically begin chemotherapy following the surgery. Patients typically undergo adjuvant chemotherapy for about six months following surgery [87]. With the use of a polymer surgical sealant such as PLCL, the drug will continuously be released from the sealant during this period, eliminating the need for a patient to continuously undergo an extensive chemotherapy regimen.

The relative hydrophobicity or hydrophilicity of both polymer and drug plays a critical role in determining interactions and the resulting model of release. It has been found that hydrophobic polymers and drugs typically portray slower release than their hydrophilic counterparts [47]. In a study conducted by Chou et al. [88] it was found that most sustained release systems to date have been limited to the delivery of biologics or small hydrophobic molecules. For hydrophilic small molecule drugs, on the other hand, the high aqueous solubility, poor partitioning, and incompatibility with hydrophobic polymers pose a challenge to long-term release. PLCL is a hydrophobic polymer, which combines PCL with PLA to optimize biocompatibility and mechanical properties [89]. Capecitabine is mostly hydrophobic due to its spontaneous dissolution in ethanol and long carbon chain [90]. The delayed release that can be seen in PLCL-capecitabine systems can be due to multiple hydrophobic interactions that have been tested experimentally in the past. A study conducted by Yuan et al. [41] found that the hydrophobic drug Dox-HCl, when interacting with the hydrophobic polymer PLA, buried itself within the polymer, rather than interacting with the polymer at its surface, leading to a slow release of the drug from the hydrophobic core of the polymer-drug complex. Similar studies have concluded that this interaction between a hydrophobic drug and the hydrophobic region of its respective polymer results in drug entrapment, leading to the subsequent slower release of the drug due to tight binding interactions between the drug and the polymer [42]–[44]. 5-FU and oxaliplatin are both relatively hydrophilic drugs, resulting in less drug entrapment. Thus, these drugs will be released earlier in surface erosion of PLCL, accounting for the faster release we observed in our experiments. Increased drug entrapment in conjunction with surface erosion further slows the rate of

release. Our results are consistent with most findings from hydrophobic polymer-drug interactions. In addition, the method of solution blow spinning produces fiber mats that are layered on top of one another during spraying. It can be hypothesized that these layers follow surface erosion in that the outermost layer degrades fully first, leading to occasional and tolerable drug release over time. However, more in depth studies of fiber arrangement would have to be conducted to confirm whether the method of blowing fibers contributes to drug release.

In order to better understand the interplay of hydrophobicity of both drug and polymer, different polymers were studied with the same methodology and the incorporation of capecitabine. Our studies focused on the delayed period before initial release that was especially unique to capecitabine.

To further understand how capecitabine was contributing to this delayed period, we tested capecitabine with PLGA, which is expected to exhibit faster release due to the faster rate of degradation. PLGA is a hydrophilic copolymer of PLA and poly glycolic acid (PGA) [91]. PGA is a highly hydrophilic and crystalline polymer that exhibits a rapid rate of degradation [92]. Typically, PLGA with higher ratios of lactic acid are less hydrophilic and thus absorb less water and degrade more slowly. However, an exception to this is the 50:50 ratio of lactic and glycolic acid PLGA, which exhibits the fastest degradation due to their higher content of hydrophilic glycolic units [92], [93]. Given that capecitabine is a hydrophobic drug, and PLGA is a hydrophilic polymer, we expected decreased drug entrapment of capecitabine in PLGA. This was supported by our findings, as capecitabine was released from PLGA much faster than PLCL. The experiments with capecitabine in combination with PLGA demonstrated that PLGA did not have a lag

period, and all of the drug was released from the polymer over the span of two to three days. PLGA is a hydrophilic, amorphous polymer that exhibits bulk erosion [94]. Bulk erosion is a homogeneous process, leading to uniform degradation throughout the polymer matrix [95] The model developed by Lao et al. [96] characterizes degradation of PLGA in a three step process. First, solvent penetration into the polymer matrix results in the initial release of surface drugs. When combined with hydrophobic drugs, PLGA exhibits a latent period with very little drug release in stage one. In stage two, degradation by hydrolysis results in further "relaxation of the network", resulting in further release. As degradation occurs, the level of entanglement decreases, resulting in shorter chains creating a more "open" network that allows for continued release. In the final stage, the drug is released through a diffusional process through an interconnected network of channels in the polymer. PLGA is also porous which increases the channels through which chemotherapeutic drugs can be released from the polymer matrix.

Our findings were consistent with the patterns described in the literature, suggesting that the release kinetics observed in the PLGA-capecitabine system may be a result of bulk degradation and reduced drug entrapment. PLGA exhibited no lag period, followed by the rapid release of the drug, typical of polymers exhibiting bulk erosion [97]. The drug release period for PLGA was significantly shorter than that of PLCL, with all of the drug release occurring within three days. This makes the PLGA-capecitabine combination incompatible for use in treatment of colorectal cancer following a tumor resection, as this would require sustained release following a delay period. However, the rapid release and degradation of PLGA presents potential applications for other forms of localized treatments requiring immediate and short-term sustained release.

The PLCL-capecitabine combination arises as the most promising candidate for further development as a localized form of chemotherapy treatment. The hydrophobic interactions of drug and polymer, as well as the erosion pattern characteristic of PLCL, optimize a delayed release that may allow for adequate healing at the surgical site prior to targeted cell death. The mechanistic action of capecitabine may also show promise in a localized treatment. Capecitabine is enzymatically converted into 5-FU by proteins that are high in concentration in cancerous cells [23]. Thus, the targeted application of this drug may provide benefit in attacking cancerous cells while preserving the health of normal tissue. Additionally, since this pro-drug is hydrophobic in comparison to 5-FU, interactions with PLCL allow for an extended release due to drug entrapment. In addition to being hydrophobic, PLCL's surface eroding properties demonstrate a slower rate of release, where the initial layers of degradation have less drug. The larger bursts of drug release then occur after delay, and the nature of surface erosion allows portions of the total concentration to be released periodically over time. This is complementary to the typical treatment of chemotherapy which consists of many rounds of treatment with breaks for recovery in between. This treatment can last for months as seen in Figure 12. An extended and periodic release of anti-cancer drug from a surgical sealant would serve to mimic this timeline, potentially without the systemic side effects present in traditional chemotherapy.

Degradation and adhesion of polymers are not impacted by incorporation of drug

The polymer degradation study has shown that PLCL degraded slowly over an extended period of time *in vitro*. If this method were applied to chemotherapy treatment,

the goal would be for the polymer to completely degrade as the chemotherapeutic drug is being delivered over an extended period of time. While there were similarities between the degradation patterns between control and experimental groups at each molecular weight (which indicates that the degradation of the polymer is not impacted by the introduction of drug to the polymer solution), there were differences in the degradation patterns between different molecular weight polymers. The 40 kDa PLCL control and capecitabine samples lost a more significant amount of mass (between 90–95% mass remaining within the first five days) than the 80 kDa PLCL control and capecitabine groups (which had 96–100% mass remaining) within the same time period. This is consistent with the literature discussed in Chapter 2, which indicates that polymers with higher molecular weight have slower surface erosion, and therefore lose mass at a slower rate than lower molecular weight polymers [31]. Subsequently, the rate of drug release from higher molecular weight samples would theoretically be slower than that of lower molecular weight polymers [30]. This is also consistent with the results from the first degradation study for 40 kDa and 80 kDa PLCL; within the first 20 days of drug release, 40 kDa PLCL had released more capecitabine at physiological conditions than the 80 kDa PLCL, most likely due to the difference in molecular weight. This has possible implications for altering the amount of drug delivered to a resection site over a specific period of time in order to maximize the efficiency of chemotherapeutic drug delivery.

The capecitabine-loaded polymer displayed two release profiles, which closely resembled these polymer degradation patterns. The results noted from the polymer's extended release pattern bear similarities to a variety of long-term chemotherapeutic treatments. Typically, stage III colorectal cancer patients who are treated with

capecitabine receive oral doses periodically over a 6 month period after surgical resection of the tumor [98]. Cancer treatments, in concurrence with tumor resection surgery (adjuvant therapy), show promise as a potential application of this polymer, allowing direct deposit of the drug onto the site of resection. Further investigation of the two release behaviors is necessary to determine efficacy in killing toxic cells and preserving healthy tissue. However, the benefit of using capecitabine as compared to other chemotherapeutic drugs, such as 5-fluorouracil, is that it is enzymatically converted to its active form by thymidine phosphorylase [98]. This enzyme is more prevalent in cancer cells than it is in healthy tissue cells [98]. This potentially indicates that an SBS drug delivery system would be effective at locally targeting specifically cancer cells while not harming healthy cells.

An important mechanical property of biodegradable polymers used on tissues is their ability to adhere to said tissues at physiological conditions. There are methods to achieve this, however, currently many adhesive surgical sealants pose certain issues to the patient and surgeon. For instance, methods such as the use of fibrin glue are complex to prepare and administer directly to the surgical site, and hydrogen or protein-based surgical sealants cause tissue reaction, inflammation, infection, and/or swelling [76]. Additionally, the cohesion of the polymer fibers is essential for the application of the polymer in a long-term treatment, especially if the drug delivery is intended to be local and protect the patient against anastomotic leakage. A 2012 *in vivo* study by Norbury et al. [99] found that the pressure at which porcine intestinal tissue fails is between 0.0174 and 11.52 mmHg with a mean of 3.4 mmHg. Ideally, the polymer-drug solutions should not fail at a pressure lower than this average since this would ultimately prevent leakage

from the intestine and promote localized treatment. While the efficacy of PLCL to withstand this amount of pressure would likely have to be determined through burst pressure testing and *in vivo* studies, we do know that the addition of drugs to the PLCL solution would not significantly influence the ability of PLCL to withstand this pressure. Additionally, sutures or surgical staples would still be used in this treatment method, which would seal the anastomosis through mechanical strength, while the fiber mat would add tensile strength to the anastomosis [76]. Therefore, the combined strength of the sutures/staples and the surgical sealant would have to withstand the pressure range discussed in the Norbury study. This has implications in future studies.

Chapter 6: Future Directions

While the current members of Team TUMOR are reaching the end of their time at University of Maryland, we feel the project could be continued. For this reason, we are hopeful that we will be able to propose this project to a younger cohort in the Gemstone Honors Program. A new team would be able to take our work and use it as a foundation to take the research in their own direction. Some possible future project directions include scanning electroscopy microscopy (SEM) imaging to observe the porosity and better characterize morphological changes during degradation. Ideally, these images would be taken on the days when we observed a burst release of drug in the Aim 2 studies. This way, the pore size of the fiber mat could be observed to determine if surface erosion is the cause of drug release. In addition to learning more about the morphological characteristics of the polymer, the identity, composition, and number of polymers in a system can be further investigated. The polymers we worked with indicated differing release patterns, so investigating mixed polymer systems could allow for more precise manipulation of drug release patterns, expanding the applications of the sealant. *In vitro* studies in cell cultures should be conducted to determine the efficacy of a drug-loaded sealant in killing cancer cells while preserving healthy cells. This is important for understanding our sealant's utility as a treatment method. While the pattern of release was characterized in this study, further cell studies must refine the concentration of drug incorporated to ensure that the dose of capecitabine released does not exceed the maximum tolerated dose at any time. Since this is a localized treatment, it is also important to confirm that the maximum tolerated dose is not different from the oral medication that is taken traditionally. *In vivo* studies with mice where the surgical sealant

is applied would be beneficial for analyzing the sealant in application and assessing the benefits or unintended consequences of localized chemotherapy. Team TUMOR is optimistic that the research we have conducted during our time in Gemstone will be well received by a younger cohort and can be used as a baseline to further study the incorporation of chemotherapeutic agents into polymers to create surgical sealants for localized and controlled drug release.

Additionally, while the current scope of the project has been focused on colorectal cancer, surgical sealants can be applied to a broad range of conditions that would benefit from a localized, extended drug release pattern. Through adjustment of the drugs incorporated and polymers used, the sealant can be used for other cancers, dermatological conditions, and periodontal diseases. As the sealant is composed of a drug and polymer, it is quite versatile; manipulating factors such as drug identity, drug concentration, polymer type, polymer weight, and method of application would allow sealants to be specialized to the conditions specific to various diseases.

Finally, whether through continued research by another Gemstone team or by the scientific community, more research can be done related to stimuli response of the polymer-drug complex. Further exploration of how conditions such as surrounding pH, temperature, and viscosity affect drug release and polymer degradation would be beneficial to our field of study as it would contribute additional understanding on how to adjust a sealant's properties to provide *in vivo* localized drug release under conditions that cannot be manipulated, such as ambient body temperature.

Appendix A: Abbreviations

kDa: kilodalton

PBS: Phosphate buffered saline

PCL: Polycaprolactone

PDLLA: Poly(DL-lactide)

PEG: Poly(ethylene glycol)

PGA: Poly(glycolic acid)

PLA: Polylactic acid

PLCL: Poly(L-lactide-co-ε-caprolactone)

PLGA: Poly(lactic-co-glycolic acid)

SBS: Solution blow spinning

SRL: Sirolimus

5-FU: Fluorouracil

Appendix B: Equity Impact Report

Commitment to Equity

The Gemstone Program is committed to creating a research environment that not only supports its diverse student population but also addresses the needs of a diverse world. Team TUMOR equally values diverse modes of thought and the accessibility of team findings to benefit all communities through research.

Colorectal cancer is not experienced equally among all people (Figure 13) [100]. The primary factor that contributes to the unequal distribution of colorectal cancer (CRC) incidence and deaths is socioeconomic status. A factor that commonly coincides with socioeconomic status is race. Age is also a large determining factor in the incidence of cases, but aging is experienced universally whereas socioeconomic status affects populations asymmetrically.

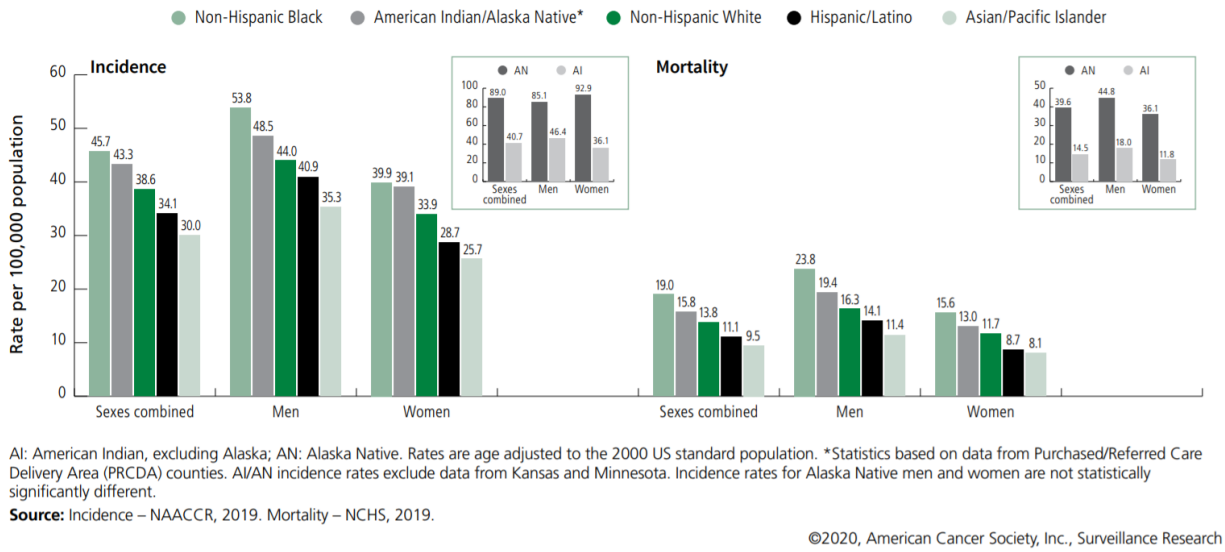

Figure 13. *Colorectal Cancer Statistics by Race/Ethnicity* [100]

In socioeconomically disadvantaged communities, the lower wages and longer work hours of the impoverished and working classes often necessitate cheaper diets that consist of large amounts of easily accessible fast foods [100]. While specific foods are difficult to correlate with CRC occurrence, the abundance of refined carbohydrates, processed sugar, and red meat in diets, typically associated with fast food and diets of socioeconomically disadvantaged populations, are associated with chronic bowel inflammation [100]. Chronic inflammation puts additional stress on the cells of the GI tract that increase the risk of the development of CRC. Obesity and diabetes also add additional cellular stress to the GI tract and metabolic pathways, and these conditions have been identified as prominent risk factors for developing cancer [101].

Numerous studies have indicated that those of lower socioeconomic status experience more frequent and severe health issues [102]. Racial minorities frequently fall within lower socioeconomic status. For example, Black and Hispanic populations have a ratio of approximately 0.06 to White populations in regards to median wealth; financial struggles commonly experienced by minorities ultimately causes poorer health as they are exposed to greater health risks and psychosocial stressors [102]. These disparities go beyond general health as racial and ethnic gaps in the incidence and mortality of CRC are noted as early as 1990 and have modulated over time [100]. In the racial and ethnic groups studied by the American Cancer Society, Blacks, Whites, and Hispanics have all decreased their incidence rates for CRC since the late 1990s. By 2017, the yearly incidence rates for new CRC cases per 100,000 people were at thirty-five for Hispanic populations, thirty-nine for White populations, and forty-seven for Black populations [100]. Also interesting to note is that the geographic distribution of CRC cases closely

resembles a geographic racial distribution with CRC cases highest in underserved minority neighborhoods and lowest in affluent neighborhoods [100]. Still remaining is the large gap between Black populations and White populations, and the American Cancer society notes that a major contributor to this gap is the lower frequency of screening and lower survival rates of stage-specific CRC cases among Black populations [100], [103]. Another emerging factor affecting screening and other preventative measures is the accessibility and availability of physicians to lower-income communities [104]. As more attention is put on screenings in the last decade, the specific Black-White gap has begun to narrow, but this progress has been slow [100]. Further research that demonstrates poorer survival rates among Black populations suggests that access to and quality of care may also play a role [105].

With further testing, this treatment method may provide a more affordable option to people of all communities while theoretically decreasing recurrence rates and limiting the amount of costly follow-up appointments and treatments. Additionally, a localized chemotherapy treatment, such as the one proposed, would eliminate the need for repeated visits to the doctor and save patients significant amounts of time on travel and follow up infusion treatments.

Commitment to Accessibility of Research

Team TUMOR's work aims to provide more affordable cancer treatment options that would allow underserved communities of all racial and ethnic identities, as well as socioeconomic backgrounds, the increased opportunity to seek treatment. While Team TUMOR's project mainly targets options for care following the development and

progression of colorectal cancer, other efforts can be made to address accessibility of preventative measures that would improve the incidence of CRC cases in the population. Efforts particularly aimed at underserved communities that do not normally have access to colonoscopies could be instrumental in bridging the gap between wealthy and underserved communities.

Team TUMOR is also dedicated to ensuring that the methods and findings of our research are easily accessible to the public, regardless of a viewer's background. As such, the team aims to submit the findings of our work to an open access journal that does not require a fee or subscription to view the work done by the Team. By appearing in an open access journal, the Team hopes to alleviate the burdens and challenges created by costly subscriptions services and viewing fees that deter socioeconomically disadvantaged populations from accessing current literature in the field. The Team is committed to creating multiple versions of the abstract so that the work done by Team TUMOR can be easily digestible to people with various educational, socioeconomic, and cultural backgrounds. Without compromising the scientific integrity of the findings, communicating the abstract in ways that target various audiences would allow for the broadest use of our research project in promoting the fields of material science, bioengineering, and CRC research.

Commitment to Diversity

In addition to our work to make cancer treatment more affordable and accessible, Team TUMOR is comprised of a diverse group of individuals. In conjunction with Gemstone's dedication to diversity, inclusion, and equity, Team TUMOR echoes these

commitments by fostering a team environment of twelve students, consisting of six women, six members of racial and ethnic minorities, and four members of the LGBTQ+ community. As a diverse team, we seek to amplify the voices of those who have been underrepresented in the scientific community. By consolidating diverse voices to ruminate and propose solutions to localizing colorectal cancer treatments, the Team fosters a forward-thinking intellectual environment that represents the Team's and program's goals of promoting diversity in research and education.

Appendix C: COVID-19 Impact

Due to the COVID-19 pandemic, the team research was halted and experienced numerous setbacks. When the University of Maryland, College Park campus shut down in mid-March of 2020, the research lab was temporarily shut down as well. Due to the lab's closure, there were limited research capabilities for the Team due to the heavy wet-lab nature of the project. As such, the Team took advantage of this time away from the lab to draft a paper to be submitted to an open access journal. Once the lab reopened for students with social distancing and mask precautions in late-September 2020, some teammates were able to return to the lab to resume experiments. The time lost in the past year prevented us from fully testing many polymer-drug combinations that we discussed in our thesis. Thus, we focused on combinations that showed the most promise in previous data in order to optimize the remaining time we had.

Due to the strong financial start to our project, the pandemic did not hinder the funding opportunities for the team. The main setback was the inability to use the majority of the funding on attending a conference or purchasing more lab materials during what

would have been the heaviest portion of the team's research from mid March through late September of 2020. These setbacks will most likely result in a surplus of team funds at the conclusion of the project.

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