Projects I Final Report

**Electrospun Fiber-Based Drug Delivery System**

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**Abstract:** Current drug delivery methods such as injections and oral medications are not ideal for treating diseases or symptoms. Current methods deliver almost the entire drug initially in a very short span of time. This causes concentrations of the drug to reach toxic levels and cause sometimes serious side effects. An ideal drug delivery mechanism avoids this initial drug burst that is released into the body and instead gradually releases the drug to an effective concentration where it will sustain release. We are going to construct fibrous patches via electrospinning out of various materials and combinations. These fibers will be embedded with drug and used as a delivery mechanism to create a more ideal release of drug over time. Each design will be electrospun into one large fibrous mat that will be cut into smaller samples for study. Spectrophotometry will be used to measure the percentage of drug released over time and high pressure liquid chromatography (HPLC) will be performed to ensure that drug retains its integrity. All of the designs will be compared to a current drug delivery method to compare its effectiveness to current treatments.

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I. **Background**

In 2009 it was estimated that the prevalence of cancer was 12,549,000 in the United States alone with prostate and breast cancer being the most common affecting 2,500,000 and 2,762,000 respectively[^1]. Chemotherapy is effectively used in combination with other techniques to treat cancers, however there are many side effects such as vomiting and nausea, loss of appetite, and fatigue. Chemotherapy-induced nausea and vomiting (CINV) has a negative impact on patient’s quality of life. Besides being very debilitating to the patients, it is frequently point as a major factor for treatment abandonment[^3]. Although the physiological mechanism of CINV is still under scrutiny, in the mid-1980s, it was first discovered that serotonin (5-hydroxytryptamine; 5-HT) was part of this process. The introduction of the 5-HT₃ receptor antagonists in the early 90s has been one of the most significant advances in supportive care of cancer patients[^4]. Since then several antiemetic drugs have been studied in the attempt to control CINV[^3]. The top four drugs approved to control CINV are ondansetron, granisetron, dolasetron and palonosetron. They are usually delivered in the form of tablets, dissolvable tablets, injections, or transdermal patches. These form of drug delivery possess the same issue of an initial high concentration of the drug that diminishes over time to levels that are largely ineffective[^2].

**Project Goal:** The objective is to develop an electrospun fibrous based drug delivery system to achieve sustained release of nausea medication. Collagen and poly(ε-caprolactone) (PCL) will be used as the material for the drug delivery system because of its ability to be safely implanted without any ill effects[^5]. Fibers will be created by electrospinning with several pre-processing and post-processing techniques to apply nausea medication.
II. Design

The design of our drug delivery system will consist of a patch that is made out of microfibers embedded with drug. One of the materials used will be the synthetic polymer PCL, chosen because of its slow degradation rate. The other material will be the natural polymer collagen, chosen because it has a much faster degradation rate. Other designs will utilize a combination of the two materials. Three types of fiber will be compared, group 1 consists of PCL fibers embedded with drug, group 2 consists of collagen fibers embedded with drug, and the third group will utilize a coaxial design with a collagen core fiber embedded with drug encapsulated by a PCL shell fiber without drug. To ensure that our study accurately reflects the effects of the materials and design, all other factors that affect drug delivery such as fiber diameter and porosity will remain constant. Because the materials chosen are biocompatible and safely degrade in the body, the patch created will have the ability to be placed under the skin. This allows for a more effective drug delivery closer to the ideal drug release profile. Because of the biodegradable nature of the materials removal is not necessary and can remain in the patient until it degrades and is excreted from the body.

![Design Schematics](image)

III. Methods

a. Patch construction

The patches that will be used as a drug delivery device will be created using a technique called electrospinning. Electrospinning is a process where a large potential field is used to pull a polymer solution onto a collection apparatus. A polymer is created and loaded into a syringe where it is slowly ejected to form a droplet at the end of the needle. When the force of the potential field overcomes the surface tension of the droplet a fiber is ejected from it towards a collection plate. As the fiber crosses the distance from the needle to the grounded collection plate the solvent evaporates and what is left is a dry fibrous mat. Each fiber design will be spun using either a stationary collection plate or a rotating mandrel. From the mat 10-16 samples will be cut out that are 0.5 x 0.5 cm to be used in subsequent drug delivery and drug activity studies.
b. Drug delivery study

UV-Visible Spectrophotometer will be utilized to measure the release of Ondansetron. UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. Spectrophotometric technique is simple, rapid, moderately specific and applicable to small quantities of compounds. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. The fundamental law that governs the quantitative spectrophotometric analysis is the Beer–Lambert law.

Beer–Lambert law: When beam of light is passed through a transparent cell containing a solution of absorbing substance, reduction of the intensity of light may occur. Mathematically, Beer – Lambert law is expressed as:

$$A = a b c$$

- $A$=absorbance or optical density
- $a$=absorptivity or extinction coefficient
- $b$=path length of radiation through sample (cm)
- $c$=concentration of solute in solution.

Both $b$ and $a$ are constant so $a$ is directly proportional to $c$.

Beer – Lambert’s law will be used to relate absorbance of light by the material to the concentration of that material dissolved in a solution. The range where concentration vs. absorbance is linear will provide the information we need to relate the wavelength absorbance by Ondansetron at a given time.

Each sample will be placed in 10 ml Phosphate Buffered Saline (PBS). Samples will be kept in a hot water bath at 37°C to mimic in vivo condition. At designated time points, 1 ml of solution will be extracted and replaced with fresh PBS. The absorbance of extracted solution will be measured to calculate the amount of drug released for till that time point.

c. Drug activity

The electrospinning process involves a very large electrical field in order to draw out the polymer and create microfiber. There is a possibility that after the electrospinning process and release of the drug that its molecular structure may have changed. Because the drug ondansetron is a receptor inhibitor, its molecular structure plays a key role in its ability to treat emesis. A drug delivery study will be done on each type of fiber using HPLC to ensure that its chemical structure has retained its integrity. HPLC does this by using a high pressure system to push a
solvent that consists of a liquid and solid phase through a sorbent tube. The liquid is absorbed into the sorbent and the solids continue to travel through the column. The structure and size of the molecules dictate how fast they are pushed through the column and acts to separate different molecules as the HPLC device uses the various retention times to identify and quantify each molecule. This study is important because any changes to the structure of the drug may compromise its effectiveness.

d. Compare to tablet

To measure the effectiveness of this experiment’s drug release, the results will be compared to tablets currently consumed by patients undergoing chemotherapy. The tablet will be obtained from GlaxoSmithKline (gsk), the top manufacture of Zofran (Ondansetron).

Fig. 3. Ondansetron 4mg tablet produced by GlaxoSmithKline

The tablet will be crushed to be in powder form to obtain the calibration curve using Beer – Lambert’s Law at varying concentration curve. The tablet will be placed in 10ml of PBS which will be kept in a hot water bath. At designated time points, 1ml of solution will be extracted and replaced with fresh PBS. The absorbance of the extracted solution will be measured to calculate the amount of drug released.

IV. Challenges

The biggest challenge to be overcome in this experiment is the electrospinning of the coaxial fiber. Coaxial spinning is significantly more challenging because of the use of two materials simultaneously. Each material is going to have a different conductivity which has a tremendous effect because the driving force that is pulling the fibers is an electrical field potential. Flow rates have to be manipulated accurately to ensure that the droplet that is produced from the coaxial tip contains an inner and outer droplet. Much practice and optimization will have to be done and various imaging methods will have to be utilized to ensure that the
core/shell morphology is being acquired. Most other challenges will be technical in nature and in such cases we will rely on the experience of others to ensure that devices are utilized correctly.

V. Broader Impact Implications

The implications for this design are many with the ability to vary the materials and drugs used to treat many forms illnesses. The type of the material can be changed or modified in order to get a different type of degradation or rate. There are many types of synthetic and natural polymers that can safely be placed in the body and will degrade to eliminate the need for explanting. Combinations of materials can be used to further customize the drug delivery rate to even incorporate different stages of release. Instead of taking multiple pills at specific times throughout the week a subcutaneous patch could be implanted that would degrade slowly and deliver drugs for days, weeks, or even months at a time. The convenience of this type of technology would encourage patient compliance and improve quality of life. This type of subcutaneous patch would be extremely useful in the surgical setting where patients are already opened up and would allow the surgeon to place it inside the body as he was closing up. With post-surgery risks such as vomiting, infection, thrombosis, and inflammation, a patch could be created for each with different delivery rates tailor designed.

VI. Future Direction

There is much further research required to produce a patch that would be fit for use on the market. We hypothesize that the core/shell morphology will give the closes to ideal drug release profile, however this cannot be known for certain until after the drug release study. Fiber design must still undergo much in vitro testing to optimize the design that gives the desired release rate. Once the effects of design parameters on drug release are known, fibers can be tailor made to have the release profile required for treating various illnesses such as nausea. The next stage would involve in vivo studies in animals to ensure the effectiveness of the drug as well as any harmful side effects that may prevent it from being safely used in humans. The final stage of experimentation would include getting FDA approval to begin clinical trials in humans either for chemotherapy or surgical patients. Ondansetron is an anti-emetic drug that is mostly used for chemotherapy patients to treat nausea but is also commonly used in surgical patients because they incur nausea through the same mechanism as chemotherapy patients. Once the various stages of clinical studies are satisfied and the patch device is approved for use scaling up the technology for the market is the final step. The electrospinning process will have to be modified to create large quantities of consistent and reliable patches.

VII. Cost Analysis

The table below gives the breakdown of the cost associated with this experiment. Through generous donation by Legends Entrepreneurial Student Award (LESA), we have obtained $2000.
Table 1. Cost Analysis

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<th>Materials/Tools</th>
<th>Cost</th>
<th>Contributors</th>
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<tbody>
<tr>
<td>PCL</td>
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<td>Collagen</td>
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<td>Chemicals &amp; Supplies</td>
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<td>Ondansetron</td>
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<td>Coaxial Needle</td>
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<td>Electrosprinter</td>
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<td>Spectrophotometer</td>
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<td>LTU</td>
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<td>HPLC Supplies (columns)</td>
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<td><strong>Total</strong></td>
<td><strong>$2500</strong></td>
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</table>

Majority of our donation will be used toward the purchase of Ondansetron and HPLC columns. Lawrence Technological University (LTU) will be supplying the space for our experiment as well as characterization tool such as Spectrophotometer, and HPLC and PCL. polyElement, a small start-up company, has lent us the electrosprinter for the use of this study.

VIII. Team Members/Responsibilities

This project’s academic advisor is Dr. Yawen Li and technical advisor is Dr. Theresa Bou-Akl. We will be consulting for Dr. Michelle Leach and Sam Tuck for any electrospinning technical challenges.

Although the each member will be working together for this study, some tasks will be divided as follows:

*Dylan McEvilly* – Electrospon fiber patch, drug release studies, HPLC analysis

*Bhavika Patel* – Collagen extraction, drug release studies, data collection

Though each member of the team has clearly defined and separable responsibilities, we conduct all physical work collectively.

References

[3] Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. Support Care Cancer 2011;19:83-832