NDnano
Notre Dame Nanoscience and Technology

NDnano Summer Undergraduate Research
2021 Project Summary

1. Student name & home university:

   Tom Monroe, University of Notre Dame

2. ND faculty name & department:

   Professor Webber, Department of Chemical and Biomolecular Engineering

3. Summer project title:

   Developing Glucose Responsive Microneedles for Insulin Delivery

4. Briefly describe new skills you acquired during your summer research:

   Rheology
   Fluorescent Release Studies
   Polymerization
   mIRage FTIR
   ASAP 2020 Physisorption (BET)
   Raman Confocal Microscope
   Xray Diffraction

5. Briefly share a practical application/end use of your research:

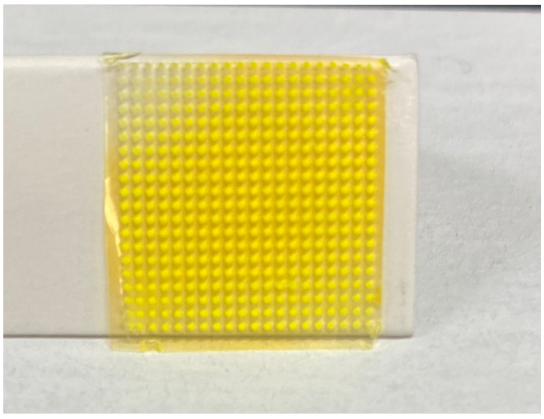
   The end goal of this research project is to have a microneedle patch that can be utilized by diabetics to regulate their blood glucose levels. This patch would replace the need for painful self-injections and mechanical pumps and would also reduce risk of hypoglycemia.

6. 50- to 75-word abstract of your project:

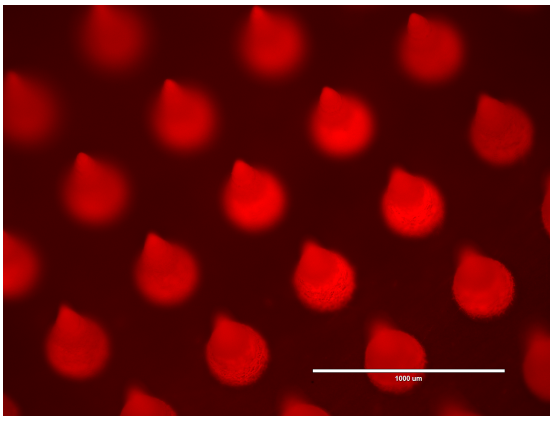
   Phenylboronic Acid (PBA) has demonstrated an affinity to bind with 1,2 and 1,3 cis diols, including glucose. This project aims to form a dynamically crosslinked hydrogel between a polymer chain containing a PBA, and a separate diol unit. The properties of this gel are altered in the presence of glucose, leading to the release of insulin that was stored within the mesh of the original gel.

The traditional means of treating diabetes are to maintain blood glucose levels by self-administering insulin, or through usage of a mechanical pump to deliver the insulin. Both methods have their faults: self-administration requires the patient's compliance to distribute the proper amount of insulin at the proper time and consistent poking from the needles can damage tissue. Mechanical pumps and the blood glucose sensors that come with them are bulky and uncomfortable, and do not always deliver correct dosages. Any error in dosage can be incredibly dangerous, whether it is leaving high glucose levels untreated, or overtreating and causing hypoglycemia.

A far more favorable solution would be to have a material that inherently responds to glucose levels in the body and administers an appropriate amount of insulin. The goal of this research project is to develop a smart insulin delivery system through phenylboronic acid (PBA)/diol-based microneedles. PBAs have an affinity towards 1,2 and 1,3 cis diols, including glucose. A dynamically crosslinked hydrogel is formed between a polymer chain containing a PBA, and a 4-arm polyethylene glycol (PEG) with diol units via an ester bond. This gel is formed while insulin is present, and the insulin gets trapped within the mesh of the hydrogel. This insulin containing gel is then formed into a microneedle patch.

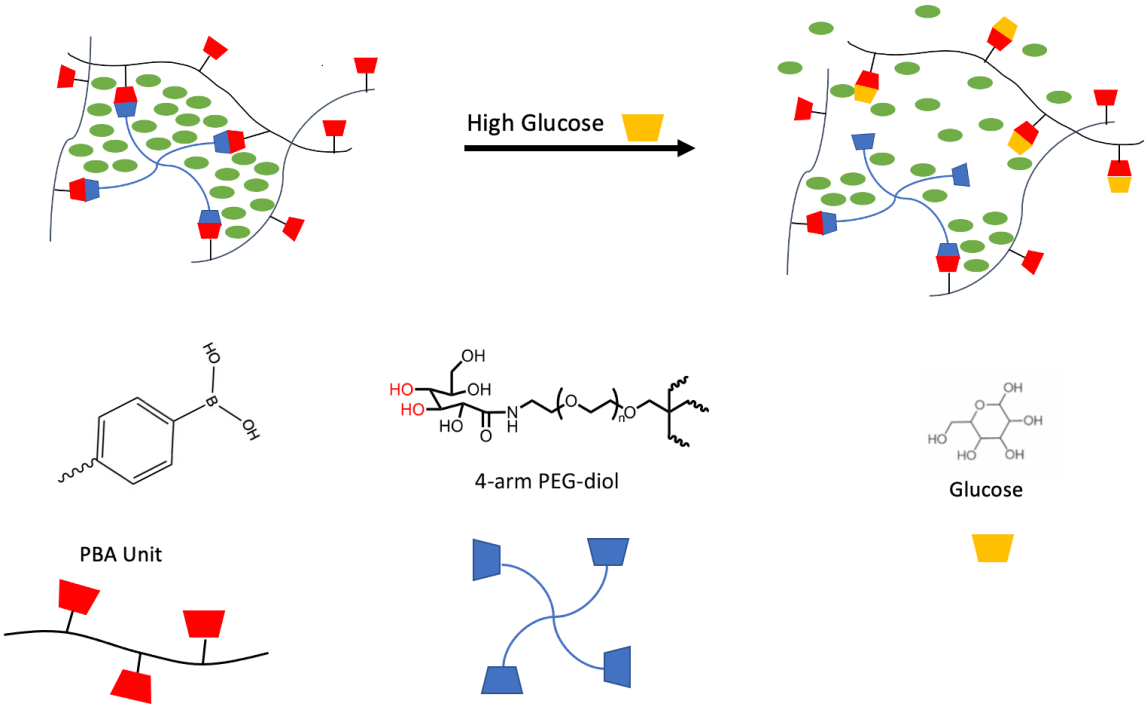


Dried Microneedle Patch Containing Fluorescent Model Drug



4X magnified image of dried microneedle patch

When this dried patch is in the presence of a solution containing glucose, the polymer network swells to a gel and the glucose begins competing with the diol to bind with the PBA. As the glucose succeeds in competing with the PEG-diol, the mesh of the hydrogel begins to break down, accelerating the release of insulin into the body.



Mechanism of gel formation and breakage in PBA system

Throughout this summer a variety of PBA:Diol systems were tested for whether they are capable of forming a gel, and then for glucose responsiveness. Two methods were utilized to test this responsiveness: rheology and fluorescent dye release studies. Testing for glucose responsiveness in rheology studies was done by creating two samples of a gel, one with no glucose present, and another with 400 mg/dL of glucose. A glucose responsive gel is defined as a gel yielding lower storage and loss moduli with glucose present when compared to the no glucose gel, due to the competition of glucose with the diol to bind with the PBA, reducing the number of crosslinks. In the fluorescent dye release studies, microneedle patches were dosed with a fluorescent model drug in the place of insulin. These patches were then submerged in buffer solutions. Half of the patches were in pure buffer solutions, and the other half in buffer solutions with 400 mg/dL glucose. Over a timespan of 24 hours, small collections of the buffer solution were collected at predetermined time points and the fluorescence was read by a plate reader. A glucose-responsive patch would present an increased release of the drug from the ones submerged in buffer solution containing glucose.

In the first tested system using carboxymethylcellulose (CMC) as the backbone, no glucose responsiveness was observed due to the affinity of the PBA for the Diol being too strong, and the glucose being unable to outcompete the bonding. Towards the end of the summer, progress has been made utilizing a system based around a n-Isopropylacrylamide polymer, which presents glucose responsiveness both in the rheology test and the fluorescent dye release study.

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