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Synthesis of a Stimuli-Responsive Magnetic Polymer Drug Delivery System

Drug delivery systems are increasingly necessary for the targeted treatment of illnesses such as cancer. In traditional drug treatments, the drug is exposed to all parts of the body regardless of where it is needed. This approach subjects a patient to many negative side effects of a drug and can include the weakening of the immune system or intestinal lining. A delivery vehicle allows a drug to be selectively exposed to only those regions of the body where the drug is needed, which will make treatment more effective and improve patients' quality of life. I have devised and am currently synthesizing and studying new drug delivery materials that are fabricated from non-toxic, biocompatible materials (proteins and iron oxide nanoparticles) whose magnetic properties will facilitate controlled delivery. Because these materials will directly target only the diseased tissue, they have the potential to reduce the cost of health care (less active pharmaceutical molecules need to be used) and increase patient quality of life (minimizing pharmaceutical side effects).

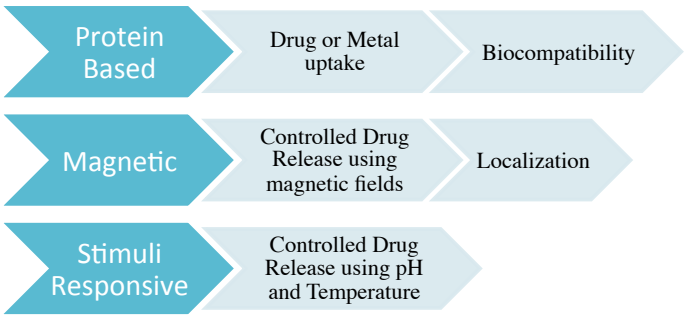


Figure 1: Benefits of the system and what they will be used for.

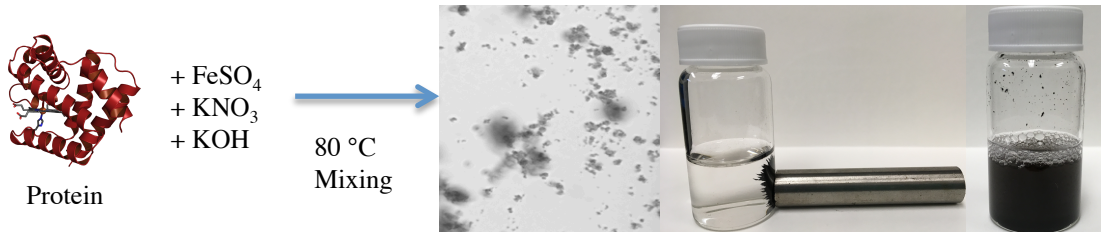
Background

Polymers are being studied as drug delivery vehicles that target specific areas of the body. The uptake and release of compounds by the polymer is responsive to stimuli such as pH and temperature (Dirk, 2006; Stuart, 2010). The most promising of these studies are pH-responsive materials, which trigger release in the low-pH environments that are found near cancerous tissues. These polymeric materials can be further altered with other chemical functional groups that can have an effect on their delivery properties. Magnetic nanoparticles, for instance, have been used to assist in localizing materials within a body as well as being used as contrast agents for magnetic resonance imaging (Yuan, 2008).

In addition to its functional properties, any drug delivery vehicle must also be constructed of biocompatible materials, or able to perform safely during a normal host response. Using proteins as the basis for these materials can help to support its biocompatibility. Previously, proteins have been used to coat polymers and have reduced absorption and nonspecific host interaction (Chen, 2008). Proteins have multiple functions and biological interactions dependent on their residues and their physical and chemical properties. It has been shown that using a protein-based material improves the blood compatibility of the polymer that reduces blood clotting and polymer aggregation (Chen, 2008). Protein-based materials can increase biocompatibility by being faceted with a ligand-like functional group that can bind to the active site of a host protein and can trigger a protein cascade in host cells (Chen, 2008). While proteins are attractive for these uses, there are very few studies in which proteins are the basis for the materials, rather than just a coating for the other polymers used.

Previous work

At American University, Matthew Hartings and his research team have been working on developing protein-based microparticles that contain iron oxide nanoparticles (Mody, 2016). Using an inexpensive and simple synthetic scheme (rapid mixing of a protein, iron sulfate, potassium nitrate, and potassium hydroxide in water at 80 °C for 90 minutes), they were able to create a matrix of organic, protein-based materials that incorporate magnetic iron oxide particles.



My Contributions

The first application that we studied for these particles was the decontamination of water containing toxic heavy metals. Some amino acids in the protein have functional groups (carboxylates, imidazoles, thiols, etc.) that are useful for binding metal ions. We are demonstrating that our particles can adsorb metal ions from solution and then be simply collected through the use of a magnet. Specifically, we are finding that our materials have a much higher affinity for lead than other metal ions. This will be beneficial as our water supplies naturally contain magnesium and calcium, which would otherwise interfere with lead uptake. We are also showing that these metal ions can be released from our materials by decreasing solution pH, which protonates the functional groups that attract the metal ion in the first place.

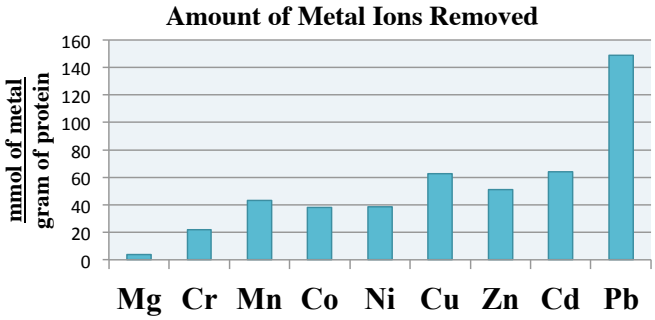


Figure 3: Amount of total metal in mmol of metal/gram of hemoglobin removed from the solution.

Proposed Research

My passion is to use research to improve the quality of patient care, whether that is to decrease risk or increase the effectiveness of a treatment. Being able to conduct research and then apply my findings to patients give me a unique and more personal approach to research and medicine. Repurposing the unique protein-based materials to become a drug delivery vehicle will be the next phase in the research described above. In order for the nanoparticles to become a drug delivery vehicle, the nanoparticles must be able to bind to a pharmaceutical drug and then release it in a controlled manner.

Optimize Drug Molecule Uptake

Previous research has shown that the particles can uptake hydrophobic dye molecules (Mody 2016). This suggests that they will also be capable of absorbing pharmaceutically active molecules. I hypothesize that the ability of the particles to uptake lipid-soluble drugs is

dependent on the protein's average hydrophobicity. Several common laboratory proteins, and their hydrophobicities are shown in the table on the left. More negative values indicate that a protein has more hydrophobic amino acids. I will synthesize particles using these proteins and test for their ability to adsorb dye molecules. I will analyze the amount of molecule adsorbed from by monitoring the solution fluorescence; decreases in fluorescence will indicate that the dye molecules are being incorporated into the particles.

Protein	Average Hydrophobicity
Hemoglobin	-0.081
HRP	-0.100
Invertase	-0.154
Lysozyme	-0.048
Pepsin	-0.282
Myoglobin	0.170

Figure 4. Hydrophobicity values of proteins.

Study Drug Molecule Release

The ability of the nanoparticles to release the adsorbed molecules is crucial in a drug delivery system. I will test for two different release mechanisms. First, I will use pH changes to trigger the release of positively charged drug molecules. As we are currently showing, protonation of amino acid side chains in our materials can facilitate the release of adsorbed metal ions. I expect that this will also hold for pharmaceutical molecules that are positively charged, such as the cancer drug doxorubicin. As a decreased pH is one property of cancerous tissues, acid-induced release is a relevant strategy for location specific drug delivery.

The second release mechanism I will test takes advantage of the particle's magnetic properties. Fluctuating magnetic fields have been shown to induce local heating surrounding iron oxide nanoparticles. Given that there is thermodynamic control over molecular binding to proteins, which should result in lower binding at higher temperatures, I will study the ability of magnetic fields to induce drug release. This has the added benefit that magnetic fields are non-invasive to biological tissue and can be directly targeted to the sites where drug release is needed.

Concluding Statement

Creating a unique protein-base drug delivery system that is stimuli responsive will vastly benefit drug treatments. The drug delivery system that I propose has the flexibility of responding to multiple stimuli such as pH, temperature, and a magnetic field. This allows this system to be tailored to specific treatments needs and offers a safer, more effective solution to traditional cancer treatments.

References:

Chen, H., et al, 21 July 2008. *Biocompatible Polymer Materials: Role of Protein-Surface Interactions*. Progress in Polymer Science. 33: 1059-1087

Dirk, S., 29 September 2006. *Thermo- and pH-Responsive Polymers in Drug Delivery*. Advances Drug Delivery Reviews. 58(15): 1655-1670.

Mody, P., et al, 10 February 2016. *Protein-Based Ferrogels*. Journal of Inorganic Biochemistry. 159: 7-13.

Stuart, M., et al, 2010 *Emerging Applications of Stimuli-Responsive Polymer Materials* Nature Materials. 9(2): 101-113.

Yuan, Q., et al, 4 February 2008. *A Stimulus-Responsive Magnetic Nanoparticle Drug Carrier: Magnetite Encapsulated by Chitosan-Grafted-Copolymer*. Acta Biomaterialia. 4: 1024-1037.