"New" UROP Proposal

Title of Proposal: Ocular drug delivery based on intraocular pressure

STATE THE PROBLEM/TOPIC

Glaucoma, a prevalent ocular condition characterized by elevated intraocular pressure (IOP), poses significant challenges to effective treatment and management [1, 2]. Left untreated, elevated IOP can lead to irreversible damage to the optic nerve and eventual vision loss [3]. Current therapeutic strategies predominantly rely on topical administration of medications aimed at reducing IOP levels. However, these treatments often suffer from limitations such as poor patient compliance and variable efficacy due to the unpredictable nature of IOP fluctuations [4].

There exists a substantial gap in the field of ocular drug delivery concerning the utilization of stimuli-responsive materials that can dynamically adjust drug release in response to changes in intraocular pressure. Mechanophores, with their unique mechanical properties, may help address this gap [5]. These materials can be harnessed to develop innovative drug delivery systems capable of delivering glaucoma medications precisely and proportionately to the fluctuating IOP levels.

Mechanophores are molecules that undergo a chemical or physical change when subjected to mechanical force. In the context of ocular drug delivery, mechanophores can be integrated into hydrogels to create a smart drug delivery system. Hydrogels, which are highly absorbent and can maintain a moist environment, provide an ideal matrix for incorporating mechanophores [6]. When the IOP increases, the mechanical stress activates the mechanophores embedded in the hydrogel, triggering a controlled release of the medication.

Therefore, this project aims to develop a proof-of-concept drug delivery device that delivers glaucoma medication in a concentration that is proportional to the change in intraocular pressure. By harnessing mechanophores and integrating them into hydrogels, our goal is to create an advanced system capable of dynamically responding to fluctuations in IOP. This innovative approach seeks not only to enhance treatment efficacy but also to significantly improve patient adherence. Addressing the unpredictability of IOP fluctuations, our proposed device aims to prevent the progression to vision impairment in glaucoma patients more effectively than current therapies allow.

RELEVANT BACKGROUND/LITERATURE REVIEW

Ocular drug Delivery

Ocular drug delivery systems for treating glaucoma are an area of significant research and innovation, aiming to improve therapeutic outcomes and patient compliance [7, 8]. Traditional treatment methods, such as topical eye drops, often suffer from poor bioavailability due to rapid tear turnover and limited corneal absorption, leading to suboptimal IOP control. To address these limitations, advanced drug delivery systems have been developed to enhance the precision and efficiency of drug administration. These new systems offer sustained and controlled release of medications, potentially reducing the frequency of dosing and minimizing side effects.

Various ocular drug delivery systems have been developed to enhance treatment effectiveness and duration for eye conditions. Punctum plugs, inserted into tear ducts, help retain moisture and extend medication contact time. Subconjunctival/episcleral implants and cul-de-sac implants provide sustained drug release directly to ocular tissues. Drug-eluting contact lenses offer controlled medication release for continuous therapy. Ocular iontophoresis enhances drug penetration using electrical currents. Posterior segment drug delivery targets the back of the eye for conditions like AMD and diabetic retinopathy. Advanced technologies like Durasert and NOVADUR systems enable long-term drug release, reducing the need for frequent treatments and improving patient compliance. These technologies represent significant advancements in ocular drug delivery, aiming to improve treatment outcomes, patient compliance, and overall safety in managing various eye conditions. Each method offers unique advantages tailored to specific medical needs and challenges in ophthalmology [9, 10].

Hydrogels

Additionally, Hydrogels have emerged as promising candidates for ocular drug delivery due to their biocompatibility, high water content, and tunable properties that can be tailored to mimic the ocular

environment [11]. These three-dimensional networks of hydrophilic polymers can absorb and retain large amounts of water while maintaining structural integrity. In ophthalmology, hydrogels offer several advantages, including prolonged drug release, reduced frequency of administration, and enhanced patient comfort.

Stimuli-responsive hydrogels

Stimuli-responsive hydrogels are a subset of hydrogels designed to undergo reversible changes in response to external stimuli such as pH, temperature, light, or mechanical forces [12]. These changes can trigger controlled drug release, making them particularly suitable for targeted and on-demand therapies in ophthalmic applications. For instance, pH-sensitive hydrogels can release drugs in response to changes in the ocular pH environment, which varies across different parts of the eye.

Molecular imprinting

Molecular imprinting involves the creation of polymer matrices with cavities or "imprints" that are complementary in shape and chemical functionality to the target molecule drug. This technique enables selective recognition and binding of the drug molecule within the hydrogel matrix, facilitating controlled release kinetics tailored to specific therapeutic needs.

Release kinetics

Drug release kinetics over a 12-hour period show that higher molecular weight hydrogels typically release drugs faster than lower molecular weight hydrogels, except for higher molecular weight drugs, which have similar release rates across different hydrogel compositions. Over a 30-day period, higher molecular weight hydrogels generally exhibit less stability, while lower molecular weight hydrogels maintain their stability better. Timolol, a high molecular weight drug, demonstrates superior long-term stability, retaining most of its loading capacity, unlike tetrahydrozoline and dorzolamide, which lose a significant portion of their loading capacity over the 30-day period. This analysis provides important insights into the short-term efficacy and long-term stability of hydrogel-based drug delivery systems, highlighting their potential practical applications [13].

Mechanophores

Mechanophores are molecules that undergo changes in their molecular structure or properties in response to mechanical forces. When integrated into hydrogel networks, mechanophores enable the hydrogels to exhibit stimuli-responsive behavior triggered by changes in IOP. This capability is crucial for developing smart hydrogels that release drugs in response to IOP fluctuations, optimizing therapeutic efficacy and patient compliance in conditions like glaucoma. The incorporation of mechanophores into hydrogels represents a promising approach to creating advanced ocular drug delivery systems that respond dynamically to the mechanical environment within the eye.

Beyond ocular drug delivery, this mechanophore/hydrogel innovation holds promise for advancing materials science in responsive biomaterials. Integrating mechanophores into hydrogels enables the development of controlled drug release systems that respond to mechanical stimuli. Mechanophores undergo structural changes under mechanical stress, triggering the release of medications. This responsive technology could extend beyond ophthalmology to fields like tissue engineering, environmental sensing, and wearable technologies, where responsiveness to mechanical cues enhances functionality and user interaction. This innovation not only expands our understanding of material science but also opens doors to diverse applications in responsive biomaterials across technological and biomedical fields.

SPECIFIC ACTIVITIES AND TIMELINE

August: Synthesize a hydrogel using 2-hydroxyethyl methacrylate

- Prepare a solution containing 2-hydroxyethyl methacrylate (HEMA) and Tetraethylene glycol dimethacrylate (TEGDMA) in appropriate ratios. Add a photoinitiator to the mixture. The photoinitiator will initiate the polymerization reaction upon exposure to UV light.
- Place the mixture in a mold or apply it onto a substrate.
- Expose the mixture to UV light to initiate polymerization. Ensure sufficient exposure time for complete cross-linking of the hydrogel.

This stage of the project should take approximately 35 hours

September: Use molecular imprinting to load the drug

- Dissolve the drug molecule (template) in a suitable solvent.
- Mix the drug solution with the pre-formed hydrogel precursor solution (from August's synthesis).
- Initiate polymerization (similar to August's procedure) to form the drug-imprinted hydrogel.
- During polymerization, the drug molecule will self-assemble within the hydrogel, forming specific binding sites (imprints).
- After polymerization, leach out the drug molecule (template) from the hydrogel using a suitable solvent or by washing.
- This leaves behind cavities (imprints) that are complementary to the drug molecule in terms of size and shape.
- This stage of the project should take approximately 15 hours.

September: Synthesize hydrogel composites using one of the additives
-Prepare a solution containing the hydrogel precursor (HEMA, TEGDMA, photoinitiator) and the additive (e.g., mechanophore). Initiate polymerization under UV light as done previously.
-Ensure the additive is uniformly distributed within the hydrogel matrix This stage of the project should take approximately 20 hours

October: Characterize the hydrogel using weigh testing, quartz crystal microbalance, FTIR, Raman spectroscopy
-Weigh Testing:
-Measure the weight of the hydrogel to determine its swelling behavior and mass changes. - Quartz Crystal Microbalance (QCM):
-Monitor changes in the hydrogel's mass in response to solvent interactions or drug release. - FTIR and Raman Spectroscopy:
-Analyze the chemical structure and composition of the hydrogel.
-Identify functional groups, cross-linking efficiency, and any interactions with additives or drugs. This stage of the project should take approximately 25 hours.

November and December: Develop a method for characterizing the release of the drug, likely using pressure sensors and UV-Vis

- Pressure Sensors:
- Incorporate pressure sensors to monitor changes in hydrogel volume or mechanical properties as the drug is released.
- This can provide real-time data on drug release kinetics.

- UV-Vis Spectroscopy:
- Prepare drug-loaded hydrogel samples and immerse them in a suitable release medium.
- Measure absorbance or fluorescence changes in the medium over time as the drug diffuses out of the hydrogel.

This stage of the project should take approximately 25 hours.

RELATIONSHIP OF WORK TO THE EXPERTISE OF THE MENTOR
Dr. XXX's research in polymer materials and their impact on biological systems is pioneering advancements across several critical domains. His work focuses on biopolymer-based biodegradable adhesives, offering sustainable solutions for medical applications where traditional adhesives may pose risks or limitations. In the

realm of hydrogel materials used in actuators, sensors, and drug delivery devices, Dr. XXX explores innovative formulations that enable precise control and sustained release of therapeutic agents. His research underscores the importance of tailored drug delivery systems that can be fine-tuned to individual patient needs, enhancing treatment efficacy and patient compliance. Moreover, Dr. XXX investigates advanced surface treatments to improve biocompatibility and functionality, crucial for integrating polymer devices seamlessly into biological systems. Through his expertise in polymer synthesis and characterization, he drives the development of reusable materials that not only reduce costs but also support broader accessibility to cutting-edge biomedical technologies.

RELATIONSHIP OF THE WORK TO YOUR FUTURE GOALS

Throughout my educational journey, I have developed a keen interest in biomaterials and polymer science. This project will provide me with the opportunity to deepen my understanding and expertise in material science and biomedical engineering, particularly in the integration of stimuli-responsive materials such as mechanophores. I am excited about the prospect of exploring the unique properties and potential applications of these materials, which respond to mechanical stress by changing their chemical structure. Additionally, this project will allow me to engage in hands-on research, honing my experimental and analytical skills. Conducting research in this cutting-edge field aligns perfectly with my career goals and aspirations, as it will equip me with the knowledge and experience necessary to contribute to advancements in biomedical technology and materials science.

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